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Clinical Pharmacokinetics in Newborns and Infants
Age-related Differences and Therapeutic Implications

Paolo L. Morselli, Rosetta Franco-Morselli and Laura Bossi

Department of Clinical Research, Synthelabo-LERS, Paris

The information available on the disposition of drugs in newborns and infants has increased considerably in the last 5 years. For several classes of drugs it is now possible to describe their pharmacokinetic profiles in various age groups. Important differences in absorption, distribution, metabolism and excretion have been observed between premature neonates, full term newborns and young infants. While it is evident that variables such as gestational and postnatal age have to be considered when designing a therapeutic schedule, the importance of previous or concomitant exposure to other drugs, as well as the relative hypoxaemia or the severity of the pathological status of the infant, are not always taken into account. Evidence indicates that these last factors may further modify drug disposition.

Because the maturational process is not fully predictable, and because other factors may interact to a varying extent, depending on the clinical picture, we have become increasingly aware of the importance and necessity of therapeutic drug monitoring in the perinatal period and early infancy (Morselli, 1977b).

Through therapeutic drug monitoring we have acquired more insight on the relative importance of the different variables and, most important, safer and more rational therapy has been achieved in many instances. The purpose of this review is to underline possible important differences in drug disposition among age groups which may appear very close on a temporal basis (such as neonates and young infants), as well as alterations of the age-determined kinetic pattern induced by pathological conditions or associated treatment.

In the first part of the review we will consider the impact of development and pathology on the physiological variables determining drug disposition, while in the second part, kinetic profiles of representative drugs used in the perinatal period and infancy will be discussed.

1. Pathophysiological Factors Affecting Drug Kinetics

1.1 Drug Absorption

1.1.1 Gastrointestinal Absorption

In the neonate most of the physiological functions important for the gastrointestinal absorption of drugs are quite variable and undergo continuous maturational changes.

Gastric emptying time may be considerably prolonged and according to Smith (1951) it approaches adult values only after 6 months of age. More recent studies have shown that in the neonate the gastric emptying rate is a function of gestational

maturity and postnatal age, as well as of the nature of the feeding (human milk or infant formula) [Gupta and Brans, 1978; Cavell, 1979]. The stomach emptying time is not affected by the posture and is characterised by a biphasic pattern with an initial rapid phase (10 to 20 min) followed by an exponential slower phase (Blumenthal et al., 1979). In the preterm newborn, such a biphasic pattern is not evident with infant formula, and the emptying rate is slower and linear (Cavell, 1979).

The irregular rate of gastric emptying associated with a very irregular and unpredictable peristalsis, which may be greatly modified by the diet and feeding habit, may have an important influence on the absorption rate of several compounds administered as a suspension, before, during or after feeding.

Gastric pH: At birth, the gastric pH is close to neutrality; it falls to 1.5-3.0 within a few hours but returns to neutrality in the following 24 hours. Such a decrease is not present in premature newborns because of immaturity of secretory mechanisms. The pH then returns close to neutrality for the first 10 to 15 days of life and subsequently it declines very gradually, reaching adult values only after 2 years of age (Morselli, 1976a; Weber and Cohen, 1975; Yaffe and Juchau, 1974).

The relative achlorhidric situation may partially explain the higher bioavailability reported in the newborn for several penicillins as well as the reduced absorption of acid compounds such as phenobarbitone, phenytoin (diphenylhydantoin), nalidixic acid (Morselli, 1976a).

Other factors which may play a variable role are the gradual maturation of biliary function, the variable colonisation rate of the intestine by the microbial flora, and the high level of β-glucuronidase activity in the newborn intestine (Long and Swenson, 1977; Murphy and Singer, 1974; Scheline, 1968; Watkins et al., 1973; Yaffe and Juchau, 1974). As a consequence of the maturational stage of the various physiological variables in a 'normal' neonate, modified bioavailability of drugs in the full term and premature infant is a relatively easily understood phenomenon, but the situation may be further complicated in the case of the severely ill infant. Severe cardiac insufficiency, for example, may in fact lead to a decreased perfusion rate of the splanchnic area and to an oedematous status of the gastrointestinal mucosa with consequent reduced and/or delayed absorption (Sondheimer and Hamilton, 1978). Similarly, reduced absorption has been described in malabsorption syndromes (Krishnaswamy, 1978).

Alteration of biliary function, which is frequently encountered in malabsorption syndromes and in the steatorrhoeas of preterm and full term newborns, may also influence considerably the absorption rate of medication given with food (de Belle et al., 1979; Heubi et al., 1979; Jonas et al., 1979; MacLean et al., 1978). Other situations which may further modify absorption processes are gastroenteritis (because of both altered transit time and modified function of the absorbing mucosal surface), as well as the presence of antibiotic therapy which may completely change the quality of the intestinal flora and the colonisation rate (Bell et al., 1979; Osfeld et al., 1977).

Rectal absorption: The data on rectal absorption are scanty; they do however, indicate that, if a proper formulation is used, this route of administration is highly efficient, as in the case of diazepam and theophylline, where peak plasma concentrations comparable or higher than those obtained by other routes may be obtained within 15 and 30 minutes respectively (Agurell et al., 1975; Bolme et al., 1979; Neese and Soyka, 1977).

Systematic data on drug absorption in infants are lacking. It appears, however, from the available data that in infants over 3 months of age the oral absorption rate of various drugs is higher with respect to grown up children and adults (Morselli, 1977a,c, 1978a).

1.1.2 Intramuscular Absorption

The ease of penetration through endothelial capillary walls, the surface area over which the solution has spread and the blood flow through the area are the main factors which influence the absorption rate of drugs following intramuscular administration (Morselli, 1977c). The marked peripheral vasomotor

instability of the newborn, the changes in relative blood flow of various muscles due to maturational adaptation, and the relative insufficiency of muscular contractions are all factors which may cause marked variations in the absorption rate of drugs. It should also be remembered that skeletal muscle mass and subcutaneous fat are reduced in the newborn with respect to the infant or grown up child, and that they contain a higher percentage of water (Widdowson, 1974).

The situation may be further complicated by the presence of circulatory insufficiency and/or respiratory distress, leading to hypoxic conditions and/or undue exposure to a cold environment.

As an example of the relative variability, depending on the characteristics of the particular drug, absorption of phenobarbitone is rapid while absorption of diazepam is delayed and that of gentamicin and digoxin reduced, both in small for gestational age preterm newborns and in full term neonates (Assael et al., 1977; Boreus et al., 1975; Morselli, 1976a; Morselli et al., 1973; Szefler et al., 1977).

1.1.3 Percutaneous Absorption

Percutaneous absorption is inversely related to the thickness of the stratum corneum and directly related to skin hydration, and is therefore increased in the newborn and young infant (Morselli, 1977c). In the newborn, the situation may be further aggravated by the use of abrasive tapes, so frequently used for monitoring or for therapeutic devices.

Such an increased permeability is well illustrated by the toxic effects reported with boric acid powders, hexachlorophane emulsions and powders, salicylic acid ointments and naphthalene (Shirkey, 1980; Tyrala et al., 1977).

1.2 Drug Distribution and Drug Protein Binding

The pharmacological and therapeutic effects of drugs depend not only on the extent and rate of absorption and elimination but also on the kinetics of distribution to various tissues and body compartments.

As already mentioned, the various body compartments in the newborn and in the infant have a different absolute and relative size as compared with children and adults (Friis-Hansen, 1961; Morselli, 1977c, 1978a).

In the newborn and in the young infant, the total body water content is larger and the ratio of extracellular to intracellular water is higher, while fat tissue is relatively scarce (15% of body weight) and it contains more water. Skeletal muscle mass is also reduced (25% of body weight). The brain and liver are much larger in relation to body weight; the composition of brain tissue is different, the myelin content being low and the cerebral flow may be higher in comparison with adults (Morselli, 1976, 1977c, 1978a; Settergren et al., 1976; Widdowson, 1974).

Other factors such as variations of blood pH, acid-base balance, cardiac output and regional blood flow, which are always present during the first days of life, may also influence drug disposition (Monin et al., 1980; Morselli et al., 1980; Payne, 1974; Shinebourne, 1974).

To the above-mentioned factors, another important physiological variable represented by the binding to plasma proteins must be added. While several reports agree on a significantly reduced *plasma protein* binding of various drugs in the premature and full term newborn, data on infants are still relatively scarce and contradictory.

The reduced plasma protein binding in newborns is due to the concurrence of several factors such as:

a) A reduced total plasma protein concentration associated with a qualitative difference in plasma protein content, persistence of fetal albumin with lower affinity for drugs and a lower level of γ-globulins and lipoproteins
b) A condition of relative hypoxaemia associated with a lower blood pH
c) A high plasma concentration of free fatty acids (FFA) and unconjugated bilirubin which may compete with acidic drugs at albumin binding sites
d) The possible presence of 'competitive' binding substances of maternal origin.

(Ecobichon and Stephens, 1973; Ehrnebo et al., 1971; Gugler et al., 1974; Krasner et al., 1973; Kurz et al., 1977a,b; Morselli, 1976a, 1977c; Odell, 1973; Øie and Levy, 1977; Wallace, 1977; Windorfer et al., 1974; Yaffe and Juchau, 1974; Yaffe and Stern, 1976).

The importance of γ-globulin for binding of non-acidic compounds has been recently stressed (Kurz et al., 1977a,b). In premature and full term newborns as well as in infants, the already low levels of γ-globulin may be further reduced because of insufficient dietary protein intake (Zoppi et al., 1978) or gastrointestinal disturbances. Furthermore, the various factors mentioned above may potentiate each other. For example, a rise in free fatty acid concentration may lead to a gher level of unconjugated bilirubin which in turn may further displace highly bound acidic drugs from albumin binding sites.

The reduced plasma protein binding, together with the considerable difference in body compartments at birth and during infancy compared with adults, may have variable effects on the apparent *volume of distribution* of different drugs. It is in fact understandable that since drugs are distributed between extracellular water and fat depots according to their lipid : water partition coefficient (depending on their physicochemical properties), the continuous modifications of the 2 compartments and the increase in organ perfusion and blood flow may significantly influence the distribution of therapeutic agents.

Blood pH variations of 0.20 to 0.25, which often :cur in postanoxic convulsive states, may provoke important fluctuations in plasma and tissue concentrations of compounds such as phenobarbitone which have a pKa close to the pH values of blood (Monin et al., 1980; Morselli et al., 1980).

In the case of perinatal respiratory distress or cardiac insufficiency, the distribution time may be significantly prolonged. The situation may be more complex in the case of relative hypoxia or perinatal asphyxia, where (at variance with what happens in the adult, because of impairment of autoregulation mechanisms) a reduction of cerebral blood flow with a preferential perfusion of brainstem structures may take place together with systemic hypotension (Lou et al., 1977; Volpe, 1979). These events may lead not only to modified brain distribution of lipophilic drugs (which are all flow-dependent), but also to alteration in absorption and excretion rates.

Because of the possibility of an abnormally expanded volume and of the influence of blood pH and other endogenous plasma constituents (FFA and bilirubin), a given plasma drug concentration in the newborn and the infant may be associated with tissue: plasma ratios lower or higher than in adults. Consequently, the simple measurement of total drug concentration in plasma or blood without information on the above-mentioned factors, may be of little value in the course of therapeutic drug monitoring, since it may not reflect the amount of drug present at the receptor site assumed from data in older children and/or adults.

Finally, it is worthwhile to remember that highly bound acidic drugs may compete for plasma albumin binding sites and also displace bilirubin, thus leading to toxic bilirubin concentrations in the brain of susceptible newborns (Morselli, 1976a; Odell, 1973; Stern, 1972).

As stated earlier, it is difficult on the basis of the available information to state when protein binding reaches values similar to that of grown up children and adults. According to Ecobichon and Stephens (1973) and Windorfer et al. (1974), values comparable with those of adults may be reached for binding of acidic drugs between the second and the third year of life. However, in the case of γ-globulin, adult values are reached only between 7 and 12 years of life, and reduced binding of imipramine has been reported by Windorfer et al. (1974) in children below 10 years of age.

1.3 Drug Biotransformation

Drug biotransformation can be due to enzyme activity associated with hepatic microsomal systems or to esterases present in plasma and various tissues. Both activities are depressed and/or reduced in the

newborn, while a different behaviour may be observed in the infant.

1.3.1 Esterase Activity

Esterase activity is apparently linked to the developmental stage and rises gradually during the first 12 months of life. Reduced hydrolysis rates of procaine as well as reduced activity of acetylcholinesterases, arylesterases and pseudocholinesterases have been reported by various authors for newborns and young infants (Augustinsson and Brody, 1962; Ecobichon and Stephens, 1973; Lehman et al., 1957; Reidenberg et al., 1972; Zsigmond and Downs, 1971).

More recently, Cook et al. (1976) showed that in the premature newborn, esterase activity is lower than in the full term neonate. An increased volume of distribution associated with a low hydrolysis rate due to the low level of blood esterases could account for the prolonged effect and partially explain the cardiorespiratory depression observed in newborns when drugs containing 'ester bonds' (e.g. some local anaesthetics) are used during delivery.

The increase in esterase activity appears to parallel that of plasma proteins and according to Ecobichon and Stephens (1973) and Windorfer et al. (1974) normal activity is achieved within 10 to 12 months.

1.3.2 Hepatic Microsomal Activity

Most of the enzymatic microsomal systems responsible for different biotransformation reactions are present at birth. However, their titres are considerably reduced in comparison with adult values and their activities appear to increase with advancing fetal and postnatal age. *In vitro* studies have shown that, *at term*, cytochrome-P-450 approaches about one half of adult values and NADPH-cytochrome-C-reductase activity is also one half of the adult values (Aranda et al., 1974). These *in vitro* studies also suggested that while aminopyrine N-demethylase activity has quite a variable behaviour, aniline-p-hydroxylase activity was linearly related to age, to NADPH-cyt-C-reductase activity as well as to cyt-P-450 content.

Several observations *'in vivo'* in preterm and full term infants confirm that enzymatic activities catalysing phase I biotransformation reactions may be significantly reduced in the newborn, and that the various metabolic activities are not influenced by age to the same extent. A different rate of 'maturation' may explain why different and sometimes contrasting results have been obtained with different drug molecules (Levy et al., 1975; Mandelli et al., 1975; Meffin et al., 1973; Mihaly et al., 1978; Morselli, 1977c; Morselli et al., 1973, 1974; Rane et al., 1975; Reynolds and Mirkin, 1973).

Part of the discrepancies could also be due to the exposure *in utero* to microsomal enzyme inducing agents. There is in fact good evidence that induction may take place *in utero* and that the various oxidative pathways may be increased or stimulated to different extents (Morselli, 1976a; Morselli et al., 1974; Sereni et al., 1973a). The basis for the differences in response to inducing agents could be on the one hand, the presence of different enzymes with a substrate specificity higher than currently thought, or on the other hand, the presence of various endogenous competitive inhibitors. The enzymatic systems involved in drug metabolism do in fact catalyse the biotransformation of fatty acids, bile acids and steroid hormones. A reduced hepatic uptake of organic anions and bilirubin may also occur, because of relative deficiency of the hepatic cytoplasmatic anion binding protein ligandin (Y protein) [Levi et al., 1970; Litwack et al., 1971].

Reduced hydroxylation rates have been reported for several compounds such as phenobarbitone, phenytoin, acetanilide, amylobarbitone (amobarbital), mepivacaine, lignocaine (lidocaine) and nortriptyline. Dealkylation reactions appear on the contrary to be less impaired when evaluating drugs such as mepivacaine, diazepam, lignocaine, etc (see Morselli, 1976a, 1977c). In the case of theophylline and caffeine, the contrary is true and the N-demethylation pathway appears to be the most deficient step (Aranda et al., 1976; Bory et al., 1979; Boutroy et al., 1979; Brazier et al., 1979). It should also be emphasised that in case of drugs with a low hepatic extraction ratio, the

reduction in metabolic degradation appears to be more important than it is in the case of drugs with a high hepatic extraction ratio (Mihaly et al., 1978; Moore et al., 1978).

Among phase II synthetic reactions, sulphate conjugation and glycine conjugation appear to be present at titres comparable with those of adults, while the conjugation with glucuronic acid is considerably reduced and reaches adult values only after 3 years of age (Dutton, 1978; Levy, 1975; Levy and Garrettson, 1974; Levy et al., 1975; Miller et al., 1976).

The reduced metabolic activity present in the preterm and full term 'not induced' newborn may be further decreased by pathological conditions such as respiratory distress, cardiac insufficiency, hyperbilirubinaemia and insufficient dietary intake. In most of these cases, the pathological situation is characterised by hypoxaemia and a trend toward acidosis, which, leading to a further increase in the free fraction and higher drug content in tissues, may further complicate a situation characterised by a very reduced elimination rate.

At present, the mechanisms which regulate the development of metabolic activities in man are still unknown. No one of the various hypotheses proposed has up to now been proven, and it is very likely that several factors are implicated at the same time (Aranda, 1974; Morselli, 1976a; Neims and Manchester, 1978; Sereni et al., 1973a).

Whatever may be the cause, a reduced capacity to dispose of drugs is constantly observed during the first 15 days of life in premature and full term newborns, unless there is an exposure to inducing agents before or immediately after birth. In this respect, it may be interesting to speculate that the response of the newborn liver to inducing agents is greater and faster than in adults.

In most cases, such a stage of reduced metabolic degradation is then followed by a dramatic increase in the metabolic rate of mainly phase I reactions (Morselli, 1976a, 1977c, 1978a; Neims and Manchester, 1978). The change is rather dramatic, since the disposition rate may pass from that of 1/3 to 1/5 of the adult to a rate 2 to 6 times faster than in adults.

It is understandable that the phenomenon may have important therapeutic consequences; we pass in fact from a situation at risk of *overdosing* to another where the major risk is *underdosing*.

As mentioned previously, it is somehow surprising to see how little attention has been paid to this period of change, both in routine clinical practice as well as in perinatal pharmacology. A better understanding of the factors determining such a dramatic increase in drug metabolising activity could in fact lead to better and safer treatment of newborns and infants. The increased metabolic disposition rate is usually very evident from 2-3 months up to 2-3 years of age, when values tend to decline gradually to reach those of adults after puberty (Morselli, 1977c, 1978a). The phenomenon is evident for several drugs with the exception of theophylline and caffeine where an increased metabolic degradation is reached slowly and progressively at later times (see later).

1.4 Renal Drug Excretion

In the newborn, although the ratio of the kidney weight to the body mass is 2-fold that of adults, the organ is anatomically and functionally immature; all aspects of renal function being reduced (Barnett et al., 1948; Guignard et al., 1975; Leake and Trygstad, 1977; McDonald and Emery, 1959). Furthermore, at birth glomerular function is more advanced than tubular function and this glomerular/tubular imbalance may persist up to 6 months of age (Braunlich, 1977; Houston and Oetliker, 1974; McDonald and Emery, 1959; Morselli, 1978a).

The 2 factors which mainly condition the development of renal function are the gestational age and the dramatic sequential haemodynamic changes in a situation initially dominated by high vascular resistances and extremely low blood flow.

As far as maturation of the glomerular function is concerned, a sudden increase in the function may be observed at about 34 weeks ($\sim$ 2000g). The reasons for this sudden increase are not evident. Such an increase in function corresponds however, to the cessa-

tion of formation of new glomeruli (Arant, 1978; Barnett et al., 1948; Leake and Trygstad, 1977; Siegel and Oh, 1976). At birth the glomerular filtration rate is 2 to 4ml/min in the full term newborn, but it may be as low as 0.7 to 0.8ml/min in preterm infants. The adaptive increase in the full term neonate is greater than in the premature neonate, and it has been shown that after 2 to 3 days of extrauterine life the GFR may be 8 to 20ml/min in full term against 2 to 3ml/min in premature infants (Arant, 1978; Guignard et al., 1975; Houston and Oetliker, 1974; Leake and Tygstad, 1977). The increase in GFR is due to several factors, such as increased cardiac output and specific changes in renal vascular resistances which result in an increase in renal blood flow, associated with changes in renal blood flow distribution with a gradual shift from the deep juxtaglomerular nephron to the outer cortex and with probable changes in the permeability of the glomerular membrane (Braunlich, 1977; Hook and Hewitt, 1977; Houston and Oetliker, 1974; Leake and Trygstad, 1977).

The tubular function at birth is even further reduced: low tubular functional capacities for the transport of glucose, phosphate, bicarbonate and PAH have been described. In the newborn the Tm of PAH may be about 12ml/min reaching childhood values only at 30 to 40 weeks of age. Reasons for the reduced transport capacity are the low blood flow in peritubular regions, the immaturity of energy-supplying processes, the small mass of tubular working cells, as well as the small size of not yet developed tubuli (Arant, 1978; Braunlich, 1977; Hook and Hewitt, 1977; Morselli, 1978; Yaffe and Stern, 1976).

Data of Gladtke and Heimann (1975) and of Yaffe et al. (1976) suggest that passive resorption may also be significantly reduced in the newborn and in the infant, thus determining in infants a higher renal clearance of those drugs which depend on glomerular filtration for their elimination.

Other variables which may play a role in drug excretion in the newborn are the lack of diurnal rhythm of renal function (Krauer, 1975); the 'physiological' presence of protein in the urinary filtrate in about 20 to 30% of term and preterm populations (Arant, 1978); and the low urinary pH associated with the already mentioned relative incapacity to concentrate urine (Braunlich, 1977; Houston and Oetliker, 1974; Morselli, 1976a, 1978a; Yaffe and Stern, 1976).

The low clearance rates and the higher half-life values of aminoglycoside antibiotics, such as gentamicin and kanamycin and of drugs like indomethacin and digoxin which are dependent on glomerular filtration for their excretion, or of compounds like penicillins and sulphonamides whose excretion depends upon tubular secretion, are good examples of how reduced renal function may modify the kinetics of several drugs and so increase the risk of toxic effects in the newborn (see Morselli, 1976a, 1978a; Yaffe and Stern, 1976).

