BRIEF COMMUNICATION

TOPICAL BIOAVAILABILITY OF METHYL SALICYLATE

Drugs are generally applied to the skin for their anticipated local action. In more recent years, there has been some interest in the topical delivery of drugs in order to achieve a systemic effect. Two drugs applied topically for a systemic effect are nitroglycerin for the management of congestive heart failure[1] and hyoscine for motion sickness.[2] The skin is readily accessible for the application and removal of medicaments. In drug treatment of chronic diseases, the skin is an ideal delivery system from the compliance aspect as delivery is unattended, controlled, non-invasive and prolonged.[2]

Methyl salicylate is widely used in a number of commercial liniments and ointments for the relief of minor muscular aches and pains. Although some studies have shown that methyl salicylate is absorbed from topical products[3,4] and is rapidly hydrolysed to salicylic acid in the body[5], limited information is available on the rate and extent of absorption of salicylate from commercial products. The present study was initiated to determine (1) the likely plasma salicylate levels resulting from the topical application of commercial products containing methyl salicylate and (2) to ascertain whether the plasma salicylate levels required to manage rheumatoid arthritis could be achieved by the topical route of administration. Since only limited information is available about the differences in skin permeability of different parts of the body, the topical availability of methyl salicylate from the abdomen, forearm, instep, heel and plantar region was also evaluated.

The products evaluated in this study were Deep Heat (Mentholatum, Richmond, Victoria), Dencorub (Carter Wallace, Brookvale, NSW), Metsal (Riker, Sydney), Thermorub (Fisons, Sydney) and Methyl Salicylate Ointment B.P.C. These products contain 12·8, 12, 25, 25 and 50% methyl salicylate respectively. Thermorub also contains 5% glycol salicylate. In the evaluation of methyl salicylate bioavailability from these products, 5 g of each product was applied to the forearm (area 50 cm^2) of five subjects in a Latin Square design in the following manner. A small portion of the product was rubbed into the area and the remaining product then spread evenly over this site. This site was covered with a sheet of aluminium foil, greaseproof paper (70 cm^2) and finally with elastoplast^R. Care was taken not to spread the ointment. The product was left in place for 10 hours and then removed with soap and warm water. No salicylate preparations were taken or applied for 72 hours before or after the application of the ointment. An interval of at least one week existed between each study. One product (Metsal) was applied to different skin sites in four subjects. The protocol for application was the same as described earlier for the forearm with the abdomen, instep, heel and plantar region being the other sites investigated.

The rate and extent of methyl salicylate absorption was estimated from the excretion of total urinary salicylate. The bladder was voided immediately before the application of the ointment and a sample retained for analysis. All urine was collected at 6, 8, 10, 12 and up to 48 hours after application of the ointment. The volumes of urine collected during each time interval were recorded and specimens corresponding to these intervals were stored at −20° prior to analysis. Total urinary salicylate was estimated by the method of Page *et al.*[6] and skin permeability coefficients estimated by a pharmacokinetic evaluation of urinary data.[7] From the permeability coefficient (k_p), an estimate of the steady-state plasma salicylate concentration (C_{ss}) likely to be achieved from a

TABLE 1

Skin permeability coefficients (k_p) for methyl salicylate, fraction of salicylate absorbed from each product (F) after application to the forearm (50 cm^2) for 10 h and the estimated steady-state salicylate concentrations (C_{ss}) arising from continuous topical absorption of