It should also be remembered that all situations and pathological conditions capable of modifying renal haemodynamics may lead to either a delay in the maturation of the kidney or to a temporary reduction of a function already poorly developed. The risk of mild and/or severe renal failure is too often underestimated and it may be more frequent than currently thought in situations like undernutrition, perinatal anoxia, hypotensive status consequent to respiratory distress, presence of patent ductus arteriosus, cardiac failure, diarrhoea and dehydration (Anan et al., 1978; Daniel and James, 1976; Dauber et al., 1976; Jonas et al., 1979). The newborn kidney is very sensitive to oxygen deprivation and, in terms of renal drug excretion, while a short mild hypoxic episode affects mostly tubular function and may be followed, in hypocapnic conditions, by an increased diuresis, a longer lasting episode may involve glomerular function too (because of persistent reduction in renal perfusion), thus leading to oliguria (Daniel and James, 1976; Dauber et al., 1976; Jones et al., 1979).

In those cases where a diuretic effect is needed, a limited response may result because of the low glomerular filtration rate and immature tubular function (Loggie et al., 1975). Furthermore, for those drugs which, like frusemide (furosemide), are protein bound and exert their action intraluminally, the presence of proteins in the urine filtrate may further

markedly diminish the effect by reducing the free fraction of the drug (Mirkin, personal communication).

Finally, recent studies indicate that at the renal level, the transport system for organic anions may increase its capacity in response to a load (Braunlich, 1977; Frenzel et al., 1977; Hook and Hewitt, 1977; Schwartz et al., 1976). As in the case of drugs cleared by hepatic mechanisms, pre- and postnatal drug administration may influence the rate of development of renal function in the newborn, so that in selected cases, unexpected high rates of drug elimination may be observed.

In the infant (2 to 24 months of age), because glomerular filtration and tubular secretion mechanisms are apparently more developed than tubular resorption, the clearance of various compounds may be markedly increased with values even higher than those observed in children (see later and Morselli, 1977c).

2. Pharmacokinetic Profiles of Drugs Commonly Used in the Perinatal Period and in Infancy

In the previous sections we have tried to describe the various physiological variables capable of determining the kinetic profile of drugs in the newborn, as well as describing their variations because of developmental maturation or pathological conditions.

In the following sections we will describe in a comparative manner either the pharmacokinetic profiles or the available kinetic data for drugs commonly used in the perinatal period and in infancy. Because of space limitations, we have in most cases restricted our literature citations to the last 2 or 3 years up to the beginning of 1980.

2.1 Local Anaesthetics

Local anaesthetics have been and are increasingly used in modern obstetrics for regional anaesthesia during labour and delivery. The rationale behind their use has been an attempt to avoid administration of systemic sedatives to the mother and consequent fetal exposure to CNS-depressing agents. It was however, quickly found that local anaesthetics rapidly enter the maternal systemic circulation and readily cross the placenta with possible unwanted effects on the newborn infant (Benowitz and Meister, 1978; Dodson, 1976; Magno et al., 1976b; Nation, 1980; Ostheimer, 1979; Tucker and Mather, 1975, 1979).

Epidural block is the most widely used technique for regional analgesia during labour and delivery, and with this technique, in contrast to paracervical block, local anaesthetic concentrations in the systemic circulation of newborns at birth are generally lower than the maternal concentration and are associated with a remarkably lower incidence of severe toxic effects in the neonate (Committee on Drugs, 1978; Crawford, 1979; Dodson, 1976; Ostheimer, 1979; Tucker and Mather, 1975, 1979). However, accidental errors in injection technique and the effect of fetal acidosis may lead to high concentrations in the fetal unit with consequent elevated concentrations at birth (Biehl et al., 1978; Brown et al., 1976; Dodson, 1976). Drug interations may also enhance the risk of neonatal toxic effects and displacement of mepivacaine from plasma protein binding sites with consequent increase of the free fraction has been observed with several drugs (Tucker and Mather, 1979). If severe drug intoxication is relatively rare, subtle behavioural and neurophysiological impairment, not reflected in Apgar scores, is probably more frequent than commonly thought (Dodson, 1976; Ostheimer, 1979).

In this respect, the knowledge of kinetic behaviour of the most commonly used compounds, both in the mother and the newborn, may help in more rational therapy, especially in those cases at high risk. The pharmacokinetic profile of bupivacaine, lignocaine (lidocaine), mepivacaine and etidocaine is summarised in the following pages, while a comparison with the kinetic profile in adults is reported in table I.

The available data, although still largely incomplete, appear to support the view that bupivacaine and etidocaine, because of their lower UV/MV (um-

bilical venous/maternal venous) ratio, may be the drugs of first choice in epidural analgesia during labour and delivery. Lignocaine and mepivacaine are probably less indicated because of their higher transfer ratio through the placenta. The total amount of drug to which the fetal unit and the newborn are exposed, that is to say the concentration achieved at birth, is in fact a more important factor than the rate at which the drug is subsequently disposed of during the first days of extrauterine life.

2.1.1 Bupivacaine

Following epidural administration, bupivacaine enters the maternal circulation rapidly with peak concentrations attained within 5 to 60 minutes (Belfrage et al., 1975; Caldwell et al., 1977a; Magno et al., 1976a). Occasionally, absorption may follow a biphasic pattern with a reduced rate for the second phase (Tucker and Mather, 1979).

Bupivacaine is detectable in the fetal circulation as early as 10 minutes after its administration to the mother and the fetal maternal concentration ratio increases rapidly up to 30-60 minutes when an apparent equilibrium may be reached (Belfrage et al., 1975; Caldwell et al., 1977a). At delivery, the umbilical venous/maternal venous concentration ratio (UV/MV) is usually relatively lower (0.14 to 0.40) than comparable ratios observed for other local anaesthetics (Belfrage et al., 1975; Magno et al., 1976a; McGuinness et al., 1978; Reynolds and Taylor, 1970; Scanlon et al., 1976; Tucker, 1975; Tucker and Mather, 1979).

According to Thomas et al. (1976), the low UV/MV ratios may be explained by different protein binding, the lower binding in the newborns being due to lower concentrations of α_1-acid glycoprotein (Mather and Thomas, 1978). While fetal acidosis can lead to increased neonatal plasma bupivacaine levels, a maternal lateral position counteracts fetal acidosis and does considerably limit fetal bupivacaine concentrations (Brown et al., 1976; Datta et al., 1979).

The apparent elimination half-life in the newborn may range from 6 to 22 hours and it is about 2 to 10-fold longer than those observed in adults (Caldwell et al., 1977a; Magno et al., 1976a; Tucker and Mather, 1975, 1979). No data are available on bupivacaine metabolism and excretion in the newborn.

2.1.2 Lignocaine (lidocaine)

After epidural administration, peak levels of lignocaine in maternal plasma are attained within 5 to 30 min (Benowitz and Meister, 1978; Tucker and Mather, 1979). The umbilical venous/maternal venous (UV/MV) concentration ratio may range from 0.5 to 0.7, but in the case of fetal acidosis, as described for bupivacaine, higher concentrations can be found in the fetal unit (Biehl et al., 1978; Brown et al., 1975; Kuhnert et al., 1979a; Tucker and Mather, 1979). The protein binding of lignocaine is considerably reduced in the newborn (free fraction : 75%) [Tucker and Mather, 1979].

Data on kinetics and metabolism in the newborn are limited. The available data suggest, however, that the terminal elimination half-life in newborns is almost double that found in adults (table I).

In prematures given lignocaine subcutaneously, Mihaly et al. (1978) observed rapid absorption followed by monoexponential elimination, with a mean apparent half-life of 3.2 hours. Similar values (2.9 to 3.2 hours) were observed in a larger group of newborns who had received the drug transplacentally (Brown et al., 1975).

The apparent volume of distribution in the newborn (2.75 L/kg) is more than double that found in adults (1.11 L/kg) and because of the expanded volume, total plasma clearance does not differ significantly from adult values (Mihaly et al., 1978). When the data are normalised for body weight, neonates apparently clear lignocaine as effectively as adults. However, despite this, because of the larger distribution volume to be cleared, the newborn infant needs about twice the time of the adult to eliminate the drug. In terms of the separate contribution of renal and hepatic clearance, it appears that the mean renal clearance is increased in newborns (range 0.010 to 0.165 L/h/kg) as compared with adults (range 0.006 to 0.014 L/h/kg). This is probably due to the fact that the lower glomerular filtration rate is offset by

Table I. Pharmacokinetic profiles of local anaesthetics in newborns and adults

Drug	Age group	UV/MV ratio	Bound fraction (%)	App Vd (L/kg)	App $t_{1/2}$ (h)	Total clearance (L/h/kg)	References
Bupivacaine	Newborns	0.1-0.4	50-70	?	6.0-22.0	?	2,3,4,8,10
	Adults		85-95	0.8-1.6	1.2-4.6 ~ 9.0[a]	0.30-0.50	
Lignocaine (lidocaine)	Newborns	0.5-0.7	~ 25	1.4-4.9	2.9-3.3	0.30-1.14	1,6,7,8,9,10
	Adults		55-65	0.2-1.0	1.0-2.2	0.30-1.09	
Mepivacaine	Newborns	0.5-0.7	?	1.2-2.8	5.3-11.3	0.10-0.18	7,8,10
	Adults		75-80	0.6-1.5	1.7-6.9	0.17-1.10	
Etidocaine	Newborns	0.2-0.5	?	?	4.0-8.2	?	5,8,10
	Adults		90-95	1.5-1.8	x 2.0-3.0 ~ 5.6[a]	0.75-1.15	

References

1) Brown et al. (1975); 2) Magno et al. (1976a); 3) Thomas et al. (1976); 4) Caldwell et al. (1977a); 5) Morgan et al. (1978); 6) Mihaly et al. (1978); 7) Moore et al. (1978); 8) Tucker and Mather (1975, 1979); 9) Benowitz and Meister (1978); 10) Mather and Cousins (1979).

a Pregnant women.

the decrease in tubular reabsorption due to a reduced ability of the neonate to concentrate urine, and by the lower pH of the urine which may further reduce tubular resorption. Even if, according to Mihaly et al. (1978), the hepatic clearance of lignocaine in neonates (0.528 L/h/kg) does not appear to differ from that found in adults (0.539 L/h/kg), from the metabolic urinary excretion profiles it appears however, that some of the metabolic pathways are less developed in premature and full term newborns than in adults.

The major metabolic pathways for lignocaine elimination in adults are N-dealkylation, amide bond cleavage, aromatic hydroxylation and conjugation (Tucker and Mather, 1979).

Premature newborns given subcutaneous lignocaine were found to excrete about 20% of the dose unchanged in the urine, while urinary metabolites (which account for more than 70% of the dose in adults) accounted for less than 30% of the dose (Mihaly et al., 1978). Furthermore, premature newborns may excrete a greater amount of the N-dealkylated metabolite (MEGX) than adults, possibly as the result of reduced subsequent metabolism; the ability to cleave the amide bond to form xylidine appears to be about the same in both adults and newborns, while a reduced capacity for hydroxylation is evident in the neonate, as 4-hydroxyxylidine, which constitutes the major urinary product in adults (63.8%), is only a minor product (8.9%) in newborns. Similar data have been reported for full term newborns who received the drug transplacentally (Blankenbaker et al., 1975; Brown et al., 1975; Kuhnert et al., 1979a).

2.1.3 Mepivacaine

Given for epidural analgesia during childbirth, mepivacaine crosses the placenta readily (Dodson, 1976; Meffin et al., 1973; Tucker and Mather, 1979) and at birth UV/MV ratios may range from 0.5 to 0.7 (Brown et al., 1975; Tucker and Mather, 1979).

Knowledge about the metabolism and kinetics of mepivacaine in newborns derives mainly from a study on premature newborns treated subcutaneously to facilitate arterial catheterisation (Moore et al.,

1978). Comparison with data from adults shows a 2- to 3-fold prolongation of the terminal elimination half-life, together with an almost 2-fold increase in the (weight corrected) volume of distribution. Furthermore, unlike lignocaine, mean plasma clearance (based on body weight) is also considerably reduced in the neonate.

Estimates of the terminal elimination half-life in newborns after epidural administration to the mother (Brown et al., 1975) agree closely with those derived from direct injection.

When clearances are divided into renal and hepatic components, the renal plasma clearance appears to be significantly elevated in newborns (range 0.59 to 0.96ml/min/kg) as compared with adults (range 0.16-0.26ml/min/kg), while hepatic blood clearance is greatly reduced (newborns: range 0.90-2.10ml/min/kg; adults: range 2.70 to 8.38ml/min/kg) [Moore et al., 1978]. Impairment of hepatic clearance of mepivacaine and not of lignocaine may be explained by a greater dependence on hepatic perfusion of the latter drug (high hepatic extraction ratio in adults of 0.6), while mepivacaine is more likely to be more affected by the function of immature liver enzyme systems (low hepatic extraction ratio in adults of 0.3).

2.1.4 Etidocaine

Etidocaine is one of the more recently available compounds of the series, and the one with the highest reported hepatic extraction ratio in adults (E = 0.81) [Tucker and Mather, 1975].

Given to pregnant women through the epidural route, etidocaine reaches peak concentrations after 5 to 30min and is cleared with a terminal plasma half-life of 5 to 6 hours, which is double the values observed in healthy volunteers after intravenous administration (Morgan et al., 1977; Tucker and Mather, 1975).

Etidocaine crosses the placenta readily, and the UV/MV ratio ranges from 0.2 to 0.5 (Morgan et al., 1977; Tucker and Mather, 1979). The extent of protein binding in the neonate is not known, but it is likely to be reduced, as the mean blood-plasma ratio in umbilical venous cord blood is significantly higher than in adults (Morgan et al., 1978a).

The half-life of etidocaine in newborns as estimated from urinary excretion data is rather long, suggesting a low metabolic clearance, as has been described for other compounds of the series (Morgan et al., 1978a).

Metabolic data after direct administration to the newborn are lacking. Studies on the urinary metabolites in newborns who received the drug transplacentally indicate a relative recovery of etidocaine and its N-dealkylated metabolite in neonatal urine smaller than that observed with mepivacaine (Moore et al., 1978; Morgan et al., 1978). This could suggest either a reduced placental passage of etidocaine, as indicated by the relatively low UV/MV ratio, or a more active metabolic degradation.

2.2 Narcotic Analgesics (pethidine/meperidine)

Pethidine is largely used in obstetrics during labour both because of its analgesic action and of its presumed favourable effect on cervical dilatation.

Although the drug has been used for many years, most of the information on the kinetics of its placental transfer and its disposition in the newborn have become available only recently. The data are of importance to the clinical use of the drug, since it is now evident that the total administered dose and the dose-delivery interval have a critical influence on the total amount transferred to the fetus, and hence on the possibility of more or less severe respiratory depression.

Administered either intravenously or intramuscularly, pethidine readily crosses the placenta and an equilibrium between maternal and umbilical cord concentrations is reached within 2 to 3 hours. At longer dose-delivery intervals, pethidine concentrations in the cord are usually higher than maternal ones. Similar data have been reported for amniotic fluid where an equilibrium may be reached within 120 to 160 minutes. Concentrations of norpethidine, the major active (and toxic) metabolite of pethidine

Table II. Digoxin pharmacokinetic profile in prematures, full term newborns, infants and adults

Age group	Absorption T_{max} (min)	F (%)	Bound fraction (%)	$t_{1/2_\alpha}$ (h)	App Vd (L/kg)	App $t_{1/2}$ (h)	Total clearance (ml/min/ 1.73m²)	Renal clearance (ml/min/ 1.73m²)	References
Preterm and low birthweight infants	60-180 (oral)	?	?	?	4.9-10.0	36-180	6.5-30.0		2,7,9,10,12
Full term newborns	60-120 (oral) 360-480 (im)	≃ 80 (20-30)[a]	14-26	0.3-1.0	6.0-10.2	20-76	18.0-68.0	32-56	1,2,3,4,5, 6,7,10,11
Infants (2-18 mths)	30-90 (oral) 240-360 (im)	80-100	?	0.5-1.5	10-22	12-42	65-247	68-150	1,2,3,4,5, 6,8,10
Adults	60-120 (oral)	70-100	23-40	0.5-1.5	51-73 (2.6-4.3)[b]	15-70 (60-180)[b]	82-223	130-150	3,4,6

References

1) Iisalo and Dahl (1974); 2) Morselli et al. (1975); 3) Jaffe et al. (1976); 4) Morselli and Bianchetti (1977); 5) Wettrell (1977); 6) Wettrell and Andersson (1977); 7) Lang and von Bernuth (1977); 8) Neutze et al. (1977); 9) Berman et al (1978); 10) Halkin et al. (1978b); 11) Chan et al. (1978); 12) Pinsky et al. (1979).

a = In severe cardiac insufficiency. Malabsorption syndromes.

b = Impaired kidney function.

(Weiner and Stambaugh, 1978), are usually very low for dose-delivery intervals of 1 to 2 hours but tend to increase steadily at longer times (Caldwell et al., 1977, 1978b; Crawford and Rudofsky, 1965; Freeman et al., 1977; Hogg et al., 1977; Kuhnert et al., 1979b; Morselli and Rovei, 1980; Szeto et al., 1978; Talafre et al., 1980).

No data is available on pethidine and norpethidine plasma protein binding in the neonate. It should be noted that in adults it has been shown that the binding may be concentration-dependent (Mather and Meffin, 1978). Such a possibility may exist in the newborn too; favoured by both the lower plasma protein content and the lower blood pH.

In the newborn, pethidine is disposed of at a rate which is significantly reduced with respect to adults. Reported values for apparent plasma half-lives range in fact from 6 to 39 hours (Caldwell et al., 1977, 1978b; Morselli and Rovei, 1980; Talafre et al., 1980). These data are in good agreement with previous estimates, based on urinary excretion, suggesting half-lives of 10 to 45 hours (Cooper et al., 1977; Hogg et al., 1977). In those cases where pethidine plasma concentrations are over 80 to 100ng/ml, the decay of pethidine is paralleled by a concomitant increase in norpethidine plasma concentrations which may reach a peak at 12 to 48 hours after birth (Morselli and Rovei, 1980; Talafre et al., 1980). The plasma disappearance rate of norpethidine is apparently slower than that of the parent compound and follows first-order kinetics. Observed values range from 15 to 36 hours (Morselli and Rovei, 1980; Talafre et al., 1980). These data indicate that the newborn metabolises, even if at a low rate, pethidine to norpethidine.

The above-mentioned data are in good agreement with previous observations on urinary excretion of pethidine and norpethidine in the neonate. Most of the excreted material during the first 24 hours is in fact mainly represented by pethidine with a ratio of norpethidine to pethidine, of about 0.2 to 0.3. On the contrary, after 30 to 35 hours, norpethidine increases remarkably in urine with a norpethidine to pethidine ratio > 1-1.5 (Cooper et al., 1977; Hogg et al., 1977; Kuhnert et al., 1979c). Acid derivatives are present in minor amounts (Caldwell et al., 1978a). The high concentration of norpethidine observed at 12 to 48 hours after birth may be partially responsible for some of the adverse effects of pethidine, as hypothesised by Morrison et al. (1977). A relationship between total amount of pethidine + norpethidine present at birth and neonatal depression has been recently described (Morselli and Rovei, 1980; Talafre et al., 1980).

2.3 Drugs Administered in Cardiorespiratory Disorders

Congenital cardiac defects with congestive heart failure, patent ductus arteriosus, respiratory distress syndromes and apnoeic spells are rather common conditions in perinatal medicine. In this section, we will describe the kinetic profile in premature and full term newborns as well as in older infants, of drugs usually prescribed in the above pathological situations and in asthmatic episodes in infancy.

2.3.1 Digoxin

Digoxin is the most commonly used drug in the treatment of congestive heart failure and arrhythmias of supraventricular origin in newborns and infants. Despite its wide and long history of use, the pharmacokinetic profile of digoxin in paediatric patients has been defined only in the last 5 to 6 years and rational therapeutic schedules in perinatal medicine have begun to be applied only in the last 2 to 3 years.

The pharmacokinetics of digoxin in the neonate and in the infant are well characterised by a linear two compartment open model (Morselli et al., 1975; Wettrell, 1977) and are summarised in comparison with adults in table II.

Administered orally, in liquid form, digoxin is rapidly and efficiently (80 to 90%) absorbed, either in full term newborns or infants, with peak plasma concentrations attained within 30 to 120 minutes. The absorption rate may be slower in preterm and low birth weight infants (peak at 90 to 180 minutes) and it may be significantly reduced, together with a lower

bioavailability (20 to 30%), in cases of severe heart failure and in malabsorption syndromes (Morselli and Bianchetti, 1977; Morselli et al., 1975; Wettrell, 1977; Wettrell and Andersson, 1977). When given intramuscularly, absorption is erratic and very slow (Morselli et al., 1975; Szefler et al., 1977). Because of the reduced bioavailability and of the possible occurrence of tissue necrosis at the injection site, the use of this parenteral route should be avoided in newborns and infants (Morselli and Bianchetti, 1977). After intravenous administration, there is a rapid distribution phase with an apparent half-life of 20 to 40 minutes (Morselli et al., 1975; Wettrell, 1977), followed by a slower exponential decay of plasma concentrations (table II).

In the full term neonate (of 3 to 10 days of extrauterine life), the drug has an apparent volume of distribution of 6 to 10 L/kg. Smaller volumes have been observed in prematures, while in infants the apparent distribution volume may range from 10 to 22 L/kg (Lang and von Bernuth, 1977; Morselli and Bianchetti, 1977; Morselli et al., 1975; Pinsky et al., 1979; Wettrell, 1977; Wettrell and Andersson, 1977). The large apparent volume of distribution (1.5 to 2 times the adult values) is in agreement with slightly lower plasma protein binding, a higher extracellular fluid volume, and an increased tissue uptake and tissue binding, as reported by several authors (Andersson et al., 1975; Gorodischer et al., 1974, 1976; Kim et al., 1975).

The apparent plasma half-life in the healthy and sick newborn is in general very long. Reported half-lives of the drug, either acquired transplacentally (healthy newborns) or received for the treatment of congestive heart failure or patent ductus, range from 20 to 70 hours for full term neonates and from 40 to 180 hours in preterm newborns.

During the first 20 days of life, body clearance values may vary from 6.5 to 68ml/min/1.73 m^2 and are closely related to the maturational stage of renal function (Halkin et al., 1978a, 1978b; Iisalo and Dahl, 1974; Lang and von Bernuth, 1977; Morselli et al., 1975; Pinsky et al., 1979; Wettrell, 1977; Wettrell and Andersson, 1977).

In infants, digoxin is disposed of at a considerably faster rate than in newborns. In parallel with the maturation of kidney function, a marked increase in clearance rate is usually observed between the second and third month of life. Reported half-life values range from 12 to 42 hours with total body clearance values which are between 100 and 250ml/min/1.73 m^2 and are on average higher than those observed in adults (Halkin et al., 1978b; Morselli et al., 1975; Wettrell, 1977; Wettrell and Andersson, 1977). More recent data, showing that digoxin renal clearance exceeds creatinine clearance (values being greater in infants than in other age groups), could suggest on the one hand, that both glomerular and tubular function are involved and on the other hand, give a partial explanation of the increased total body clearance in young infants (Halkin et al., 1978b; Yaffe et al., 1976). An increase in glomerular filtration and tubular secretion not accompanied by a similar increase in tubular reabsorption could in fact lead to higher clearance in the first 4 to 6 months of life (Krasula et al., 1972; Morselli and Bianchetti, 1977). Additional possible causes for such an increased clearance and the apparent requirement of higher doses in young infants have been discussed previously (Krasula et al., 1972; Morselli et al., 1975). Up to now, however, no one of the hypotheses proposed has been firmly proven.

The large apparent volume of distribution, the higher clearance values as well as the greater concentrations of digoxin found in myocardial tissue and red cells of infants, could apparently justify the traditional assumption that infants tolerate digoxin better than adults and that higher doses are needed because of this.

Recent data, however, seem to contradict such assumptions. Careful monitoring studies have shown that, in infants too, toxic signs become evident at plasma concentrations > 3ng/ml and that appropriate pharmacodynamic responses may be attained with digoxin concentrations of 1.5 to 2ng/ml (Berman et al., 1978; Halkin et al., 1978a; Levy et al., 1972; Nyberg and Wettrell, 1978; Pinsky et al., 1979). Furthermore, if the higher concentrations found in

Table III. Recommended doses for digoxin (mg/kg/day)

Age group	Loading dose	Maintenance dose
Premature newborns	0.020	0.006-0.010
Full term neonates	0.029	0.010
Infants	0.034	0.015-0.020

According to: Nyberg and Wettrell (1978); Pinsky et al. (1979).

the myocardial tissue have been explained finalistically with a higher Na^+-K^+-ATPase activity, a higher amount of drug in the myocardium biophase does not necessarily mean higher concentrations at receptor sites. The observed higher tissue concentrations could in addition be the result of nonlinear kinetics present at higher dosages.

On the basis of the current knowledge, most authors agree that the doses of digoxin used in the past have been too high in most instances and that lower doses should be used, especially in premature and full term newborns. The currently recommended loading and maintenance doses are reported in table III. In cases of very severe heart failure, because of the haemodynamic consequences on kidney function, digoxin daily dosages should be further reduced.

2.3.2 *Theophylline*

Theophylline is largely used for the treatment of apnoeic-bradycardiac spells in the premature infant and for the treatment of asthma in older ages (Ogilvie, 1978). The characterisation of its pharmacokinetics in various age groups (table IV) has permitted, during the last 4 to 5 years, the development of rational therapeutic schedules as well as the identification of therapeutic and toxic plasma concentration ranges, both in apnoeas and in asthmatic episodes. More recent data indicate that theophylline may undergo saturation elimination kinetics, that it distributes to erythrocytes, saliva and breast milk and that it can cross the placenta with the possibility of high fetal concentrations (Hendeles et al., 1978; Lesko, 1979; Loughnan et al., 1976; Miceli et al., 1980; Ogilvie, 1978; Weinberger and Ginchansky, 1977).

Premature Infants

In the premature newborn, theophylline, administered either orally in liquid form or as a rectal solution, is rapidly and efficiently absorbed with peak plasma concentrations attained within 30 to 60 minutes (Brazier et al., 1978, 1979; Neese and Soika, 1977).

In the premature, theophylline is bound 32 to 48% to plasma proteins (Aranda et al., 1976; Demarquez et al., 1978) and distributes rapidly to tissues. At variance with adult data, in the newborn the whole blood/plasma ratio is close to unity (Koup and Hart, 1979). The apparent volume of distribution on average tends to be higher in premature than in grown up children and adults, although reported values are very variable and range from 0.18 to 1.13 L/kg. The increased apparent volume of distribution can be explained by the lower plasma protein binding, the relative acidaemia of the apnoeic premature (theophylline is a weak acid with a pKa of 8.8) and the higher ratio of extracellular water to body fat.

The apparent plasma half-life in the premature newborn is markedly longer than those observed in infants and children and it may range from 12 to 64 hours with clearance values of 9 to 50ml/h/kg (Aranda et al., 1976; Bory et al., 1979; Boutroy et al., 1979; Brazier et al., 1978, 1979; Demarquez et al., 1978; Hilligoss et al., 1980; Latini et al., 1978; Neese and Soika, 1977; Wells and Ferlauto, 1979) [table IV].

The high interindividual variability encountered in the various reports for distribution volume, clearance and half-life values is probably associated with the heterogenicity of the populations studied, the variable degree of the illness, different associated pathologies, different haemodynamic conditions and variable gestational ages (27 to 34w). As a matter of fact, the clearance of theophylline increases constantly with age during the first year of life (Hilligoss et al., 1980;

Rosen et al., 1979) and in young premature infants (1 to 2 months of extrauterine life), plasma half-lives of 12 to 29 hours with clearance values of 23 to 68ml/h/kg have been described by Giacoia et al. (1976).

In the older infant, treated for asthma, both oral and rectal absorption of liquid forms are very rapid and complete. The distribution phase is also very rapid and an apparent distribution volume of 0.16 to 0.83 L/kg has been reported. The apparent plasma half-life is 2 to 5 times faster and the computed values range from 1.8 to 8.6 hours with clearances of 28 to 161ml/h/kg (Bolme et al., 1979; Rosen et al., 1979; Simons and Simons, 1978).

In both newborns and infants, as well as in children, saturation elimination kinetics may occur at plasma concentrations > 20μg/ml. It should be remembered that the concomitant use of macrolide antibiotics, which are frequently prescribed in asthmatics, may significantly impair the rate of elimination of theophylline, while phenobarbitone also frequently administered to prematures, may accelerate the metabolic degradation of the drug (Hendeles et al., 1978; Ogilvie, 1978; Wells and Ferlauto, 1979). On the other hand, it should be remembered that theophylline does induce a rapid, pronounced and prolonged rise in free fatty acid levels which may have some displacing effect on concomitantly administered highly bound acidic drugs (Cathcart-Rake et al., 1979).

Various authors agree on the fact that in the case of apnoeas in premature infants, a significant reduction of their frequency or their complete resolution may be observed at plasma concentrations lower than those useful for the treatment of asthmatic episodes in older infants. Thus, plasma concentrations of 2 to 10 μg/ml have in fact been shown to be efficacious for apnoeas of prematurity (Boutroy et al., 1979; Davi et al., 1978; Demarquez et al., 1978; Dietrich et al., 1978; Gerhardt et al., 1978).

Furthermore, most of the possible side effects such as tachycardia, gastrointestinal disturbances (vomiting, regurgitation) are related to excessive plasma concentrations. A significant increase in heart rate may be observed at concentrations of 15μg/ml, while concentrations > 30μg/ml may be associated with convulsions (Demarquez et al., 1978; Dietrich et al., 1978; Hendeles et al., 1978; Wells and Ferlauto, 1979).

The recommended loading doses for premature infants according to various authors are 5mg/kg intravenously or 6mg/kg orally with a maintenance dose of 1.1mg/kg every 8 hours or 2mg/kg every 12 hours, accompanied by individualised dose adjustment based on monitoring of drug plasma concentrations within 48 to 72 hours.

In asthmatic infants, therapeutic plasma concentrations appear to range from 6 to 20μg/ml, while toxic effects are frequently observed at concentrations > 20μg/ml (Bolme et al., 1979; Hendeles et al., 1978; Rosen et al., 1979; Simons and Simons, 1978). The doses actually recommended for asthmatic infants are 6 to 8mg/kg as loading doses with maintenance doses of 0.2 to 0.8mg/kg/h for the first 24 to 48 hours, followed by careful plasma concentration monitoring (Bolme et al., 1979; Simons and Simons, 1978; Weinberger and Hendeles, 1980).

In the premature infant, evidence suggests the coexistence of N-methylase metabolic activity with deficiency in N-demethylation. Several authors have in fact recently shown, that theophylline in premature newborns, at variance with what is seen in infants and adults, may be metabolised to caffeine (Aranda et al., 1976; Bada et al., 1979; Bory et al., 1979; Boutroy et al., 1979; Brazier et al., 1978). Plasma concentrations of caffeine attained during repeated theophylline treatment may range from 25 to 50% of the parent compound and tend to increase with treatment time (Boutroy et al., 1979; Brazier et al., 1978, 1979).

This observation has important therapeutic implications since caffeine is also effective in recurrent apnoeic spells at concentrations of 4 to 10μg/ml (Aranda et al., 1977, 1979; Bory et al., 1979).

In the preterm neonate, caffeine, which is less protein bound than theophylline, appears to have a distribution volume of 0.47 to 1.28 L/kg and, more important, an apparent plasma half-life of 43 to 231

Table IV. Theophylline pharmacokinetics in prematures, full term newborns, infants, children and adults

Age group	Absorption T_{max} (min)	$t_{1/2\alpha}$ (min)	Bound fraction (%)	Vd (L/kg)	App $t_{1/2}$ (h)	Total body clearance (ml/h/kg)	Metabolites	References
Premature newborns (5-26 days)	30-60 (oral) 60-120 (rectal solution)		32-48	0.18-1.13	12-64	9-50	Caffeine	1,4,6,7,8, 11,14,15
Full term newborns	?		?	?	?	?	?	
Premature infants (25-57 days)	?		?	0.70-2.82	12-29	23-68		2
Infants	30-60 (oral) 30-45 (enema)	3-20	?	0.16-0.83	0.8-8.6	28-161	?	9,10,12
Children	30-120 (oral) (F ≃ 100%)	5-15	?	0.20-0.68	1.9-8.5	60-221	?	3,5,10,13,16
Adults	60-120 (oral) (F ≃ 100%)	30-40	53-65	0.44-0.50	2.9-8.3	35-131	Theoph = 14% 3 MX = 13% 1 MU = 17% 1,3 DMU = 50% 1 MX = 5%	5

References

1) Aranda et al. (1976); 2) Giacoia et al. (1976); 3) Loughnan et al. (1976); 4) Neese and Soyka (1977); 5) Ogilvie (1978); 6) Latini et al. (1978); 7) Demarquez et al. (1978); 8) Brazier et al. (1978, 1979); 9) Simons and Simons (1978); 10) Bolme et al. (1979); 11) Boutroy et al. (1979); 12) Rosen et al. (1979); 13) Selvig et al. (1979); 14) Bory et al. (1979); 15) Hilligos et al. (1980); 16) Miceli et al. (1980).

Abbreviations

3 MX = 3 methylxanthine
1 MU = 1 methyluric acid
1,3 DMU = 1,3 dimethyluric acid
1 MX = 1 methylxanthine

hours with clearance values of 2.5 to 16.8ml/h/kg (Aranda et al., 1979). Such a low elimination rate would lead to accumulation in the course of theophylline therapy. Adult rates for caffeine clearances (100ml/h/kg) are usually reached at 4 to 5 months of age (Aranda et al., 1979). According to Aranda, caffeine could usefully be substituted for theophylline. Recommended schedules are 10mg/kg as a loading dose followed after 24 hours by maintenance doses of 2.5mg/kg/day. The concomitant presence of caffeine in the plasma of theophylline-treated apnoeic premature newborns could lead to a synergistic or potentiating effect, and could explain the apparent lower therapeutic thresholds as well as the apparent lower threshold for toxic effects observed with theophylline in the premature infant with apnoeic spells.

2.3.3 Indomethacin

Indomethacin, a potent inhibitor of the synthesis of prostaglandins of type E, is currently used in the premature infant for the treatment of patent ductus arteriosus with congestive heart failure, as a useful alternative to surgical ligation (Friedman et al., 1976, 1978; Halliday et al., 1979; Heymann et al., 1976; Marchal et al., 1980).

As in adults, the pharmacokinetic profile of indomethacin may be adequately described in the premature infant by a two compartment open model (Bianchetti et al., 1980). Following oral and rectal administration of 0.2 to 0.3mg/kg, peak plasma concentrations of 0.4 to 1.5µg/ml are attained within 1 to 3 hours and are followed by a distribution phase of variable duration ($t_{1/2\alpha}$ = 60-150 minutes) and by a slower exponential elimination phase (Bianchetti et al., 1980). In the case of intravenous administration, the α phase is faster ($t_{1/2}$ = 20-50 minutes) [Marchal et al., 1980].

The drug is highly bound (95 to 98%) to plasma proteins; however, at the concentrations usually attained with doses of 0.2 to 0.3mg/kg by the oral route (0.4-1.5µg/ml) or of 0.2mg/kg intravenously (1.5-3.0µg/ml), no displacement of bilirubin seems to occur (Evans et al., 1979; Rasmussen et al., 1978).

The apparent volume of distribution computed after intravenous administration tends to be smaller (0.23 to 0.53L/kg) than after the oral route (0.53 to 1.50L/kg), suggesting that, at variance with adults, the oral absorption of indomethacin in the premature newborn is far from complete (Bianchetti et al., 1980; Kwan et al., 1976; Marchal et al., 1980; Vert et al., 1980b). Apparent terminal elimination phase half-lives may range from 15 to 90 hours, with clearance values of 0.076 to 0.385ml/min/kg (Bianchetti et al., 1980; Evans et al., 1979; Friedman et al., 1978). In full term newborns, a mean half-life of 14 hours has been reported by Traeger et al. (1973).

The large interindividual variability in elimination rate is probably due to variable gestational ages, different haemodynamic situations and to previous or associated treatment. The exposure to high or low doses of phenobarbitone may have an important effect on the clearance rate of indomethacin in the premature; faster clearances being associated with higher phenobarbitone exposure (Vert et al., 1980b).

In general, indomethacin is cleared in the premature newborn at a rate 10 to 20 times slower than in adults, where half-lives of 4 to 10 hours and clearances of 1.5-2.2ml/min/kg are usually observed (Kwan et al., 1976).

In adults indomethacin is metabolised by demethylation and deoxylation and also by direct conjugation with glucuronic acid. The molecule is excreted in urine as such and conjugated for about 35 to 50% of the dose. The reduced clearance of indomethacin in the newborn is probably due to the concurrence of a reduced metabolic activity and a reduced renal clearance.

Preliminary observations suggest that the effect of the drug on patent ductus arteriosus closure could depend on both gestational age and indomethacin plasma concentrations (Bianchetti et al., 1980) and that at plasma concentrations up to 1.25µg/ml no serious renal and gastrointestinal toxicity are encountered (Vert et al., 1980b). On the basis of available information, 2 to 3 doses of 2mg/kg intravenously administered every 36 to 48 hours should permit a therapeutic effect without serious adverse reactions.

2.3.4 Frusemide (furosemide)

Frusemide is an effective and safe diuretic which is frequently used in premature and full term newborns as well as in infants in the treatment of cardiac failure, pulmonary oedema and renal failure (Engle et al., 1978; Ross et al., 1978; Woo et al., 1978). Recently, its use has been also suggested in the treatment of hyaline membrane disease with controversial results (Marks et al., 1978). Furthermore, the drug may be used during pregnancy for the treatment of oedema and hypertension.

Recent observations have documented that a substantial quantity of the drug can cross the placenta and can be present in both amniotic fluid and cord blood at concentrations comparable with those present in the mother's plasma (Beerman et al., 1978; Vert et al., 1980a). These data are in good agreement with earlier reports describing increased diuresis in newborns of frusemide-treated mothers.

In the newborn, frusemide kinetics may be adequately described by a two compartment open model with a relatively rapid α phase followed by a slower elimination phase. Reported half-life values for the α phase range in general between 0.5 and 2 hours, but in cases of very severe cardiac failure values of 6 to 7 hours have been observed (Vert et al., 1980a). Apparent plasma half-lives of the terminal elimination phase are quite variable and appear to depend on several factors such as gestational and postnatal age, presence of associated phenobarbitone treatment and severity of the pathological condition. In the case of healthy newborns who received the drug transplacentally, plasma half-lives appear to correlate with gestational age with values of 6 to 19 hours at 41 to 42 weeks and of 28 to 48 hours for 36 to 39 weeks (Vert et al., 1980a). In premature infants treated for cardiac insufficiency, reported values may range from 4 to 44 hours (Aranda et al., 1978; Vert et al., 1980a).

No data are available on plasma protein binding of frusemide in newborns. According to Aranda et al. (1978), concentrations of 0.5 to 3μg/ml do not have any significant effect on bilirubin binding capacity in normobilirubinaemic newborns. However, a clear displacing effect has been previously reported in case of hyperbilirubinaemic serum (Shankaran and Poland, 1977) at concentrations of frusemide of 2 to 4μg/ml. According to Wennberg et al. (1977), the drug should be avoided in patients with free bilirubin concentrations over > 10nmol/L.

The apparent volume of distribution is considerably increased in most cases in newborns (0.25 to 1.13L/kg) compared with adults (0.07 to 0.18L/kg) while reported clearance values in newborns range from 2.8 to 165ml/h/kg (Aranda et al., 1978; Vert et al., 1980a) compared with 108 to 180ml/h/kg in adults.

The values reported by Aranda et al. (1978) for the elimination rate constant, apparent volume of distribution and clearances are on average considerably higher than those reported by Vert et al. (1980). One explanation could be that in the former case a one compartment open model was used for computation, while in the latter study, a two compartment open model was applied.

In the newborn, the urinary excretion of frusemide is very slow, because of the low glomerular filtration rate and immature tubular function. The slow secretion into the tubular lumen could well explain the sustained diuretic effect in the newborn.

It has been observed that perinatal asphyxia and concomitant use with indomethacin may decrease the response to frusemide in the newborn (Brater, 1979; Woo et al., 1977). In both cases, the cause is most probably a haemodynamic one, since both situations may lead to a decrease in renal blood flow. A reduced response, together with a shorter plasma half-life, has also been reported following previous or concomitant phenobarbitone treatment (Vert et al., 1980). In this case, the reduced response is due to more rapid metabolic degradation of frusemide, with reduced presentation of frusemide to the tubular lumen. The diuretic effect of frusemide may also be reduced by the presence of proteins in the tubular fluid binding frusemide, so reducing the free fraction of the drug capable of acting at the intraluminal site (Mirkin, personal communication).

On the basis of the kinetic data, doses of 1mg/kg

Table V. Pharmacokinetic profiles of anticonvulsant drugs in newborns and infants, compared with adults

Drug	Age group	Absorption T_{max} (h)	Protein binding (%)	App Vd (L/kg)	App $t_{1/2}$ (h)
Phenytoin	Newborns	Poorly absorbed (im and oral)	71-86	0.8-2.0	15-105
	Infants	2-6 (oral) Poorly absorbed (im)	82-88	0.3-1.0	2-7
Phenobarbitone	Newborns	Poorly absorbed (oral) 2-4 (im)	28-43	0.6-1.5	45-500
	Infants	2-4 (oral) 2-4 (im)	46-48	0.4-1.3	20-133
	Adults	4-12 (oral) 4-6 (im)	36-38	0.6-1.5	60-180
Primidone	Newborns				7-29
	Infants				
	Adults	3-8 (oral)	≃0.10		4-12
Ethosuximide	Newborns				
	Infants	1-2 (oral)			≃40
	Adults	1-3 (oral)	≃10	0.6	55-66
Carbamazepine	Newborns	4-6 (oral)		1.1-2.6	8 27
	Infants	4-6 (oral)	~75 (?)	1.4-1.7	2.5-15
	Adults	2-8 (oral)	~75	0.8-1.8	15-25
Valproic acid	Newborns	3-9 (oral)	~85	0.2-0.4	60-107 14-88
	Infants	1-3 (oral)			~10
	Adults	1-2 (oral)	~85	0.2-0.4	10-15
Diazepam	Newborns	1-2 (oral) 4-6 (im)	84	1.8-2.1	40-400
	Infants	< 1 (oral) 2-3 (im)	98	1.3-1.15	10-12
	Adults	0.5-2 (oral) 4-6 (im)	~98	1.6-3.2	20-30

For references, see text.

intravenously repeated every 24 to 48 hours appear to be safe in premature newborns (Aranda et al., 1978; Cutler and Blair, 1979; Vert et al., 1980a). No kinetic data are available for young infants.

2.3.5 Other Diuretics

No kinetic data exist on other diuretics in the newborn infant. Recent data on chlorthalidone (Mulley et al., 1978) show that the molecule is present in cord blood and amniotic fluid at concentrations considerably lower than in maternal blood (CB/MB $= \sim 0.15$). The low content of chlorthalidone in cord blood is probably due to the lower carbonic anhydrase level in red blood cells.

2.4 Anticonvulsant Drugs

Seizures are a frequent event both in the neonatal period and during infancy. Their incidence may vary from 0.8% in a normal nursery population to 20% in the high risk population of intensive care units (Painter et al., 1978). In infancy, convulsive episodes, which are not necessarily associated with epileptic syndromes, may also be rather frequent. Anticonvulsant drugs are hence frequently prescribed to newborns and infants. Furthermore, they can be administered, as in the case of phenobarbitone and diazepam, as sedatives and in the course of drug withdrawal syndromes. Phenobarbitone is also currently used as an enzyme inducer for the preventive treatment of neonatal hyperbilirubinaemia. Newborns born of epileptic mothers may be exposed to high amounts of transplacentally acquired anticonvulsant drugs (Bossi et al., 1980a, 1980b).

The pharmacokinetics of anticonvulsant drugs in newborns and infants has been the subject of several recent reviews (Morselli, 1977a, 1977c, 1978b; Morselli and Baruzzi, 1978; Rane and Wilson, 1976). Here we will outline the major pharmacokinetic differences between newborns and infants compared with adults (table V). For more detailed information, the reader is referred to the above-mentioned reviews.

2.4.1 Phenobarbitone

In the premature and full term newborn, the gastrointestinal absorption of phenobarbitone is slow, incomplete and unpredictable. On the contrary, the drug is readily and efficiently absorbed if administered intramuscularly (Boreus et al., 1975; Brachet-Liermain et al., 1975). After the first 3 to 4 weeks of extrauterine life, phenobarbitone is efficiently absorbed from the gastrointestinal tract, and at a rate which in most cases is faster than that observed in adults (Boreus et al., 1975; Jalling, 1976; Morselli, 1977b, 1977c). In newborns born of epileptic mothers, plasma concentrations similar to the maternal concentration have been observed at birth, while breast milk : plasma ratios may range from 0.4 to 0.6 (Boreus et al., 1978b; Bossi et al., 1980b; Kaneko et al., 1979; Vert et al., 1979).

Phenobarbitone plasma protein binding is considerably reduced in the newborn; reported values for the 'free fraction' range from 57 to 64% in normobilirubinaemic neonates, and from 70 to 72% in cases of hyperbilirubinaemia (Ehrnebo et al., 1971; Meyer et al., 1977; Morselli, 1977b, 1977c, 1978b). Direct data on plasma protein binding in infants are not available. However, CSF measurements in infants 3 to 6 months of age suggest binding values similar to those observed in adults (46 to 48%) [Brachet-Liermain et al., 1975; Jalling, 1976].

In both newborns and infants, the apparent volume of distribution of phenobarbitone is greater than in grown up children and adults (table V). Values may range from 0.65 to 1.5L/kg for newborns and from 0.48 to 1.3L/kg for infants (Boreus et al., 1975, 1978a; Heimann and Gladtke, 1977; Heinze and Kampffmeyer, 1971; Jalling, 1976; Morselli, 1977c; Painter et al., 1978; Pitlick et al., 1978). The distribution of phenobarbitone, because of its pK_a of 7.4, may be greatly affected by variations of acid-basic balance and of blood pH, which are so frequent in newborns with postanoxic seizures (Monin et al., 1980; Morselli et al., 1980).

In neonates treated postnatally, the apparent plasma half-life is extremely prolonged (100 to 500h) while it may be shorter in cases of intrauterine ex-

posure to the drug (40 to 300h), probably because of autoinduction (Albani et al., 1977; Boreus et al., 1975, 1978a, 1978b; Bossi et al., 1980b; Heimann and Gladtke, 1977; Painter et al., 1978; Pitlick et al., 1978; Wallin et al., 1974). An inverse relationship between the length of extrauterine exposure and phenobarbitone apparent plasma half-life has in fact been described (Boreus et al., 1975; Jalling et al., 1973).

During the first 15 to 30 days of life, the plasma disappearance rate of phenobarbitone increases steadily and half-life values of 30 to 100 hours can be observed at 3 to 4 weeks of age. In older infants (2 to 12 months), reported half-lives may range from 40 to 60 hours, suggesting an increased clearance of the drug with respect to adults (table V; Heimann and Gladtke, 1977; Jalling, 1976; Morselli, 1977c; Rossi et al., 1979).

The reduced clearance of phenobarbitone during the first days of life is probably due to several mechanisms such as the low glomerular filtration rate, the relatively low urinary pH, a relatively reduced hydroxylation and subsequent conjugation with glucuronic acid. After 7 to 8 days of life, the ratio between hydroxyphenobarbitone and phenobarbitone reaches values comparable with adults, while the conjugated derivative in urine is still about a third of adult values (Boreus et al., 1975, 1978a; Morselli, 1977). No data are available on the urinary excretion of phenobarbitone in infancy.

Suggested therapeutic plasma concentrations are 15 to 25μg/ml in the neonate and 10 to 20μg/ml in the infant (Lockman et al., 1979; Morselli, 1978b). The higher plasma concentrations apparently required in the neonate may be partially due to alteration in acid-base status determining a lower tissue : plasma ratio. Indeed, we have recently observed that in several cases of postanoxic convulsions, blood pH shifts over 7.35 were often associated with a concomitant rise in phenobarbitone plasma concentrations. Furthermore, a linear relationship could be observed between blood pH values, Pco_2 values and phenobarbitone plasma concentrations (Morselli et al., 1980).

Suggested loading doses for newborns are 5 to 10mg/kg intravenously or intramuscularly with maintenance doses of 5mg/kg/day. In infants, higher loading (15 to 20mg/kg) and maintenance (10mg/kg/day) doses are necessary (Lockman et al., 1979; Morselli et al., 1980; Painter et al., 1978).

2.4.2 Phenytoin

Data on gastrointestinal absorption of phenytoin in newborns and young infants are controversial. While most authors agree on very poor bioavailability of the drug during the first month of life (Jalling et al., 1970; Morselli, 1977b, 1977c; Morselli and Baruzzi, 1978; Painter et al., 1978), high plasma concentrations of phenytoin have been reported by Loughnan et al. (1977) in newborns 1 week of age following oral administration of 8mg/kg/day in suspension form. Differences in the formulations employed are probably the reason for the conflicting findings.

In older infants, the drug is efficiently absorbed with peak plasma concentrations attained within 2 to 6 hours (Morselli, 1977c). In newborns born of epileptic mothers, plasma phenytoin concentrations at birth are similar to the maternal ones, and milk : plasma ratios may range from 0.15 to 0.55 (Bossi et al., 1980b; Kaneko et al., 1979; Mirkin, 1971; Morselli, 1978b; Rane et al., 1974).

Plasma protein binding of phenytoin is reduced in normobilirubinaemic newborns (free fraction = 15 to 20%) and it may be further decreased in hyperbilirubinaemia (free fraction = 25-30%), while in infants 3 to 24 months of age, plasma protein binding is close to adult values (free fraction in infant = 10-15%; in adult = 7-11%) [Ehrnebo et al., 1971; Fredholm et al., 1975; Loughnan et al., 1977; Meyer et al., 1977; Morselli, 1977c; Rane and Wilson, 1976].

In newborns and young infants, the apparent volume of distribution of phenytoin is increased, with values ranging from 0.7 to 2.0L/kg; adult figures (table V) are usually reached at 5 to 6 months of age (Loughnan et al., 1977; Morselli, 1978b; Painter et al., 1978; Rane et al., 1974; Rane and Wilson, 1976).

In premature newborns, phenytoin is cleared very slowly and apparent plasma half-lives up to 160 hours have been reported (Loughnan et al., 1977). Corresponding values for full term newborns are between 30 and 70 hours. After 5 to 10 days of life, the plasma half-life of phenytoin is usually much shorter with values ranging between 6 and 15 hours; a further decrease of the apparent plasma half-life can be observed over the following 2 to 3 months (Loughnan et al., 1977; Morselli, 1976, 1977c; Painter et al., 1978; Rane et al., 1974). Autoinduction has been invoked to explain such a dramatic decrease in apparent plasma half-life values. However, the biphasic pattern of elimination observed in newborns born of epileptic mothers, with a first phase of 1 to 4 days apparently following zero-order kinetics, and a second more rapid phase following first-order kinetics (Bossi et al., 1980a, 1980b; Mirkin et al., 1971; Rane et al., 1974) suggests that the abrupt increase in disposition rate is linked to maturational changes of both hydroxylating activity and renal excretory mechanisms.

Unfortunately, no study is available on the urinary excretion of phenytoin metabolites after direct administration to the newborn. Available data deal with newborns who received the drug and its metabolites transplacentally and they do not permit a comparative evaluation of phenytoin metabolism in the neonate (Morselli, 1977c; Rane, 1974; Reynolds and Mirkin, 1973). Recent data of Rane et al. (1979) do confirm an impaired capacity in the newborn to conjugate parahydroxyphenytoin.

The large interindividual variability observed in the disposition rate of phenytoin, the possibility of saturation elimination kinetics and possible pathological conditions associated with seizures with consequent alteration in both haemodynamics and acid-base balance make the selection of rational dosage schedules very difficult.

According to Loughnan et al. (1977), a loading dose of 8mg/kg intravenously followed by an oral maintenance dose of 6mg/kg/day for the first week of life and 8mg/kg/day for the second week (all divided in 3 daily doses) permits therapeutic plasma concentrations (6 to 14μg/ml) to be obtained in the newborn.

For infants aged between 1 and 12 months, recommended loading doses are 20 to 30mg/kg intravenously followed by maintenance doses of 8 to 10mg/kg/day. In infants, therapeutic plasma concentrations are of the order of 10 to 20μg/ml (Albani, 1977; Loughnan et al., 1977). These suggestions should be regarded as a guide and monitoring of phenytoin plasma concentrations is absolutely necessary to permit correct individual dosage adjustment, particularly because of the possibility of Michaelis-Menten elimination kinetics.

2.4.3 Carbamazepine

As in adults, gastrointestinal absorption of carbamazepine in neonates and infants is slow and erratic, peak concentrations being achieved within 4 and 10 hours in most cases (Morselli, 1977c; Pynnonen et al., 1977a; Rey et al., 1979).

Once in the circulatory system, the drug distributes rapidly to various organs and body tissues with an apparent volume of distribution of 1.1 to 2.6L/kg (Pynnonen et al., 1977a; Rey et al., 1979).

No data are available on plasma protein binding in newborns. A CSF : plasma ratio of 0.24 observed in a 2.5 months old infant (Pynnonen et al., 1977a) suggests that in infants, the binding is similar to that described in adults (Morselli, 1977c). In newborns born of chronically treated mothers, plasma concentrations at birth are similar to those found in maternal plasma (Bossi et al., 1980b; Rane et al., 1975). Milk : plasma ratios range from 0.4 to 0.6 (Kaneko et al., 1979; Niebyl et al., 1979; Pynnonen et al., 1977a).

The available data on plasma half-lives of carbamazepine in both newborns and infants are very variable. The wide interindividual variability may be due to the fact that on one hand carbamazepine is a very strong 'autoinducer', and on the other, to the fact that in most cases there was either a previous exposure or an associated treatment with other drugs capable of both induction or inhibition of metabolism. The active metabolite, carbamazepine epoxide was

usually found to be present at concentrations comparable with those reported for adults.

According to the various authors, carbamazepine apparent plasma half-life values range from 8 to 28 hours in neonates, and from 2.5 to 36 hours in infants (Bossi et al., 1980b; Pynnonen et al., 1977; Rane et al., 1974; Rey et al., 1979). In a recent large study on infants and children, Battino et al. (1980) showed that the plasma concentration : dose ratios for carbamazepine, in infants of 11 to 24 months, were significantly lower than in older age groups. These data support, and are in good agreement with that seen for other drugs, an increased clearance rate in infancy (Morselli, 1976b, 1977c).

2.4.4 Sodium Valproate

The gastrointestinal absorption of sodium valproate in the premature and full term newborn is relatively slow, peak plasma concentrations being attained at 3 to 8 hours. In infants, the absorption rate is much faster (peak at 1 to 3 hours) and comparable with that in adults (Brachet-Liermain and Demarquez, 1977).

Recent data of Plasse et el. (1979), indicate plasma protein binding of 84 to 90% in the newborn, while previous data estimated from CSF : plasma ratios suggested slightly higher values (Brachet-Liermain and Demarquez, 1977). The apparent volume of distribution is 0.2 to 0.4L/kg. As with the other drugs, valproic acid is cleared at a slower rate in the newborn. Plasma half-life values may range from 10 to 67 hours for the first 10 days of extrauterine life, from 9 to 22 hours for infants aged 0.5 to 2 months and from 7 to 13 hours for infants older than 2 months (Brachet-Liermain and Demarquez, 1977; Dickinson et al., 1979).

In the newborn, the urinary excretion of valproic acid as such is comparable with that observed in adults (5%). No other data are available on metabolic degradation of the molecule in paediatric patients.

Recommended dosage schedules are: 20-30mg/kg/day for premature newborns, 40mg/kg/day for full term newborns and 50 to 60mg/kg/day for older infants (Brachet-Liermain and Demarquez, 1977).

2.4.5 Primidone and Ethosuximide

The only available data in newborns on these 2 compounds derives from studies on neonates born of epileptic mothers who received the drug transplacentally. For both drugs, plasma concentrations in newborns at birth are similar to the maternal ones, and milk : plasma ratios range from 0.8 to 1.0 (Bossi et al., 1980a; Kaneko et al., 1979; Koup et al., 1978; Morselli, 1978b). Primidone apparent plasma half-life in newborns may range from 7 to 29 hours (Bossi et al., 1980a, 1980b), while in the only case available for ethosuximide the disappearance rate was similar to that observed in adults (Koup et al., 1978).

2.4.6 Diazepam and Related Compounds

Diazepam is often used in newborns and infants, either as an anticonvulsant or a sedative drug. Furthermore, it may be used during pregnancy and labour. Its clinical pharmacokinetics have been recently reviewed (Mandelli et al., 1978; Morselli, 1977c, 1978b) and we will report here the most relevant age-related kinetic differences.

In the premature and full term newborn, given either orally or as rectal suspension, diazepam is very efficiently and rapidly absorbed with peak plasma concentrations attained between 10 and 60 minutes (Agurell et al., 1975; Knudsen, 1977; Morselli, 1977c). On the contrary, following intramuscular administration, peak plasma concentrations are attained between 1 and 4 hours (Morselli, 1977c; Morselli et al., 1973). It should also be remembered that in the case of extemporaneous dilution with saline or glucosate solutions, there is the possibility of *'in loco'* precipitation with slower and incomplete absorption. The use of suppositories is not advisable because of incomplete, slow and erratic absorption.

In infants, diazepam is efficiently absorbed after either oral or intramuscular administration with peak concentrations at 15 to 30 minutes and 30 to 40 minutes respectively (Agurell et al., 1975).

Diazepam and its metabolites readily cross the placenta and plasma concentrations of diazepam, desmethyldiazepam, methyloxazepam and oxazepam at birth are similar to those found in maternal plasma

(Mandelli et al., 1975; Tomson et al., 1979). Concentrations of diazepam in human breast milk are about 1/10 of those in mother's plasma (Mandelli et al., 1978; Morselli, 1978b).

The plasma protein binding of diazepam is considerably reduced at birth (~ 86%), although no difference in binding properties in terms of affinity constant and binding sites could be demonstrated between cord and adult serum (Krasner et al., 1973; Morselli, 1977c, 1978b).

The apparent volume of distribution in newborns and infants is slightly reduced (1.3 to 2.6L/kg) with respect to values observed in adults (1.6 to 3.2L/kg), in good agreement with the physicochemical properties of the drug, the scarce adipose tissue and the high extracellular water value (Morselli, 1977c).

In the newborn, not exposed to inducing agents, the plasma disappearance rate of diazepam is reduced and apparently related to the degree of maturation of metabolic activity. Apparent plasma half-lives of 40 to 400 hours have in fact been observed in premature newborns, while in full term neonates half-life values may range from 20 to 50 hours. In infants, the disposition rate of diazepam is markedly increased, with plasma half-lives of 8 to 14 hours (Mandelli et al., 1975; Morselli, 1977c; Morselli et al., 1973, 1975). Apparent plasma half-lives of transplacentally acquired oxazepam are in the newborn 2- to 4-fold longer (12 to 27 hours) than in the mothers (5 to 8 hours) [Tomson et al., 1979]. No information is available on the disposition rate of desmethyldiazepam in either newborns or infants.

The slower clearance of diazepam in the premature and full term newborn is apparently due to reduced metabolic degradation. Hydroxylation and subsequent conjugation seem to be the metabolic processes mostly impaired in the first days of life, while demethylating activities, even if reduced with respect to children, are less impaired (Mandelli et al., 1978; Morselli, 1977c).

These data are in good agreement with that observed for other compounds such as phenobarbitone, phenytoin, mepivacaine and pethidine (meperidine). A faster elimination rate associated with an increased formation and urinary output of hydroxylated and conjugated derivatives may be observed in premature and full term newborns exposed to inducing agents, either *'in utero'* or during the first days of life (Mandelli et al., 1975; Morselli et al., 1975).

Recommended intravenous or rectal doses in newborns are of the order of 0.2 to 0.3mg/kg, while doses of 0.5 to 0.6mg/kg should be administered to infants.

No information is at present available on *clonazepam* pharmacokinetics in newborns and infants despite considerable use of this drug in paediatric patients.

2.5 Antibiotics

Antibiotics are frequently prescribed in paediatrics for a variety of infective conditions. Their indications and their use in newborns, infants and children have been recently reviewed in extensive monographs (Eichenwald and McCracken, 1978; Marks, 1979; McCracken et al., 1978; Tognoni, 1977). In the following sections, we will outline the major kinetic differences between the various classes together with a discussion of new information which has appeared in the last 2 to 3 years (table VI).

2.5.1 Aminoglycoside Antibiotics

Aminoglycoside antibiotics are weakly basic compounds not subjected to metabolic degradation, not bound to a significant extent to plasma proteins and mainly eliminated through the kidney by glomerular filtration. Since their clearance depends mostly on renal function it is understandable that important age-related differences may be observed in their disposition (table VI). In addition, their distribution volume may be influenced by the changing ratios of extracellular water to other body compartments. Concomitant haemodynamic alterations capable of modifying regional blood flow may alter both distribution and elimination rates.

Furthermore, recent observations suggest the possibility of high tissue sequestration with subsequent

Table VI. Pharmacokinetic profile of some aminoglycoside antibiotics in various age groups[a]

Drug	Age group	Absorption T_{max} (h)	App Vd (L/kg)	App $t_{1/2}$ (h)	Total body clearance (ml/min/1.73 m²)	References
Kanamycin	Premature newborns (2d → 22d)	1.0 (im)		18 → 6	7-9[b]	4,6,12
	Premature + full term newborns + infants	0.34-1.0 (im)	0.37	1.5-6.6	0.9-10.2 (ml/min)	
	Adults	0.8-2.0 (im)	0.23-0.26	2.1-2.4	95-99	
Gentamicin	Premature newborns	1.0 (im)	0.77-1.62	51-110[f] (14-4)[e]	11.7-12.8[f] (12-34)[e]	3,7,8, 9,10,12
	Infants + children	1.0 (im)	1.16	15-46[f]	50.4 (117)[c]	
	Adults		0.3-0.67	87-173[f]		
Amikacin	Premature newborns 0-1 week → 5 weeks	0.5-1.0 (im)	0.66	9.6 → 5.1	11.5-70	1,2,5, 11,12
	Full term newborns 2-8 days			5.75	36.0	
	Infants + children	0.5-1.0 (im)	0.24	2.1 (0.8)[d]	73.0-181.0	
	Adults	1.0-2.0 (im)	0.16-0.17	1.4-2.3	100.0	

References

1) Khan et al. (1976); 2) Sardemann et al. (1976); 3) Schentag and Jusko (1977); 4) Tognoni (1977); 5) Vogelstein et al. (1977); 6) Driessen et al. (1978); 7) Yoshioka et al. (1978; 8) Assael et al. (1979); 9) Evans et al. (1978); 10) Haughey et al. (1979); 11) Kafetzis et al. (1979); 12) Kramer et al. (1979); 13) Morselli and Olive (1980).

a = The values in the table are generally mean values reported by different authors.
b = 2 days old.
c = renal insufficiency.
d = after intravenous infusion.
e = computed on a one compartment open model.
f = computed on a two compartment open model.

slow release, so determining three compartment open model kinetics. The clinical implications of this third (γ) terminal elimination phase are not fully understood at the present time.

In general, in premature and full term newborns as well as in infants, gentamicin, kanamycin and amikacin are efficiently and rapidly absorbed after intramuscular administration with peak plasma concentrations attained within 20 to 60 minutes (Driessen et al., 1978, 1979; Kafetzis et al., 1979; McCracken et al., 1971a; Paisley et al., 1973; Sardemann et al., 1976).

Recommended doses of kanamycin and amikacin in newborns less than 2000g body weight are 7.5mg/kg every 12 hours, while doses of 10mg/kg and 7.5mg/kg every 8 hours are advised for older infants and children (Eichenwald and McCracken, 1978). In the case of gentamicin, doses of 2.5mg/kg

every 12 hours in newborns of less than 1 week of age or every 8 hours in older neonates and infants appear to allow peak plasma concentrations of 4 to 4.5μg/ml and predose levels < 1μg/ml. However, Assael et al. (1977) reported, in low gestational age prematures (< 35w), reduced absorption with therapeutic plasma concentrations attained only in 30% of the cases. Furthermore, in most of the cases of very low gestational age (< 30w), predose concentrations were considerably higher than 1μg/ml, suggesting the risk of accumulation and the necessity of longer dosing intervals in this age group.

The apparent volumes of distribution of kanamycin, gentamicin and amikacin in newborns and infants are rather variable. They tend, however, to be higher in neonates than in infants or adults (table VI) [Assael et al., 1979; Driessen et al., 1978, 1979; Haughey et al., 1979; Kramer et al., 1979; Pechere and Dugal, 1979; Plantier, 1976; Sardemann et al., 1976]. It may be interesting to note that the volume of distribution observed in prematures with very immature renal function is similar to values reported for adults with severely impaired renal function (Pechere and Dugal, 1979). The 3 drugs distribute very little to CSF (1/10 to 1/20 of serum levels) but the amount may be increased in the case of inflamed meninges.

In autopsy studies, a significant amount of gentamicin has been found bound to the kidney cortex (Schentag and Jusko, 1977) and effective concentrations of amikacin (3 to 10μg/ml or g) have been described in viscera, muscle, joint space, bone and peritoneal space (Yow, 1977). These data suggest that aminoglycoside antibiotics distribute to tissues more than currently thought and that tissue sequestration may play an important role in their toxicity.

The apparent disappearance rates have been described by a 1, 2 or 3 compartment open model, depending on the sensitivity of the assay and the length of time the plasma concentrations of the drug have been monitored. In general, after an initial very rapid distribution phase, there is a slower β-phase determined mainly by the elimination of the drug by glomerular filtration and an even slower third (γ)-phase conditioned by the slow release of the drug from the tissues (Assael et al., 1979; Evans et al., 1978; Haughey et al., 1979). Information on the third phase is available only for gentamicin, with terminal half-lives from 51 to 110 hours in prematures and from 28 to 46 hours in infants (Assael et al., 1979).

In terms of a one compartment model, greater values are usually observed in prematures ($t_{1/2}$ = 4 to 18 hours) than in full term newborns ($t_{1/2}$ = 2 to 5 hours) or older infants ($t_{1/2}$ = 1 to 3 hours) [Driessen et al., 1978, 1979; Howard and McCracken, 1975a,b; Kramer et al., 1979; McCracken and Nelson, 1977; Paisley et al., 1973; Sardemann et al., 1976; Simon and Axline, 1966]. Exchange transfusions seem to have little effect on aminoglycoside antibiotic plasma concentrations (Yakatan et al., 1978).

Total clearance values in newborns are about 1/10 to 1/3 of those observed in adults and they appear to increase gradually with age, maturation of renal function and improvement of perfusion pressures. In fact, the urinary excretion of aminoglycoside antibiotics is closely related to the maturation of the glomerular function and does correlate well with creatinine clearance (Kafetzis et al., 1979; Khan et al., 1976; McCracken et al., 1971b). In infants and children with kwashiorkor, reduction of the apparent plasma β-phase half-life, together with an increase in apparent distribution volume has been observed during the nutritional rehabilitation phase (Buchanan et al., 1979).

Finally, it should be mentioned that the occurrence of toxic effects in newborns and infants appears to be considerably lower than in grown up children and adults. Whether this difference is due to modified tissue binding is presently unknown.

2.5.2 Rifampicin (rifampin)

A comprehensive review of the clinical pharmacokinetics of rifampicin in various age groups and pathological situations has been recently published by Acocella (1978) [table VII].

In contrast to the aminoglycoside antibiotics, renal function is not important for the disposition of rifam-

Table VII. Available pharmacokinetic information on chloramphenicol, erythromycin, rifampicin in various age groups

Drug	Age group	Absorption T_{max} (h)	App $t_{1/2}$ (h)	References
Chloramphenicol	Premature newborn	~ 12.0 (oral)	28[a] ⟶ 8[b]	4
	Children + adults	1.0-3.0 (oral)	1.5-5	
Erythromycin estolate	Infants + children	0.5-1.0 (oral)	3.5-4.2	2,3,5
	Adults	2.0 (oral)	3.8-4.5	
Erythromycin ethylsuccinate	Infants + children	0.8-1.2 (oral)	1.4-1.7	
Rifampicin	Newborns	6.0-8.0 (oral)	~ 6	1
	Infants	2.0-4.0 (oral)	2.55	
	Children	2.0-4.0 (oral)		
	Adults	3.0-4.0 (oral)	2.6-5.1[c]	

References
1) Acocella (1978); 2) Coyne et al. (1978); 3) McCracken et al. (1978); 4) Meissner and Smith (1979); 5) Welling et al. (1979).
a = 2 days.
b = 13-23 days.
c = dose-dependent kinetics.

picin which is extensively metabolised and eliminated mostly by biliary excretion.

The main (80%) degradation pathway, desacetylation, does not appear to be a limiting step for the disposition of rifampicin in the newborn.

In neonates of 2 to 3 days of life, the oral absorption of the drug is reduced and relatively slow, with peak plasma concentrations attained at 6 to 8 hours. In older neonates and infants, rifampicin is efficiently and rapidly absorbed by the gastrointestinal tract with maximal concentrations attained within 2 hours. The reduced absorption rate in newborns is probably related to the immaturity of biliary function (Acocella, 1978).

There are no data on protein binding of rifampicin in newborns or infants. In adults, the drug is about 80 to 85% bound to albumin and γ-globulins and reduced binding in the neonates is very likely. *In vitro* studies have shown that rifampicin may reduce bilirubin binding in newborn plasma. No data are available on the disposition rate in newborns, but in infants the apparent plasma half-life may range from 2 to 3 hours.

Dosages for newborns have not been accurately defined. In older infants, recommended doses are 10 to 20mg/kg/day (Acocella, 1978; Eichenwald and McCracken, 1978).

2.5.3 Chloramphenicol

Chloramphenicol is a very liposoluble substance which is usually administered in ester form as chloramphenicol palmitate.

In the newborn, the absorption rate from the gastrointestinal tract is reduced and delayed (peaks at 12 hours) compared with infants or adults (peaks at 2 hours). This has been related to a lack of gastrointestinal lipase activity with consequent reduced and delayed hydrolysis of the palmitate ester and liberation of free chloramphenicol (Meissner and Smith, 1979; Weiss et al., 1960).

Because of its high lipophilicity, chloramphenicol distributes rapidly throughout the various body tissues. In premature and full term newborns as well as in infants, CSF concentrations are about 30% of serum concentrations, but they may rise to 60% in cases of inflamed meninges.

Chloramphenicol elimination depends mainly on metabolic degradation. As with rifampicin, chloramphenicol is extensively metabolised in the liver and is excreted as such in the urine only to a very limited extent (5 to 10%). The drug is mostly degraded in the liver to a monoglucuronide derivative (~ 80%) and for smaller quantities to inactive arylamines by gastrointestinal bacteria. The inactive monoglucuronide derivative is mainly excreted by tubular secretion and only a limited amount (5 to 10%) by glomerular filtration. A glycolic acid derivative has also been found to be present in newborns, but not in adults. Usually in the premature and full term newborn, higher concentrations of conjugated metabolite are present in serum because of the reduced tubular function. Even if the monoglucuronide derivative is inactive, it should be remembered that the metabolite undergoes enterohepatic recycling and that intestinal β-glucuronidase activities are very high in the newborn, thus the possibility of a higher hydrolysis rate of the glucuronide and reabsorption of chloramphenicol.

All situations which may further impair tubular function, such as transient hypoxia, reduction of renal blood flow, or concomitant use with compounds capable of competing for organic anion tubular transport, may increase the risk of toxic effects from chloramphenicol.

The reported elimination rates for premature and full term newborns are considerably prolonged, with values of the serum half-life ranging from 15 to 28 hours and 6 to 10 hours respectively. As for many other drugs, whose elimination is dependent on hepatic microsomal enzyme activity, a dramatic increase in total clearance may be observed after 10 to 15 days of life, with a plasma half-life of 1.5 to 4 hours (table VII; Black et al., 1978; Meissner and Smith, 1979; Sereni and Principi, 1968).

Interactions with other drugs are possible and they may be of particular clinical significance in the newborn. Lower chloramphenicol plasma concentrations may be observed in the case of concomitant phenobarbitone treatment because of hepatic microsomal enzyme induction, while in the case of combined use with penicillins, an increase in the plasma concentration of chloramphenicol has been reported (Windorfer et al., 1977). This is probably due, as already mentioned, to competitive inhibition of the excretion of the glucuronide derivative, associated with an enhanced hydrolysis in the gut and further resorption of free chloramphenicol.

Because of the possibility of severe toxic effects, clearly linked to the circulating concentration of the drug (Meissner and Smith, 1979; Suhrland and Weisberger, 1963), careful monitoring of chloramphenicol serum levels should always be performed in cases of drug administration to newborns.

Recommended doses are 20 to 25mg/kg (bid) in newborns and infants less than 38 weeks of gestational age and not treated with phenobarbitone. In older newborns or in cases where induction of liver enzymes has occurred, doses of 50mg/kg/day may be used. After the first month of life, doses of 50 to 100mg/kg/day (qid) are recommended (Eichenwald and McCracken, 1978; Meissner and Smith, 1979).

2.5.4 Macrolide Antibiotics (erythromycin)

This group of antibiotics includes erythromycin, novobiocin and triacetyloleandomycin (troleandomycin). However, because of toxicity, erythromycin is the only agent of this series commonly used in paediatrics. It may be considered one of the least toxic of antibiotics (Welling et al., 1979) and, because of its activity against Gram-positive bacteria as well as some Gram-negative organisms, it is useful for a variety of infectious conditions.

Numerous preparations are available for oral use and among them the laurylsulphate of the 2'-propionylester (estolate) is the best absorbed. McCracken et al. (1978), compared the kinetics of erythromycin estolate and ethylsuccinate in a large group of infants and observed that the estolate ester gave serum erythromycin levels 75 to 80% higher than those ob-

Table VIII. Available pharmacokinetic information on some cephalosporins in various age groups

Drug	Age group	Absorption T_{max} (h)	App Vd (L/kg)	App $t_{1/2}$ (h)	References
Cephalothin	Infants + children		0.93	0.25-0.40	1,2
	Adults	0.5-1.0 (im)	0.21	0.19-0.28	
Cephaloridine	Newborns	3.0-4.0 (im)		?	2
	Infants	2.0-3.0 (im)		3.0	
	Children	2.0-3.0 (im)		2.2	
	Adults	1.0 (im)	13-20 (L/1.73m²)	1.1-1.5	
Cephalexin	Premature newborns	4.0-5.0 (oral)		3.4-4.5	1,2,3
	Full term newborns	2.5-3.0		3.4-5.0	
	Infants + children	1.5-2.0		0.95-1.3	
	Adults	1.0-1.6	13-18 (L/1.73m²)	0.9-1.1	

References
1) Rolenwicz et al. (1977); 2) Tognoni (1977); 3) McCracken et al. (1978).

tained with the ethylsuccinate ester, with a longer apparent plasma half-life for the estolate (table VII). However, the apparent advantage in absorption is partially compensated by a reduced hydrolysis rate of the estolate, thus leading to a not complete availability of active erythromycin. Similar data have been reported for adults by Welling et al. (1979). Concomitant administration of milk does not affect the absorption of the estolate while it enhances that of the ethylsuccinate ester (Coyne et al., 1978; McCracken et al., 1978).

No other recent data have appeared on erythromycin in newborns or infants and for more detailed description of the kinetic profile the reader is referred to the above-mentioned reviews.

Recommended doses for infants and children are 20 to 30mg/kg (Eichenwald and McCracken, 1978).

2.5.5 Cephalosporins

This group of antibiotics is chemically related to the penicillins. However, their nucleus is not degraded by β-lactamase enzymes and so they can be usefully employed in penicillin-resistant staphylococcal diseases. They can also be used in cases where the infant is allergic to penicillins. According to Eichenwald and McCracken (1978), 'the widespread use of these agents as broad spectrum antibiotics has no logical or practical basis'.

The information on the pharmacokinetic profile of cephalosporins in newborns and infants is rather limited (table VIII). Available data suggest that the various members of this class are efficiently absorbed after intramuscular (cephalothin and cephaloridine) or oral (cephazolin, cephalexin) administration to infants, while a reduced absorption rate may be observed in premature and full term newborns (Anders et al., 1975; McCracken et al., 1978; Pickering et al., 1976; Rolewicz et al., 1977; Tognoni, 1977).

The apparent volume of distribution is increased in infants and very likely in newborns too. With the exception of cephazolin, in general in the infant, this class of antibiotic is cleared very rapidly, and frequent dosing (every 4 to 6 hours) is necessary to maintain effective serum levels ($> 1\mu g/ml$).

Apparent clearance may be reduced in premature and full term neonates, in good agreement with the reduced renal function. Cephalosporins depend in fact on both glomerular filtration and tubular secretion for their elimination (Tognoni, 1977).

2.5.6 Penicillins

Among antibiotics, the penicillins can be considered as the most useful in paediatrics because of their efficacy and low toxicity. They are usually divided into 3 groups: benzylpenicillin (penicillin G); β-lactamase-resistant penicillins (methicillin, nafcillin, etc); and broad spectrum ampicillin-like penicillins (ampicillin, pivampicillin, amoxycillin, carbenicillin). The pharmacokinetic profiles of the single drugs at different ages are reported in table IX. Here we will put forward few more general comments.

Because of erratic absorption after oral intake and of gastrointestinal side effects, the usual route of administration for penicillins is intramuscular. By this route, absorption of penicillins is efficient and peak plasma concentrations in infants and grown up children are usually attained within 1 to 2 hours. However, delayed absorption of penicillin has been observed in premature newborns (24 hours of life) with peak concentrations at about 6 hours (McCracken and Nelson, 1977). At variance, in the case of ampicillin, an absorption rate faster than in adults has been reported in newborns and infants (Driessen et al., 1978, 1979).

In order to improve the oral absorption of benzylpenicillin, products such as phenethicillin or phenoxymethylpenicillin (penicillin V) were introduced. No kinetic studies in paediatric patients are, however, available on these compounds.

In the group of ampicillins, amoxycillin and pivampicillin do show better bioavailability than the parent compound following oral administration (Brogden et al., 1979; Marget et al., 1973; McCracken, 1974; Pedersen-Bjergaard and Petersen, 1977). Furthermore, in contrast to benzylpenicillin, food intake has minimal or no effect on the gastrointestinal absorption of amoxycillin. It is also efficiently absorbed during the acute diarrhoeal phase of shigellosis but for unexplained reasons is ineffective (Ginsburg et al., 1979; McCracken et al., 1978; Nelson and Haltalin, 1974). In the case of pivampicillin (the pivaloyloxymethylester of ampicillin), increased oral bioavailability over ampicillin is seen in older infants and children. However, in infants less than 1 year old, the compound gives rise to serum levels consistently lower than those obtained in older infants (Pedersen-Bjergaard and Petersen, 1977; Simon et al., 1974). Since this does not occur with ampicillin, a difference in the elimination rate cannot be the cause; the data suggest, as previously mentioned (see section 1.3.1), a developmental deficit in hydrolysing enzyme activity in blood and tissues of young infants which hydrolyses pivampicillin to ampicillin.

Plasma protein binding, in the few cases where it has been measured, appears to be reduced in the newborn if compared with older infants and adults (table IX).

With the exception of nafcillin, the apparent volume of distribution of various penicillins is of the order of 0.15 to 0.20L/kg in adults. In newborns and infants, because of lower protein binding and higher extracellular water content, the apparent distribution volume is generally increased (Nelson et al., 1978).

Long lasting activity of long acting type penicillins such as benzathine penicillin and procaine penicillin has been observed in tonsils and urine (Breese and Disney, 1958; Klein et al., 1973). However, these forms of penicillin usually give lower plasma concentrations than with benzylpenicillin and their use should be restricted to a few definite indications (Eichenwald and McCracken, 1978). With aqueous benzylpenicillin and procaine penicillin, therapeutic CSF concentrations are attained shortly after dosing, while with benzathine penicillin optimal CSF concentrations may be achieved only at 20 to 24 hours after dosing (McCracken and Kaplan, 1974; Speer et al., 1977). Ampicillin CSF levels are usually very low unless the meninges are inflamed, and a different penetration rate has been described in different forms of meningitis (Wilson and Haltalin, 1975). Further-

Table IX. Pharmacokinetic profile of some penicillins in various age groups

Drug	Age group	Absorption T_{max} (h)	Binding (%)	App Vd (L/kg)	App $t_{1/2}$ (h)	Total body clearance (ml/min/1.73m²)	References
Benzylpenicillin	Premature newborns < 2000g → > 2000g	6.0 → 0.5 (im) 2.0 (oral)			4.9 → 2.1	30.4-75.2	1,3,6,10
	Full term newborns	0.5-1.0 (im)			1.2 → 1.3		
	Infants + children				0.95-1.2		
	Adults		46-45	≈ 0.53-0.67	0.41-0.93	550	
Methicillin	Premature newborns	1.0 (oral)		0.25-0.35	3.3 → 1.0		3
	Full term newborns	1.0 (oral)	65		3.3 → 0.8		
	Adults		75	≈ 0.31	0.5	560	
Ticarcillin (given together with kanamycin)	Newborns < 2000g	1.0-2.0 (im)		0.66	5.6	31	7
	Newborns > 2000g			0.71	4.9	54	
	1-8 weeks			0.76	2.2	118	
	Children (5-13y)			0.35	0.9	176	
Nafcillin	Infants			0.89	0.7	550	5
	Children			0.89	0.8	660	
	Adults			0.63-0.81	0.5	410	
Ampicillin	Premature newborns (2 days → 30 days)	0.5-2.0 (im)			6.2 → 1.7	210 → 30	1,3,6,7, 10
	Full term newborns	0.5-2.0 (im)	7.6-12.0	0.47	3.5 → 1.7	41.5-63	
	Infants	1.0-2.0 (im)		(0.31-0.73)	0.9-1.4	329-448	
	Children						
	Adults		19-24	0.22	0.58-1.58	260-420	
Amoxycillin	Premature newborns	4.5 (oral)				-	3,4,8
	Full term newborns	3-4.5 (oral)			~ 3.7		
	Infants + children	1.0-2.0 (oral)			0.9-1.9		
	Adults	2.0 (oral)	17		0.6-1.5		
Carbenicillin	Newborns < 2000g 0 → 7 days	1.0-2.0 (im)		0.50	6.6 → 6.0		3
	Newborns > 2000g 0 → 7 days	1.0-2 (im)		0.59	6.7 → 2.9		
	Infants	1.0 (im)		0.67	1.5-1.8		
	Children			0.25-0.50	0.8-1.5		
	Adults		47-70	≈ 0.14-0.30	0.7-1.3	93-189	

The values in the table are generally mean values reported by various authors.

References

1) McCracken and Nelson (1977); 2) Pedersen-Bjergaard and Petersen (1977); 3) Tognoni (1977); 4) Weingartner et al. (1977); 5) Feldman et al. (1978); 6) McCracken et al. (1978); 7) Nelson et al. (1978); 8) Ehrnebo et al. (1979); 9) Ginsburg et al. (1979); 10) Morselli and Olive (1980).

more, the CSF penetration appears to be faster in infants than in children (McCracken, 1974).

Penicillins are mainly eliminated as such through the kidney mostly by tubular secretion. It is understandable, on the basis of the immaturity of renal function, that prolonged serum half-lives are usually observed in premature and full term newborns (table IX). However, since an inverse relationship between creatinine clearance and the serum half-lives of various penicillins have been observed by several authors, it is possible that in the early neonatal period, glomerular filtration also plays a significant role (Driessen et al., 1978; Klein et al., 1973; McCracken et al., 1973). An exception is represented by nafcillin: only 10% of parenterally administered nafcillin is excreted in the urine, while 90% of the dose is eliminated through biliary excretion (Klein and Finland, 1973). It is interesting in this respect to note that no effect of age on its disposition rate could be shown by Feldmann et al. (1978).

For recommended doses of individual agents the reader is referred to recent reviews or specific papers (Brogden et al., 1978; Eichenwald and McCracken, 1978; Ginsburg et al., 1979; Nelson et al., 1978; Pedersen-Bjergaard and Petersen, 1977).

2.6 Salicylates and Paracetamol (Acetaminophen)

The clinical pharmacokinetics of these two compounds as well as the practical management of their toxicity in newborns, infants and children has been the subject of several exhaustive reviews in a recent supplement issue of Pediatrics (Rumack, 1978) to which the interested reader is referred.

3. Conclusions

The reported data clearly illustrate that the risk of both overdosing or underdosing drugs is greatly increased in the perinatal period. Because of continuous development of the functions important for drug disposition and of the superimposed pathological status, there is practically no way to predict or to foresee, *a priori*, the amount of drug we should administer or the length of the dosing interval in a given patient. A rational individualised dosage regimen becomes, in the perinatal period and early infancy, a very difficult if not an impossible task. For these reasons, services for therapeutic monitoring of administered drug should be present within perinatal units.

We strongly believe that the only possible way to achieve a correct therapeutic approach in each individual patient is by therapeutic drug monitoring. Such monitoring should not be regarded as experimentation, but on the contrary, as an integral part of the therapeutic intervention (Morselli, 1976b; 1977c).

References

Acocella, G.: Clinical pharmacokinetics of rifampicin. Clinical Pharmacokinetics 3: 108-127 (1978).

Agurell, S.; Berlin, A.; Fengren, H.G. and Hellström, B.: Plasma levels of diazepam after parenteral and rectal administration to children. Epilepsia 16: 277-283 (1975).

Albani, M.: An effective dose schedule for phenytoin treatment of status epilepticus in infancy and childhood. Neuropädiatrie 8: 286-292 (1977).

Albani, M.; Gabriel, M. and Michaelis, L.: Phenobarbitaltherapie bei Frühgeborenen unter fortlaufender Blutspiegelkontrolle. Monatsschrift für Kinderheilkunde 125: 446-448 (1977).

Anan, S.K.; Northway, J.D. and Crussi, F.G.: Acute renal failure in newborn infants. Journal of Pediatrics 92: 985-988 (1978).

Anders, M.W.; Cooper, M.J.; Rolewicz, T.F. and Mirkin, N.L.: Application of high-pressure liquid chromatography in pediatric pharmacology: Pharmacokinetics of cephalothin in man; in Morselli, Garattini and Sereni (Eds) Basic and Therapeutic Aspects of Perinatal Pharmacology, pp.405-409 (Raven Press, New York 1975).

Andersson, K.E.; Bertler, A. and Wettrel, G.: Post mortem distribution and tissue concentrations of digoxin in infants and adults. Acta Paediatrica Scandinavica 64: 497-504 (1975).

Aranda, J.V.; MacLeod, S.M.; Renton, K.W. and Eade, N.R.: Hepatic microsomal drug oxidation and electron transport in newborn infants. Journal of Pediatrics 85: 534-542 (1974).

Aranda, J.V.; Sitar, D.S.; Parson, W.D.; Loughnan, P.M. and Niems, H.H.: Pharmacokinetic aspect of theophylline in premature newborn. New England Journal of Medicine 295: 413-416 (1976).

Aranda, J.V.; Gorman, W.; Bergsteinsson, H. and Gunn, T.: Efficacy of caffeine in treatment of apnea in the low-birthweight infant. Journal of Pediatrics 90: 467-472 (1977).

Aranda, J.V.; Perez, J.; Sitar, D.S.; Collinge, J.; Portuguez-Malavasi, A.; Duffy, B. and Dupont, C.: Pharmacokinetic disposition and protein binding of furosemide in newborn infants. Journal of Pediatrics 93: 507-511 (1978).

Aranda, J.V.; Cook, C.E.; Gorman, W.; Collinge, J.M.; Loughnan, P.M.; Outerbridge, E.W.; Aldridge, A. and Neims, A.H.: Pharmacokinetic profile of caffeine in the premature newborn infant with apnea. Journal of Pediatrics 94: 663-668 (1979).

Arant, B.S.: Developmental patterns of renal functional maturation compared in the human neonate. Journal of Pediatrics 92: 705-712 (1978).

Assael, B.M.; Gianni, V.; Marini, A.; Peneff, P. and Sereni, F.: Gentamicin dosage in preterm and term neonates. Archives of Disease in Childhood 52: 883-886 (1977).

Assael, B.M.; Cavanna, G.; Jusko, W.J.; Marini, A.; Parini, R.; Sereni, F. and Vigano, A.: Multiexponential elimination of gentamicin. A kinetic study during development. Developmental Pharmacology. Submitted for publication (1979).

Augustinsson, K.B. and Brody, S.: Plasma arylesterases activity in adults and newborn infants. Clinica Chimica Acta 7: 560-565 (1962).

Bada, H.S.; Khanna, N.N.; Somani, S.M. and Tin, A.V.: Interconversion of theophylline and caffeine in newborn infants. Journal of Pediatrics 94: 993-995 (1979).

Barnett, H.L.; Hare, W.K.; McNamara, N. and Hare, R.S.: Influence of postnatal age on kidney function of premature infants. Proceedings of the Society for Experimental Biology and Medicine 69: 55-67 (1948).

Battino, D.; Bossi, L.; Croci, D.; Franceschetti, S.; Gomeni, C.; Moise, A.; Vitali, A. and Breschi, F.: Carbamazepine plasma levels in children. In preparation (1980).

Beerman, B.; Groschinsky-Grind, M.; Fahraeus, L. and Lindstrom, B.: Placental transfer of furosemide. Clinical Pharmacology and Therapeutics 24: 560-562 (1978).

Belfrage, P.; Raabe, N.; Thalme, B. and Berlin, A.: Lumbar epidural analgesia with bupivacaine in labor. Determination of drug concentration and pH in fetal scalp blood, and continuous fetal heart rate monitoring. American Journal of Obstetrics and Gynecology 121: 360-365 (1975).

Bell, M.J.; Shackelford, P.G.; Feigin, R.D.; Ternberg, J.L. and Brotherton, T.: Alterations in gastrointestinal microflora during antimicrobial therapy for necrotizing enterocolitis. Pediatrics 63: 425-428 (1979).

de Belle, R.C.; Vaupshas, V.; Vitullo, B.B.; Haber, L.R.; Shaffer, E.; Mackie, G.G.; Owen, H.; Little, J.M. and Lester, R.: Intestinal absorption of bile salts: Immature development in the neonate. Journal of Pediatrics 94: 472-476 (1979).

Benowitz, M.L. and Meister, W.: Clinical pharmacokinetics of lignocaine. Clinical Pharmacokinetics 3: 177-201 (1978).

Berman, W.; Dubynsky, O.; Whitman, V.; Friedman, Z.; Maisels, M.J. and Musselman, J.: Digoxin therapy in low-birth-weight infants with patent ductus arteriosus. Journal of Pediatrics 93: 652-655 (1978).

Bianchetti, G.; Monin, P.; Marchal, F.; Dubruc, C.; Boutroy, M.J.; Morselli, P.L. and Vert, P.: Pharmacokinetics of indomethacin in the premature infant. Developmental Pharmacology and Therapeutics. In press (1980).

Biehl, D.; Shnider, S.M.; Levinson, G. and Callender, K.: Placental transfer of lidocaine: Effect of acidosis. Anesthesiology 48: 409-412 (1978).

Black, S.B.; Levine, P. and Shinefield, H.R.: The necessity for monitoring chloramphenicol levels when treating neonatal meningitis. Journal of Pediatrics 92: 235-236 (1978).

Blankenbaker, W.L.; Difazio, C.A. and Berry, F.A.: Lidocaine and its metabolites in the newborn. Anesthesiology 42: 325-330 (1975).

Blumenthal, I.; Ebel, A. and Pildes, R.S.: Effect of posture on the pattern of stomach emptying in the newborn. Pediatrics 63: 532-536 (1979).

Bolme, P.; Edlund, P.O.; Eriksson, M.; Paalzow, L. and Winbladh, B.: Pharmacokinetics of theophylline in young children with asthma: Comparison of rectal enema and suppositories. European Journal of Clinical Pharmacology 16: 133-139 (1979).

Boreus, L.O.; Jalling, B. and Kallberg, N.: Clinical pharmacology of phenobarbital in the neonatal period: in Morselli, Garattini and Sereni (Eds) Basic and Therapeutic Aspects of the Perinatal Pharmacology, pp.331-340 (Raven Press, New York, 1975).

Boreus, L.O.; Jalling, B. and Kallberg, N.: Phenobarbital metabolism in adults and in newborn infants. Acta Paediatrica Scandinavica 67: 193-200 (1978a).

Boreus, L.O.; Jalling, B. and Wallin, A.: Plasma concentrations of phenobarbital in mother and child after combined prenatal and postnatal administration for prophylaxis of hyperbilirubinemia. Journal of Pediatrics 93: 695-698 (1978b).

Bory, C.; Baltassat, P.; Porthault, M.; Bethenod, M.; Frederich, A. and Aranda, J.V.: Metabolism of theophylline to caffeine in premature newborn infants. Journal of Pediatrics 94: 988-993 (1979).

Bossi, L.; Assael, B.M.; Avanzini, G.; Battino, D.; Caccamo, M.L.; Canger, R. et al: Plasma levels and clinical effects of antiepileptic drugs in pregnant epileptic patients and their newborns: in Johannesen, Morselli, Pippenger, Richens, Schmidt and Meinardi (Eds) Antiepileptic Therapy: Advances in Drug Monitoring, pp.9-14 (Raven Press, New York 1980a).

Bossi, L.; Battino, D.; Caccamo, M.L.; Croci, D.; Marini, A.; Porro, M.G. and Rovei, V.: Kinetics of antiepileptic drugs in newborns of chronically treated epileptic mothers. In preparation (1980b).

Boutroy, M.J.; Vert, P.; Royer, R.J.; Monin, P. and Royer-Morrot, M.J.: Caffeine, a metabolite of theophylline during the treatment of apnea in the premature infant. Journal of Pediatrics 94: 996-998 (1979).

Brachet-Liermain, A. and Demarquez, J.L.: Pharmacokinetics of

dipropyl acetate in infants and young children. Pharmaceutisch Weekblad 112: 293-297 (1977).

Brachet-Liermain, A.; Goutieres, F. and Aicardi, J.: Absorption of phenobarbital after the intramuscular administration of single doses in infants. Journal of Pediatrics 87: 624-626 (1975).

Brater, C.D.: Analysis of the effect of indomethacine on the response to furosemide in man: Effect of dose of furosemide. Journal of Pharmacology and Experimental Therapeutics 210: 386-390 (1979).

Braunlich, H.: Kidney-development-drug elimination mechanisms: in Morselli (Ed) Drug Disposition During Development, pp.89-100 (Spectrum, New York 1977).

Brazier, J.L.; Renaud, H.; Ribon, B.; Faucon, G. and Sassard, J.: Evolution du taux plasmatique des xanthines dans le traitement de l'apnee du premature. Therapie 33: 341-355 (1978).

Brazier, J.L.; Renaud, H.; Ribon, B. and Salle, B.L.: Plasma xanthine levels in low birthweight infants treated or not treated with theophylline. Archives of Disease in Childhood 54: 194-199 (1979).

Breese, B.B. and Disney, F.A.: Penicillin in the treatment of streptococcal infections: Comparison of effectiveness of five different oral and one parenteral form. New England Journal of Medicine 259: 57-62 (1958).

Brogden, R.N.; Heel, R.C.; Speight, T.M. and Avery, G.S.: Amoxycillin injectable: A review of its antibacterial spectrum, pharmacokinetics and therapeutic use. Drugs 18: 169-184 (1979).

Brown, W.U.; Bell, G.C.; Lurie, A.O.; Weiss, J.B.; Scanlon, J.W. and Alper, M.H.: Newborn blood levels of lidocaine and mepivacaine in the first postnatal day following maternal epidural anesthesia. Anesthesiology 42: 698-707 (1975).

Brown, W.U.; Bell, G.C. and Alper, M.H.: Acidosis, local anesthetics and the newborn. Obstetrics and Gynecology 48: 27-30 (1976).

Buchanan, N.; Davis, M.D. and Eyberg, C.: Gentamicin pharmacokinetics in kwashiorkor. British Journal of Clinical Pharmacokinetics 8: 451-453 (1979).

Caldwell, J.; Moffatt, J.R.; Smith, R.L.; Lieberman, B.A.; Beard, R.W.; Snedden, W. and Wilson, B.W.: Determination of bupivacaine in human fetal and neonatal blood samples by quantitative single ion monitoring. Biomedical Mass Spectrometry 4: 322-325 (1977a).

Caldwell, J.; Wakile, L.A.; Notarianni, L.J.; Smith, R.L.; Lieberman, B.A.; Jeffs, J.; Coy, Y. and Beard, R.W.: Transplacental passage and neonatal elimination of pethidine given to mothers in childbirth. Proceedings British Pharmacological Society, September: 46 (1977b).

Caldwell, J.; Notarianni, L.J. and Smith, T.R.: Impaired metabolism of pethidine in the human neonate. Proceedings British Pharmacological Society, January: 362-363p (1978a).

Caldwell, J.; Wakile, L.A.; Notarianni, L.J.; Smith, R.L.; Correy, G.J.; Lieberman, B.A.; Beard, R.W.; Finnie, M.D.A. and Snedden, W.: Maternal and neonatal disposition of pethidine in childbirth. A study using quantitative gas chromatography-mass spectrometry. Life Sciences 22: 589-596 (1978b).

Cathcart-Rake, W.F.; Kyner, J.L. and Azarnoff, D.L.: Metabolic responses to plasma concentrations of theophylline. Clinical Pharmacology and Therapeutics 26: 89-95 (1979).

Cavell, B.: Gastric emptying in preterm infants. Acta Paediatrica Scandinavica 68: 725-730 (1979).

Chan, V.; Tse, T.F. and Wong, V.: Transfer of digoxin across the placenta and into breast milk. British Journal of Obstetrics and Gynaecology 85: 605-609 (1978).

Committee on Drugs, American Academy of Pediatrics: Effect of medication during labor and delivery on infant outcome. Pediatrics 62: 402-403 (1978).

Cook, D.R.; Wingard, L.B. and Taylor, E.H.: Pharmacokinetics of succinylcholine in infants, children and adults. Clinical Pharmacology and Therapeutics 20: 493-498 (1976).

Cooper, L.V.; Stephen, G.W. and Aggett, P.J.A.: Elimination of pethidine and bupivacaine in the newborn. Archives of Disease in Childhood 52: 638-641 (1977).

Coyne, T.E.; Shum, S.; Chun, A.H.C.; Jeansonne, L. and Shirkey, H.C.: Bioavailability of erythromycin ethylsuccinate in pediatric patients. Journal of Clinical Pharmacology 18: 194-202 (1978).

Crawford, J.S.: Continuous lumbar epidural analgesia for labour and delivery. British Medical Journal 1: 72-74 (1979).

Crawford, J.S. and Rudofsky, S.: The placental transmission of pethidine. British Journal of Anaesthesia 37: 929-933 (1965).

Cutler, R.E. and Blair, A.D.: Clinical pharmacokinetics of furosemide. Clinical Pharmacokinetics 4: 279-296 (1979).

Daniel, S.S. and James, L.S.: Abnormal renal function in the newborn infant. Journal of Pediatrics 88: 856-858 (1976).

Datta, S.; Alper, M.H.; Ostheimer, G.W.; Brown, W.U. and Weiss, J.B.: Effects of maternal position on epidural anesthesia for cesarean section, acid-base status, and bupivacaine concentrations at delivery. Anesthesiology 50: 205-209 (1979).

Dauber, I.M.; Kraus, A.N.; Symchych, P.S.; Ault, P.A.M.: Renal failure following perinatal anoxia. Journal of Pediatrics 88: 851-855 (1976).

Davi, M.J.; Sankaran, K.; Simons, K.J.; Simons, F.E.R.; Seshia, M.M. and Rigatto, H.: Physiologic changes induced by theophylline in the treatment of apnea in preterm infants. Journal of Pediatrics 92: 91-95 (1978).

Demarquez, J.L.; Brachet-Lierman, A.; Paty, J.; Deliac, M.M.; Philippe, J.C.; Paix, M.; Babin, J.P. and Martin, C.: Traitement preventif des apnees du premature par la theophylline: Etude clinique, pharmacocinetique, neurophysiologique. Archives Françaises de Pediatrie 35: 793-805 (1978).

Dickinson, R.G.; Harland, R.C.; Lynn, R.K.; Smith, W.B. and Gerber, N.: Transmission of valproic acid (Depakene) across the placenta: Half-life of the drug in mother and baby. Journal of Pediatrics 94: 832-835 (1979).

Dietrich, J.; Krauss, A.N.; Reidenberg, M.; Drayer, D.E. and Auld, P.A.M.: Alterations in state apneic pre-term infants

receiving theophylline. Clinical Pharmacology and Therapeutics 24: 474-478 (1978).

Dodson, W.E.: Neonatal drug intoxication: Local anesthetics. Pediatric Clinics of North America 23: 399-411 (1976).

Driessen, O.M.J.; Sorgedrager, N.; Michel, M.F.; Kerrebijn, K.F. and Hermans, J.: Pharmacokinetic aspects of therapy with ampicillin and kanamicin in newborn infants. European Journal of Clinical Pharmacology 13: 449-457 (1978).

Driessen, O.M.J.; Sorgedrager, N.; Michel, M.F.; Kerrebijn, K.F. and Hermans, J.: Variability and predictability of the plasma concentration of ampicillin and kanamicin in newborn infants. European Journal of Clinical Pharmacology 15: 133-137 (1979).

Dutton, G.J.: Developmental aspects of drug conjugation with special reference to glucuronidation. Annual Review of Pharmacology and Toxicology 18: 17-35 (1978).

Ecobichon, D.J. and Stephens, D.S.: Perinatal development of human blood esterases. Clinical Pharmacology and Therapeutics 14: 11-17 (1973).

Ehrnebo, M.; Agurell, S.; Jalling, B. and Boréus, L.O.: Age differences in drug binding by plasma proteins: Studies on human foetuses, neonates and adults. European Journal of Clinical Pharmacology 3: 189-193 (1971).

Ehrnebo, M.; Nilsson, S.O. and Boréus, L.O.: Pharmacokinetics of ampicillin and its prodrugs bacampicillin and pivampicillin in man. Journal of Pharmacokinetics and Biopharmaceutics 7: 429-451 (1979).

Eichenwald, H.F. and McCracken, G.H.: Antimicrobial therapy in infants and children. Journal of Paediatrics 93: 337-377 (1978).

Engle, M.A.; Lewy, J.E.; Lewy, P.R. and Metcoff, J.: The use of furosemide in the treatment of edema in infants and children. Pediatrics 62: 811-818 (1978).

Evans, W.E.; Feldman, S.; Barker, L.F.; Ossi, M. and Chaudhary, S.: Use of gentamicin serum levels to individualize therapy in children. Journal of Pediatrics 93: 133-137 (1978).

Evans, M.A.; Bhat, R.; Vidyasagar, D.; Vadapalli, M.; Fisher, E. and Hastreiter, A.: Gestational age and indomethacin elimination in the neonate. Clinical Pharmacology and Therapeutics 26: 746-751 (1979).

Feldman, W.E.; Nelson, J.D. and Stanberry, L.R.: Clinical and pharmacokinetic evaluation of nafcillin in infants and children. Journal of Pediatrics 93: 1029-1033 (1978).

Fredholm B.B.; Rane, A. and Persson, B.: Diphenylhydantoin binding to proteins in plasma and its dependence on free fatty acid and bilirubin concentration in dogs and newborn infants. Pediatric Research 9: 26-30 (1975).

Freeman, D.S.; Gjika, H.B. and Van Vunakis, H.: Radioimmunoassay for normeperidine: Studies on the n-dealkylation of meperidine and anileridine. Journal of Pharmacology and Experimental Therapeutics 203: 203-212 (1977).

Frenzel, J.; Bräunlich, H.; Schramm, D.; Kersten, L. and Zwacka, G.: Effect on maturation of kidney function in newborn infants of repeated administration of water and electrolytes. Eur. J. Clin. Pharmacol. 11: 317-320 (1977).

Friedman, W.F.; Hirschklau, M.J.; Printz, M.P.; Pitlick, P.T. and Kirkpatrick, S.E.: Pharmacologic closure of patent ductus arteriosus in the premature infant. New England Journal of Medicine 295: 526-529 (1976).

Friedman, Z.V.I.; Whitman, V.; Maisels, M.J.; Berman, W.; Marks, K.H. and Vesell, E.S.: Indomethacin disposition and indomethacin-induced platelet dysfunction in premature infants. Journal of Clinical Pharmacology 18: 272-279 (1978).

Friis-Hansen, B.: Body water compartments in children: changes during growth and related changes in body composition. Pediatrics 28: 169-181 (1961).

Gerhardt, T.; McCarthy, J. and Bancalari, E.: Aminophylline therapy for idiopathic apnea in premature infants: Effects on lung function. Pediatrics 62: 801-804 (1978).

Giacoia, G.; Jusko, W.; Menke, J. and Koup, J.R.: Theophylline pharmacokinetics in premature infants with apnea. Journal of Pediatrics 89: 829-832 (1976).

Ginsburg, C.M.; McCracken, G.H.; Thomas, M.L. and Clahsen, J.: Comparative pharmacokinetics of amoxicillin and ampicillin in infants and children. Pediatrics 64: 627-631 (1979).

Gladtke, E. and Heimann, G.: The rate of development of elimination functions in kidney and liver of young infants: in Morselli, Garattini and Sereni (Eds) Basic and Therapeutic Aspects of Perinatal Pharmacology, p.393 (Raven Press, New York 1975).

Gorodischer, R.; Krasner, J. and Yaffe, S.J.: Serum protein binding of digoxin in newborn infants. Research Communications in Pathology and Pharmacology 9: 387-390 (1974).

Gorodischer, R.; Jusko, W.J. and Yaffe, S.J.: Tissue and erithrocyte distribution of digoxin in infants. Clinical Pharmacology and Therapeutics 19: 256-263 (1976).

Gugler, R.; Shoeman, D.W. and Azarnoff, D.L.: Effect of in vivo elevation of free fatty acids on protein binding of drugs. Pharmacology 12: 160-165 (1974).

Guignard, J.P.; Torrado, A.; Da Cunha, O. and Gautier, E.: Glomerular filtration rate in the first three weeks of life. Journal of Pediatrics 87: 268-272 (1975).

Gupta, M. and Brans, Y.W.: Gastric retention in neonates. Pediatrics 62: 26-29 (1978).

Halkin, H.; Radomsky, M.; Blieden, L.; Frand, M.; Millman, P. and Boichis, H.: Steady state serum digoxin concentration in relation to digitalis toxicity in neonates and infants. Pediatrics 61: 184-188 (1978a).

Halkin, H.; Radomsky, M.; Millman, P.; Almog, S.; Blieden, L. and Boichis, H.: Steady state serum concentrations and renal clearance of digoxin in neonates, infants and children. European Journal of Clinical Pharmacology 13: 113-117 (1978b).

Halliday, H.L.; Hirata, T. and Brady, J.P.: Indomethacin therapy for large patent ductus arteriosus in the very low birth weight infant. Results and complications. Pediatrics 64: 154-159 (1979).

Haughey, D.B.; Hilligoss, D.M.; Grassi, A. and Schentag, J.J.: Two-compartment gentamicin pharmacokinetics in premature neonates: A comparison to adults with decreased glomerular filtration rates. Journal of Pediatrics. In press (1979).

Heimann, G. and Gladtke, E.: Pharmacokinetics of phenobarbital in childhood. European Journal of Clinical Pharmacology 12: 305-310 (1977).

Heinze, E. and Kampffmeyer, H.G.: Biological half-life of phenobarbital in human babies. Klinische Wochenschrift 49: 1146-1147 (1971).

Hendeles, L.; Weinberger, M. and Johnson, G.: Monitoring serum theophylline levels. Clinical Pharmacokinetics 3: 293-312 (1978).

Heubi, J.E.; Balistreri, W.F.; Partin, J.C.; Schubert, W.K. and McGraw, C.A.: Refractory infantile diarrhea due to primary bile acid malabsorption. Journal of Pediatrics 94: 546-551 (1979).

Heymann, M.A.; Rudolph, A.M. and Silverman, N.H.: Closure of the ductus arteriosus in premature infants by inhibition of prostaglandin synthesis. New England Journal of Medicine 295: 530-533 (1976).

Hilligoss, D.M.; Jusko, W.J.; Koup, J.R. and Giacoia, G.: Factors affecting theophylline pharmacokinetics in premature infants with apnea. Developmental Pharmacology and Therapeutics 1: 6-15 (1980).

Hogg, M.I.J.; Wiener, P.C.; Rosen, M. and Mapleson, W.W.: Urinary excretion and metabolism of pethidine and norpethidine in the newborn. British Journal of Anaesthesia 49: 891-899 (1977).

Hook, J.B. and Hewitt, W.R.: Development of mechanisms for drug excretion. American Journal of Medicine 62: 497 (1977).

Houston, I.B. and Oetliker, O.: The growth and the development of the kidneys; in Davis and Dobbing (Eds) Scientific Foundations of Pediatrics, pp.297-307 (Heinemann, London 1974).

Howard, J.B. and McCracken, G.H.: Pharmacological evaluation of amikacin in neonates. Antimicrobial Agents and Chemotherapy 8: 86 (1975a).

Howard, J.B. and McCracken, G.H.: Reappraisal of kanamycin usage in neonates. Journal of Pediatrics 86: 949-956 (1975b).

Iisalo, E. and Dahl, M.: Serum level and renal excretion of digoxin during maintenance therapy in children. Acta Paediatrica Scandinavica 63: 699-704 (1974).

Jalling, B.: Plasma and cerebrospinal fluid concentrations of phenobarbital in infants given single doses. Developmental Medicine and Child Neurology 16: 785-793 (1976).

Jalling, B.; Boréus, L.O.; Rane, A. and Sjöqvist, F.: Plasma concentrations of diphenylhydantoin in young infants. Pharmacologia Clinica 2: 200-202 (1970).

Jalling, B.; Boréus, L.O.; Kallberg, N. and Agurell, S.: Disappearance from the newborn of circulating prenatally administered phenobarbital. European Journal of Clinical Pharmacology 6: 234-238 (1973).

Jonas, A.; Avigad, S.; Diver-Haber, A. and Katznelson, D.: Disturbed fat absorption following infectious gastroenteritis in children. Journal of Pediatrics 95: 366-372 (1979).

Jones, A.S.; James, E.; Bland, H.; Groshong, T.: Renal failure in the newborn. Clinical Pediatrics 18: 286-291 (1979).

Jusko, W.F.: Pharmacokinetic principles in pediatric pharmacology. Pediatric Clinics of North America 19: 81 (1972).

Kafetzis, D.A.; Sinaniotis, C.A.; Papadatos, C.J. and Kosmidis, J.: Acta Paediatrica Scandinavica 68: 419-422 (1979).

Kaneko, S.; Sato, T. and Suzuki, K.: The levels of anticonvulsants in breast milk. British Journal of Clinical Pharmacology 7: 624-627 (1979).

Khan, A.J.; Evans, H.E.; Jhaveri, R.; Chang, C.T. and Hochstein, L.: Amikacin pharmacokinetics in the therapy of childhood urinary tract infection. Pediatrics 58: 873-876 (1976).

Kim, P.W.; Krasula, R.W.; Soyka, L.F. and Hastreiter, A.R.: Post mortem tissue digoxin concentrations in infants and children. Circulation 52: 1128-1131 (1975).

Klein, J.O. and Finland, M.: The new penicillins. New England Journal of Medicine 269: 1074 (1973).

Klein, J.O.; Schaberg, M.J.; Buncin, M. and Gezon, H.M.: Levels of penicillin in serum of newborn infants after single intramuscular doses of benzathine penicillin G. Journal of Pediatrics 82: 1065-1068 (1973).

Knudsen, F.O.: Plasma diazepam in infants after rectal administration in solution and by suppository. Acta Paediatrica Scandinavica 66: 563-567 (1977).

Koup, J.R. and Hart, B.A.: Relationship between plasma and whole blood theophylline concentration in neonates. Journal of Pediatrics 94: 320-321 (1979).

Koup, J.R.; Rose, J.Q. and Cohen, M.E: Ethosuximide pharmacokinetics in a pregnant patient and her newborn. Epilepsia 19: 535-539 (1978).

Kramer, W.G.; Cleary, T.; Frankel, L.S.; Kohl, S. and Pickering, L.K.: Multiple-dose amikacin kinetics in pediatric oncology patients. Clinical Pharmacology and Therapeutics 26: 635-640 (1979).

Krasner, J.; Giacoia, G.P. and Yaffe, S.J.: Drug-protein binding in the newborn infant. Annals of the New York Academy of Sciences 226: 101-114 (1973).

Krasula, R.W.; Pellegrino, P.A.; Hastraiter, A.R. and Soyka, L.F.: Serum levels of digoxin in infants and children. Journal of Pediatrics 81: 566-569 (1972).

Krauer, B.: The development of diurnal variation in drug kinetics in the human infant; in Morselli, Garattini and Sereni (Eds) Basic and Therapeutic Aspects of Perinatal Pharmacology, pp.347-356 (Raven Press, New York 1975).

Krishnaswamy, K.: Drug metabolism and pharmacokinetics in malnutrition. Clinical Pharmacokinetics 3: 216-240 (1978).

Kuhnert, B.R.; Knapp, D.R.; Kuhnert, P.M. and Prochaska, A.L.: Maternal, fetal, and neonatal metabolism of lidocaine. Clinical Pharmacology and Therapeutics 26: 213-220 (1979a).

Kuhnert, B.R.; Kuhnert, P.M.; Tu, A.L. and Lin, D.C.K.: Meperidine and normeperidine levels following meperidine

administration during labor. II. Fetus and neonate. American Journal of Obstetrics and Gynecology 133: 909-914 (1979b).

Kuhnert, B.R.; Kuhnert, P.M.; Tu, A.L.; Lin, D.C.K. and Foltz, R.L.: Meperidine and normeperidine levels following meperidine administration during labor. I. Mother. American Journal of Obstetrics and Gynecology 133: 904-908 (1979c).

Kurz, H.; Mauser-Ganshorn, A. and Stickel, H.H.: Differences in the binding of drugs to plasma proteins from newborn and adult man. I. European Journal of Clinical Pharmacology 11: 463-467 (1977a).

Kurz, H.; Michels, H. and Stickel, H.H.: Differences in the binding of drugs to plasma proteins from newborn and adult man. II. European Journal of Clinical Pharmacology 11: 469-472 (1977b).

Kwan, K.C.; Breault, G.O.; Umbenhauer, E.R.; McMahon, F.G. and Duggan, D.E.: Kinetics of indomethacin absorption, elimination and enterohepatic circulation in man. Journal of Pharmacokinetics and Biopharmaceutics 4: 255-279 (1976).

Lang, D. and von Bernuth, G.: Serum concentration and serum half-life of digoxin in premature and mature newborns. Pediatrics 59: 902-906 (1977).

Latini, R.; Assael, B.M.; Bonati, M.; Caccamo, M.L.; Gerna, M.; Mandelli, M.; Marini, A.; Sereni, F. and Tognoni, G.: Kinetics and efficacy of theophylline in the treatment of apnea in the premature newborn. European Journal of Clinical Pharmacology 13: 203-207 (1978).

Leake, R.D. and Trygstad, C.W.: Glomerular filtration rate during the period of adaptation to extrauterine life. Pediatric Research 11: 959-962 (1977).

Lehmann, H.; Cook, J. and Ryan, E.: Pseudocholinesterase in early infancy. Proceedings of the Royal Society of Medicine 50: 147-150 (1957).

Lesko, L.J.: Dose-dependent elimination kinetics of theophylline. Clinical Pharmacokinetics 4: 449-459 (1979).

Levi, A.J.; Gatmaitan, Z. and Arias, I.M.: Deficiency of hepatic organic anion binding protein, impaired organic anion uptake by liver and physiologic jaundice in newborn monkeys. New England Journal of Medicine 283: 1136-1139 (1970).

Levy, A.M.; Leaman, D.M. and Hanson, J.S.: Effects of digoxin on systolic time intervals of neonates and infants. Circulation 46: 816-823 (1972).

Levy, G. and Garrettson, L.K.: Kinetics of salicylate elimination by newborn infants of mothers who ingested aspirin before delivery. Pediatrics 53: 201-210 (1974).

Levy, G.: Salicylate pharmacokinetics in the human neonate: in Morselli, Garattini and Sereni (Eds) Basic and Therapeutic Aspects of Perinatal Pharmacology, pp.319-330 (Raven Press, New York 1975).

Levy, G.; Khanna, N.N.; Soda, D.M.; Tsuzuki, O. and Stern, L.: Pharmacokinetics of acetaminophen in the human neonate: formation of acetaminophen glucuronide and sulfate in relation to plasma bilirubin concentration and D-glucaric acid excretion. Pediatrics 55: 818-825 (1975).

Litwack, G.; Ketterer, B. and Arias, I.M.: Ligandin: A hepatic protein which binds steroids, bilirubin, carcinogens and a number of exogenous organic anions. Nature 234: 446-467 (1971).

Lockman, L.A.; Kriel, R.; Zaske, D.; Thompson, T. and Virnig, N.: Phenobarbital dosage for control of neonatal seizures. Neurology 29: 1445-1449 (1979).

Loggie, J.M.H.; Kleinman, L.I. and Van Maanen, E.F.: Renal function and diuretic therapy in infants and children. I, II and III. Journal of Pediatrics 86: 485-496, 657-669, 825-832 (1975).

Long, S.S. and Swenson, R.M.: Development of anaerobic fecal flora in healthy newborn infants. Journal of Pediatrics 91: 298-301 (1977).

Lou, H.C.; Lassen, N.A. and Friis-Hansen, B.: Low cerebral blood flow in hypotensive perinatal distress. Acta Neurologica Scandinavica 56: 343-352 (1977).

Loughnan, P.M.; Sitar, D.S.; Ogilvie, R.I.; Eisen, A.; Fox, Z. and Neims, A.H.: Pharmacokinetic analysis of the disposition of intravenous theophylline in young children. Journal of Pediatrics 88: 874-879 (1976).

Loughnan, P.M.; Greenwald, A.; Purton, W.W.; Aranda, J.V.; Watters, G. and Neims, A.H.: Pharmacokinetic observations of phenytoin disposition in the newborn and young infant. Archives of Disease in Childhood 52: 302-309 (1977).

MacLean, W.C.; Klein, G.L.; Lopez de Romana, G.; Massa, E. and Graham, G.G.: Transient steatorrhea following episodes of mild diarrhea in early infancy. Journal of Pediatrics 92: 562-565 (1978).

Magno, R.; Berlin, A.; Karlsson, K. and Kjellmer, I.: Anesthesia for cesarean section IV: Placental transfer and neonatal elimination of bupivacaine following epidural analgesia for elective cesarean section. Acta Anaesthesiologica Scandinavica 20: 141-146 (1976a).

Magno, R.; Kjellmer, I. and Karlsson, K.: Anesthesia for cesarean section III: Effects of epidural analgesia on the respiratory adaptation of the newborn in elective cesarean section. Acta Anaesthesiologica Scandinavica 20: 73 (1976b).

Mandelli, M.; Morselli, P.L.; Nordio, S.; Pardi, G.; Principi, N.; Sereni, F. and Tognoni, G.: Placental transfer of diazepam and its disposition in the newborn. Clinical Pharmacology and Therapeutics 17: 564-572 (1975).

Mandelli, M.; Tognoni, G. and Garattini, S.: Clinical pharmacokinetics of diazepam. Clinical Pharmacokinetics 3: 72-91 (1978).

Marchal, F.; Bianchetti, G.; Monin, P.; Dubrucq, C.; Morselli, P.L.; Boutroy, M.J. and Vert, P.: Pharmacocinétique et effets pharmacodynamiques de l'indométhacine chez le nouveau-né. Symposium International de Néonatalogie, Narbonne, June 1979. INSERM. In press (1980).

Marget, W. and Wagner, M.: Orale Anwendung von Propicillin, Ampicillin und Dicloxacillin im Säuglingsalter. Medizinische Klinik 62: 300-305 (1967).

Marget, W.; Daschner, F. and Unert, L.K.: Investigations on pivampicillin treatment in newborns and infants. Infection 1: 41-45 (1973).

Marks, K.H.; Berman, W.; Friedman, Z.; Whitman, V.; Lee, C. and Maisels, M.J.: Furosemide in hyaline membrane disease. Pediatrics 62: 785-788 (1978).

Marks, M.I.: Common Bacterial Infections in Infancy and Childhood (ADIS Press, Sydney; MTP, Lancaster; University Park Press, Baltimore 1979).

Mather, L.E. and Cousins, M.J.: Local anaesthetics and their current clinical use. Drugs 18: 185-205 (1979).

Mather, L.E. and Meffin, P.J.: Clinical pharmacokinetics of pethidine. Clinical Pharmacokinetics 3: 352-368 (1978).

Mather, L.E. and Thomas, J.: Bupivacaine binding to plasma protein fractions. Journal of Pharmacy and Pharmacology 30: 653-654 (1974).

McCracken, G.H.: Pharmacological basis for antimicrobial therapy in newborn infants. American Journal of Diseases of Children 128: 407-419 (1974).

McCracken, G.H. and Kaplan, J.M.: Penicillin treatment for congenital syphilis: A critical reappraisal. Journal of the American Medical Association 228: 855-858 (1974).

McCracken, G.H. and Nelson, J.J.D.: In Oliver (Ed) Antimicrobial Therapy for Newborns. Monograph in Neonatology, pp.177 (Grune and Stratton, New York 1977).

McCracken, G.H.; Chrane, D.F. and Thomas, M.L.: Pharmacologic evaluation of gentamicin in newborn infants. Journal of Infectious Diseases 124 (Suppl.): S214-S223 (1971a).

McCracken, G.H.; West, N.R. and Horton, L.J.: Urinary excretion of gentamicin in the neonatal period. Journal of Infectious Diseases 123: 257-262 (1971b).

McCracken, G.H.; Ginsberg, C.; Chrane, D.F.; Thomas, M.L. and Horton, L.J.: Clinical pharmacology of penicillin in newborn infants. Journal of Pediatrics 82: 692-698 (1973).

McCracken, G.H.; Ginsburg, C.M.; Clahsen, J.C. and Thomas, M.L.: Pharmacologic evaluation of orally administered antibiotics in infants and children: Effect of feeding on bioavailability. Pediatrics 62: 738-743 (1978).

McDonald, M.S. and Emery, J.L.: The late intrauterine and postnatal development of human renal glomeruli. Journal of Anatomy 93: 331-340 (1959).

McGuinness, G.A.; Merkow, A.J.; Kennedy, R.L. and Erenberg, A.: Epidural anesthesia with bupivacaine for cesarean section: Neonatal blood levels and neurobehavioral responses. Anesthesiology 49: 270-273 (1978).

Meffin, P.; Long, G.J. and Thomas, J.: Clearance and metabolism of mepivacaine in the human neonate. Clinical Pharmacology and Therapeutics 14: 218-225 (1973).

Meissner, H.C. and Smith, A.L.: The current status of chloramphenicol. Pediatrics 64: 348-356 (1979).

Meyer, F.P.; Walther, H. and Quednow, B.: Zur bindung von Diphenylhydantoin und Phenobarbital an die Serumproteine beim Neugeborenen und Erwachsenen in therapeutisch relevanten Konzentrationen. Paediatrie und Grenzgebiete 16: 1-7 (1977).

Miceli, J.N.; Clay, B.; Fleischmann, L.E.; Sarnaik, A.P.; Aronow, R. and Done, A.K.: Pharmacokinetics of severe theophylline intoxication managed by peritoneal dialysis. Developmental Pharmacology and Therapeutics 1: 16-25 (1980).

Mihaly, G.W.; Moore, R.G.; Thomas, J.; Triggs, E.J.; Thomas, D. and Shanks, C.A.: The pharmacokinetics and metabolism of the anilide local anaesthetics in neonates. I. Lignocaine. European Journal of Clinical Pharmacology 13: 143-152 (1978).

Miller, R.P.; Roberts, R.J. and Fischer, L.J.: Acetaminophen elimination in neonates, children and adults. Clinical Pharmacology and Therapeutics 19: 284-294 (1976).

Mirkin, B.L.: Diphenylhydantoin: Placental transport, fetal localization, neonatal metabolism, and possible teratogenic effects. Journal of Pediatrics 78: 329-337 (1971).

Monin, P.; Sanjuan, M.; Vibert, M.; Rovei, V.: Influence de l'alcalose gazeuse hypocapnique sur le taux plasmatique de phenobarbitol chez le porcelet nouveau-ne. Proceedings 2eme colloque International de Pharmacologie perinatale - Narbonne May 31, 1979. INSERM. In press (1980).

Moore, R.G.; Thomas, J.; Triggs, E.J.; Thomas, D.B.; Burnard, E.D. and Shanks, C.A.: The pharmacokinetics and metabolism of the anilide local anesthetics in neonates. III. Mepivacaine. European Journal of Clinical Pharmacology 14: 203-212 (1978).

Morgan, D.J.; Cousins, M.J.; McQuillan, D. and Thomas, J.: Disposition and placental transfer of etidocaine in pregnancy. European Journal of Clinical Pharmacology 12: 359-365 (1977).

Morgan, D.J.; McQuillan, D. and Thomas, J.: Pharmacokinetics and metabolism of the anilide local anaesthetics in neonates. II. Etidocaine. European Journal of Clinical Pharmacology 13: 365-371 (1978).

Morrison, J.C.; Whybrew, W.D.; Rosser, S.L.; Bucovaz, E.T.; Wiser, W.L. and Fish, S.A.: Metabolites of meperidine in the fetal and maternal serum. American Journal of Obstetrics and Gynecology 126: 997-1002 (1976).

Morselli, P.L.: Clinical pharmacokinetics in neonates. Clinical Pharmacokinetics 1: 81-98 (1976a).

Morselli, P.L.: Pediatric clinical pharmacology: Routine monitoring or clinical trials?; in Gouveia, Tognoni and Van Der Kleijn (Eds) Clinical Pharmacy and Clinical Pharmacology, pp.277-287 (Elsevier North Holland, Amsterdam 1976b).

Morselli, P.L.: Clinetique de distribution des médicaments chez le nouveau-ne et l'enfant normal et patholigique. INSERM 73: 92-128 (1977a).

Morselli, P.L.: Pharmacokinetics of antiepileptic drugs during development; in Gardner-Thorpe, Janz, Meinardi and Pippenger (Eds) Antiepileptic Drug Monitoring, pp.57-68 (Pitman Medical, England 1977b).

Morselli, P.L.: Drug Disposition during Development (Spectrum, New York 1977c).

Morselli, P.L.: Problems of drugs administration in the neonatal period; in Duchene-Marullaz (Ed) Advances in Pharmacology and Therapeutics, Vol. 6, Clinical Pharmacology, pp.57-66 (Pergamon, Oxford and New York 1978a).

Morselli, P.L.: Problems of antiepileptic drugs administration in the neonatal period; in Barneepilepsi, Johaunessen and Munthe-Kass (Eds) pp.173-192 (Ciba Geigy, Oslo 1978b).

Morselli, P.L. and Baruzzi, A.: Serum levels and pharmacokinetics of anticonvulsants in the management of seizure disorders; in Mirkin (Ed) Clinical Pharmacology, pp.89-106 (Year Book Medical Publishers, Chicago and London 1978).

Morselli, P.L. and Bianchetti, G.: Cardiovascular drugs, in Morselli (Ed) Drug Disposition During Development, pp.393-429 (Spectrum, New York 1977).

Morselli, P.L. and Olive, G.: Pharmacokinetics and metabolism of drugs in the neonatal period; in Siest and Young (Eds) Drug Measurement and Drug Effects in Laboratory Health Science. th Int. Coll. Prospective Biology, Pont-a-Mousson 1978, pp.61-75 (Karger, Basel 1980).

Morselli, P.L. and Rovei, V.: Pharmacokinetics of pethidine and norpethidine in the newborn. European Journal of Clinical Pharmacology. In press (1980).

Morselli, P.L.; Principi, N.; Tognoni, G.; Reali, E.; Belvedere, G.; Standen, S.M. and Sereni, F.: Diazepam elimination in premature and full term infants, and children. Journal of Perinatal Medicine 1: 133-141 (1973).

Morselli, P.L.; Mandelli, M.; Tognoni, G.; Principi, N.; Pardi, G. and Sereni, F.: Drug interactions in the human fetus and in the newborn infant; in Morselli, Garattini and Sereni (Eds) Drug Interactions, pp.259-270 (Raven Press, New York 1974).

Morselli, P.L.; Assael, B.M.; Gomeni, R.; Mandelli, M.; Marini, A.; Reali, E.; Visconti, U. and Sereni, F.: Digoxin pharmacokinetics during human development; in Morselli, Garattini and Sereni (Eds) Basic and Therapeutic Aspects of Perinatal Pharmacology, pp.377-392 (Raven Press, New York 1975).

Morselli, P.L.; Vibert, M.; Monin, P.; André, M.; Sanjuan, M. and Rovei, V.: Surveillance du taux plasmatique du phenobarbital chez le nouveau-né. Proceedings 2ème Colloque International de Pharmacologie Périnatale. INSERM, Narbonne May 1979. In press (1980).

Mulley, B.A.; Parr, G.D.; Pau, W.K.; Rye, R.M.; Mould, J.J. and Siddle, N.C.: Placental transfer of chlorthalidone and its elimination in maternal milk. European Journal of Clinical Pharmacology 13: 129-131 (1978).

Murphy, G.M. and Singer, E.: Bile acid metabolism in infants and children. Gut 15: 151-163 (1974).

Nation, R.L.: Drug kiretics in childbirth. Clinical Pharmacokinetics 5: 340-364 (1980).

Neese, A.L. and Soyka, L.F.: Development of a radioimmunoassay for theophylline. Application to studies in premature infants. Clinical Pharmacology and Therapeutics 21: 633-641 (1977).

Neims, A.H. and Manchester, D.K.: Drug disposition in the developing human; in Mirkin (Ed) Clinical Pharmacology and Therapeutics. A Pediatric Perspective, pp.35-48 (Year Book Medical Publishers, Chicago and London 1978).

Nelson, J.A. and Haltalin, K.C.: Amoxycillin less effective than ampicillin against Shigella *in vitro* and *in vivo*. Journal of Infectious Diseases 129: 222 (1974).

Nelson, J.D.; Kusmiesz, H.; Shelton, B.S. and Woodman, E.: Clinical pharmacology and efficacy of ticarcillin in infants and children. Pediatrics 61: 858-863 (1978).

Neutze, J.M.; Rutherford, J.D. and Hurley, P.J.: Serum digoxin levels in neonates, infants and children with heart diseases. New Zealand Medical Journal 86: 7-10 (1977).

Niebyl, J.R.; Blake, D.A.; Freeman, J.M. and Luff, R.P.: Carbamazepine levels in pregnancy and lactation. Obstetrics and Gynecology 53: 139-140 (1979).

Nyberg, L. and Wettrell, G.: Digoxin dosage schedules for neonates and infants, based on pharmacokinetic considerations. Clinical Pharmacokinetics 3: 453-461 (1978).

Odell, G.B.: Influence of binding on the toxicity of bilirubin. Annals of the New York Academy of Sciences 226: 225-237 (1973).

Ogilvie, R.I.: Clinical pharmacokinetics of theophylline. Clinical Pharmacokinetics 3: 267-293 (1978).

Øie, S. and Levy, G.: Interindividual differences in the effect of drugs on bilirubin plasma binding in newborn infants and in adults. Clin. Pharmacol. Therapeut. 21: 627-632 (1977).

Osfeld, E.; Rubinstein, E.; Gazit, E. and Smetana, Z.: Effect of systemic antibiotics on the microbial flora of the external ear canal in hospitalized children. Pediatrics 60: 364-366 (1977).

Ostheimer, G.W.: Neurobehavioural effects of obstetric analgesia. British Journal of Anaesthesia 51: 355-405 (1979).

Painter, M.J.; Pippenger, C.; MacDonald, H. and Pitlick, W.: Phenobarbital and diphenylhydantoin levels in neonates with seizures. Journal of Pediatrics 92: 315-319 (1978).

Paisley, J.W.; Smith, A.L. and Smith, D.H.: Gentamicin in newborn infants. Comparison of intramuscular and intravenous administration. American Journal of Diseases of Children 126: 473-477 (1973).

Payne, W.W.: Biochemical adaptations at birth; in Davis and Dobbing (Eds) Scientific Foundations of Pediatrics, pp.86-94 (Heinemann, London 1974).

Pechere, J.C. and Dugal, R.: Clinical pharmacokinetics of aminoglycoside antibiotics. Clinical Pharmacokinetics 4: 170-199 (1979).

Pedersen-Bjergaard, L. and Petersen, E.K.: Oral absorption of pivampicillin and ampicillin in young children: Cross-over study using equimolar doses of a suspension. Clinical Pharmacokinetics 2: 451-456 (1977).

Pickering, L.K.; O'Connor, D.M.; Anderson, D.; Bairan, A.C.; Feigin, R.D. and Cherry, J.D.: Comparative evaluation of cefazolin and cephalothin in children. Journal of Pediatrics 85: 842-847 (1974).

Pinsky, W.W.; Jacobsen, J.R.; Gillette, P.C.; Adams, J.; Monroe, L. and McNamara, D.G.: Dosage of digoxin in premature infants. Journal of Pediatrics 94: 639-642 (1979).

Pitlick, W.; Painter, M. and Pippenger, C.: Phenobarbital pharmacokinetics in neonates. Clinical Pharmacology and Therapeutics 23: 346-350 (1978).

Plantier, J.; Forrey, A.W.; O'Neill, M.A.; Christopher, T.G. and Cutler, R.E.: Pharmacokinetics of amikacin in patients with normal or impaired renal function: Radioenzymatic acetylation assay. Journal of Infectious Disease 134: 5323-5330 (1976).

Plasse, J.C.; Revol, M.; Chabert, G. and Ducerf, F.: Neonatal pharmacokinetics of valproic acid; in Schaaf and Van Der Kleijn (Eds) Progress in Clinical Pharmacy, pp.247-252 (Elsevier North Holland, Amsterdam 1979).

Pynnönen, S.; Kanto, J.; Sillanpää, M. and Erkkola, R.: Carbamazepine: Placental transport, tissue concentrations in foetus and newborn, and level in milk. Acta Pharmacologica et Toxicologica 41: 244-253 (1977a).

Pynnönen, S.; Sillanpää, M.; Frey, H. and Iisalo, E.: Carbamazepine and its 10, 11-epoxide in children and adults with epilepsy. European Journal of Clinical Pharmacology 11: 129-133 (1977b).

Rane, A.: Urinary excretion of diphenylhydantoin metabolites in newborn infants. Journal of Pediatrics 85: 543-545 (1974).

Rane, A. and Wilson, J.T.: Clinical pharmacokinetics in infants and children. Clinical Pharmacokinetics 1: 2-24 (1976).

Rane, A.; Garle, M.; Borga, O. and Sjöqvist, F.: Plasma disappearance of transplacentally transferred diphenylhydantoin in the newborn studied by mass fragmentography. Clinical Pharmacology and Therapeutics 15: 39-45 (1974).

Rane, A.; Bertilsson, L. and Palmér, L.: Disposition of placentally transferred carbamazepine (Tegretol) in the newborn. European Journal of Clinical Pharmacology 8: 283-284 (1975).

Rane, A.; Hoppel, C. and Höjer, B.: Kinetics of placentally transferred phenytoin and its p-hydroxylated metabolites in newborn infants. British Journal of Clinical Pharmacology 8: 465-468 (1979).

Rasmussen, L.F.; Ahlfors, C.E. and Wennberg, R.P.: Displacement of bilirubin from albumin by indomethacin. Journal of Clinical Pharmacology 18: 477-481 (1978).

Reidenberg, M.M.; James, M. and Dring, L.G.: The rate of procaine hydrolysis in serum of normal subjects and diseased patients. Clinical Pharmacology and Therapeutics 13: 279-284 (1972).

Rey, E.; d'Athis, P.; de Lauture, D.; Dulac, O.; Aicardi, J. and Olive, G.: Pharmacokinetics of carbamazepine in the neonate and in the child. International Journal of Clinical Pharmacology and Biopharmacy 17: 90-96 (1979).

Reynolds, F. and Taylor, G.: Maternal and neonatal blood concentrations of bupivacaine. A comparison with lignocaine during continuous extradural analgesia. Anaesthesia 25: 14-23 (1970).

Reynolds, J.W. and Mirkin, B.L.: Urinary corticosteroid and diphenylhydantoin metabolite patterns in neonates exposed to anticonvulsant drugs in utero. Clinical Pharmacology and Therapeutics 14: 891-897 (1973).

Rolewicz, T.F.; Mirkin, B.L.; Cooper, M.J. and Anders, M.W.: Metabolic disposition of cephalotin and deacetylcephalotin in children and adults: Comparison of high-performance liquid chromatographic and microbial assay procedures. Clinical Pharmacology and Therapeutics 22: 928-935 (1977).

Rosen, J.P.; Danish, M.; Ragni, M.C.; Lopez Saccar, C.; Yaffe, S.J. and Lecks, H.I.: Theophylline pharmacokinetics in the young infant. Pediatrics 64: 248-251 (1979).

Ross, B.S.; Pollak, A. and Oh, W.: The pharmacologic effects of furosemide therapy in the low-birth-weight infant. Journal of Pediatrics 92: 149-152 (1978).

Rossi, L.N.; Nino, L.M. and Principi, N.: Correlation between age and plasma level/dosage ratio for phenobarbital in infants and children. Acta Paediatrica Scandinavica 68: 431-434 (1979).

Rumack, B.E.: Aspirin and acetaminophen. Pediatrics 62 (Suppl.): 867-946 (1978).

Sardemann, H.; Colding, H.; Hendel, J.; Kampmann, J.P.; Hvidberg, E.F. and Vejlsgaard, R.: Kinetics and dose calculations of amikacin in the newborn. Clinical Pharmacology and Therapeutics 20: 59-66 (1976).

Scanlon, J.W.; Ostheimer, G.W.; Lurie, A.O.; Brow, W.V.; Weiss, J.B. and Alper, M.H.: Neurobehavioral responses and drug concentrations in newborns after maternal epidural anesthesia with bupivacaine. Anesthesiology 45: 400-405 (1976).

Scheline, R.R.: Drug metabolism by intestinal microorganism. Journal of Pharmaceutical Sciences 57: 2021-2028 (1968).

Schentag, J.J. and Jusko, W.J.: Renal clearance and tissue accumulation of gentamicin. Clinical Pharmacology and Therapeutics 22: 364-370 (1977).

Schwartz, G.J.; Hegyi, T. and Spitzer, A.: Subtherapeutic dicloxacillin levels in a neonate. Possible mechanisms. Journal of Pediatrics 89: 310 (1976).

Selvig, K.; Lingaas Holmen, T.; Aas, K.; Rugstad, H.E. and Bjerve, K.S.: Serum concentrations of theophylline in children following the administration of doses generally recommended: New dosage regimen required. Acta Paediatrica Scandinavica 68: 435-439 (1979).

Sereni, F.; Mandelli, M.; Principi, N.; Tognoni, G.; Pardi, G. and Morselli, P.L.: Induction of drug metabolizing enzyme activities in the human fetus and in the newborn infant. Enzyme 15: 318-329 (1973a).

Sereni, F.; Morselli, P.L. and Pardi, G.: Postnatal development of drug metabolism in human infants; in Bossart, Cruz, Huber, Prod'Hom and Sistek (Eds) Perinatal Medicine, pp.63-77 (Huber, Bern 1973b).

Sereni, F. and Principi, N.: Developmental pharmacology. Annual Review of Pharmacology 8: 453-466 (1968).

Settergren, G.; Lindblad, B.S. and Persson, H.B.: Cerebral blood

flow and exchange of oxygen, glucose, ketone bodies, lactate, pyruvate and aminoacids in infants. Acta Paediatrica Scandinavica 65: 343-353 (1976).

Shankaran, S. and Poland, R.L.: The displacement of bilirubin from albumin by furosemide. Journal of Pediatrics 90: 642-646 (1977).

Shinebourne, E.A.: Growth and development of the cardiovascular system. Functional development: in Davis and Dobbing (Eds) Scientific Foundations of Pediatrics, pp.198-213 (Heinemann, London 1974).

Shirkey, H.C.: Paediatric clinical pharmacology and therapeutics: in Avery (Ed) Drug Treatment, 2nd ed, p.100 (ADIS Press, Sydney and New York: Churchill Livingstone, Edinburgh 1980).

Siegel, S.R. and Oh, W.: Renal function as a marker of human fetal maturation. Acta Paediatrica Scandinavica 65: 481-492 (1976).

Simon, C.; Nehls, R.; Malerczyk, W.; Toeller, W.; Zierott, G. and Lehmann, K.: Pivampicillin, ein neues Ampicillin — derivat. Deutsche Medizinische Wochenschrift 99: 137-141 (1974).

Simon, H.J. and Axline, S.G.: Clinical pharmacology of kanamycin in premature infants. Annals of the New York Academy of Sciences 132: 1020-1025 (1966).

Simons, F.E.R. and Simons, K.J.: Pharmacokinetics of theophylline in infancy. Journal of Clinical Pharmacology 18: 472-476 (1978).

Smith, C.A.: The Physiology of the Newborn Infant, 2nd ed., pp.180-198 (Thomas, Springfield 1951).

Sondheimer, J.M. and Hamilton, J.R.: Intestinal function in infants with severe congenital heart disease. Journal of Pediatrics 92: 572-578 (1978).

Speer, M.E.; Taber, L.H.; Clarck, D.B. and Rudolph, A.J.: Cerebrospinal fluid levels of benzathine penicillin G in the neonate. Journal of Pediatrics 92: 996-997 (1977).

Stern, L.: Drug interaction. Pt. II. Drugs, the newborn infant and the binding of bilirubin to albumin. Pediatrics 49: 916-918 (1972).

ihrland, L.G. and Weisberger, A.S.: Chloramphenicol toxicity in liver and renal disease. Archives of Internal Medicine 112: 747-752 (1963).

Szefler, S.J.; Koup, J.R. and Giacoia, G.P.: Paradoxical behavior of serum digoxin concentrations in an anuric neonate. Journal of Pediatrics 91: 487-489 (1977).

Szeto, H.H.; Zervoudakis, I.A.; Cederqvist, L.L. and Inturrisi, C.E.: Amniotic fluid transfer of meperidine from maternal plasma in early pregnancy. Obstetrics and Gynecology 52: 59-62 (1978).

Talafre, M.L.; Rovei, V.; Barrier, G.; Lassner, J.; Sanjuan, M.; Morselli, P.L. and Sureau, C.: Pharmacocinétique de la péthidine chez le nouveau-né et la mère pendant le travail. Proceedings 2ème Colloque International de Pharmacologie Périnatale, Narbonne May 1979. INSERM. In press (1980).

Thomas, J.; Long, G.; Moore, G. and Morgan, D.: Plasma protein binding and placental transfer of bupivacaine. Clinical Pharmacology and Therapeutics 19: 426-434 (1976).

Tognoni, G.: Antibiotics: in Morselli (Ed) Drug Disposition During Development, pp.123-217 (Spectrum, New York 1977).

Tomson, G.; Lunell, N.O.; Sundwall, A. and Rane, A.: Placental passage of oxazepam and its metabolism in mother and newborn. Clinical Pharmacology and Therapeutics 25: 74-81 (1979).

Traeger, A.; Noschel, H. and Zaumseil, J.: Zur Pharmakokinetik von Indomethazin bei Schwangeren, Kreissenden und deren Neugeborenen. Zentralblatt fur Gynäkologie 95: 635-641 (1973).

Tucker, G.T.: Plasma binding and disposition of local anesthetics. International Anesthesiology Clinics 13: 33-59 (1975).

Tucker, G.T. and Mather, L.E.: Pharmacokinetics of local anaesthetic agents. British Journal of Anaesthesia 47: 213-224 (1975).

Tucker, G.T. and Mather, L.E.: Clinical pharmacokinetics of local anesthetics. Clinical Pharmacokinetics 4: 241-278 (1979).

Tyrala, E.E.; Hillman, L.S.; Hillman, R.E. and Dodson, W.E.: Clinical pharmacology of hexachlorophene in newborn infants. Journal of Pediatrics 91: 481-486 (1977).

Vert, P.; André, M. and Deblay, M.F.: Infants of epileptic mothers: in Stern (Ed) Intensive Care in the Newborn, II, pp.347-360 (1979).

Vert, P.; Legagneur, M.; Broquaire, M. and Morselli, P.L.: Pharmacocinétique du furosemide chez le nouveau-né. Proceedings 2ème Colloque International de Pharmacologie Périnatale, Narbonne May 31 1979. INSERM. In press (1980a).

Vert, P.; Marchal, F.; Bianchetti, G.; Monin, P.; Morselli, P.L.: Pharmacokinetics of indomethacin after intravenous and enteral administration in the premature infant. European Journal of Clinical Pharmacology. In press (1980b).

Vogelstein, B.; Kowarski, A.A. and Leitman, R.S.: The pharmacokinetics of amikacin in children. Journal of Pediatrics 91: 333-339 (1977).

Volpe, J.J.: Cerebral blood flow in the newborn infant: Relation to hypoxic-ischemic brain injury and periventricular hemorrhage. Journal of Pediatrics 94: 170-173 (1979).

Wallace, S.: Altered plasma albumin in the newborn infant. British Journal of Clinical Pharmacology 4: 82-85 (1977).

Wallin, A.; Jalling, B. and Boréus, L.O.: Plasma concentrations of phenobarbital in the neonate during prophylaxis for neonatal hyperbilirubinemia. Journal of Pediatrics 85: 392-397 (1974).

Watkins, J.B.; Ingall, D.; Szczepanik, P.; Klein, P.D. and Lester, R.: Bile salt metabolism in the newborn. Measurement of pool size and synthesis by stable isotope technique. New England Journal of Medicine 288: 431-434 (1973).

Weber, W.W. and Cohen, S.N.: Aging effects and drugs in man: in Gillette and Mitchell (Eds) Concepts in Biochemical Pharmacology, Vol. 28, pp.213-233 (Springer, Berlin 1975).

Weinberger, M. and Ginchansky, E.: Dose-dependent kinetics of theophylline disposition in asthmatic children. Journal of

Pediatrics 91: 820-824 (1977).

Weinberger, M. and Hendeles, L.: Role of dialysis in the management and prevention of theophylline toxicity. Developmental Pharmacology and Therapeutics 1: 26-30 (1980).

Weiner, I.W. and Stambaugh, J.E.: GLC determination of meperidine and normeperidinic acid in urine. Journal of Pharmaceutical Sciences 116: 117 (1978).

Weingärtner, L.; Sitka, U.; Patsch, R. and Richter, I.: Experience with amoxycillin in neonates and premature babies. International Journal of Clinical Pharmacology 15: 184-188 (1977).

Weiss, C.F.; Glazko, A.J. and Westein, J.K.: Chloramphenicol in the newborn infant: a physiologic explanation of its toxicity when given in excessive doses. New England Journal of Medicine 262: 787-794 (1960).

Welling, P.G.; Elliott, R.L.; Pitterle, M.E.; Corrick-West, H.P. and Lyons, L.L.: Plasma levels following single and repeated doses of erythromycin estolate and erythromycin stearate. Journal of Pharmaceutical Sciences 68: 150-155 (1979).

Wells, D.H. and Ferlauto, J.J.: Survival after massive aminophylline overdose in a premature infant. Pediatrics 64: 252-253 (1979).

Wennberg, R.P.; Rasmussen, L.F. and Ahlfors, C.E.: Displacement of bilirubin from normal albumin by three diuretics. Journal of Pediatrics 90: 647-650 (1977).

West, J.R.; Smith, H.W. and Chasis, H.: Glomerular filtration rate, effective renal blood flow and maximal tubular excretory capacity in infancy. Journal of Pediatrics 32: 10-18 (1948).

Wettrell, G.: Distribution and elimination of digoxin in infants. European Journal of Clinical Pharmacology 11: 329-335 (1977).

Wettrell, G. and Andersson, K.E.: Absorption of digoxin in infants. European Journal of Clinical Pharmacology 9: 49-55 (1975).

Wettrell, G. and Andersson, K.E.: Clinical pharmacokinetics of digoxin in infants. Clinical Pharmacokinetics 2: 17-31 (1977).

Widdowson, E.M.: Changes in body proportions and composition during growth; in Scientific Foundations of Pediatrics, p.153 (Heinemann, London 1974).

Wilson, H.D. and Haltalin, K.C.: Ampicillin in haemophilus influenzae meningitis. American Journal of Diseases of Children 129: 208-215 (1975).

Windorfer, A.; Kuenzer, W. and Urbanek, R.: The influence of age on the activity of acetylsalicylic acid-esterase and protein salicylate binding. European Journal of Clinical Pharmacology 7: 227-231 (1974).

Windorfer, A. and Pringsheim, W.: Studies on the concentrations of chloramphenicol in the serum and cerebrospinal fluid of neonates, infants, and small children. Reciprocal reactions between chloramphenicol, penicillin and phenobarbitone. European Journal of Pediatrics 124: 129-138 (1977).

Woo, W.C.R.; Dupont, C.; Collinge, J. and Aranda, J.V.: Effects of furosemide in the newborn. Clinical Pharmacology and Therapeutics 23: 266-271 (1978).

Yaffe, S.J.; Gorodischer, R. and Jusko, W.J.: Digoxin disposition (tissue distribution and renal clearance) in infants; in Gouveia, Tognoni and Van Der Kleijn (Eds) Clinical Pharmacy and Clinical Pharmacology, pp.289-294 (Elsevier North Holland, Amsterdam 1976).

Yaffe, S.J. and Juchau, M.R.: Perinatal pharmacology. Annual Review of Pharmacology 14: 219-238 (1974).

Yaffe, S.J. and Stern, L.: Clinical implications of perinatal pharmacology; in Mirkin (Ed) Perinatal Pharmacology and Therapeutics, pp.355-427 (Academic Press, New York, San Francisco and London 1976).

Yakatan, G.J.; Smith, R.B.; Leff, R.D. and Kay, J.L.: Pharmacokinetic considerations in exchange transfusion in neonates. Clinical Pharmacology and Therapeutics 24: 90-94 (1978).

Yoshioka, H.; Takimoto, M.; Matsuda, I. and Hattori, S.: Dosage schedule of gentamicin for chronic renal insufficiency in children. Archives of Disease in Childhood 53: 334-337 (1978).

Yow, M.D.: An overview of pediatric experience with amikacin. American Journal of Medicine 63: 167-171 (1977).

Zoppi, G.; Zamboni, G.; Siviero, M.; Bellini, P. and Lanzoni Cancellieri, M.: γ-globulin level and dietary protein intake during the first year of life. Pediatrics 62: 1010-1018 (1978).

Zsigmond, E.K. and Downs, J.R.: Plasma cholinesterase activity in newborns and infants. Canadian Anaesthesists' Society Journal 18: 278-285 (1971).

Author's address: Dr *Paolo L. Morselli*, Department of Clinical Research, Synthelabo-LERS, 58 Rue de la Glasière, *75013 Paris* (France).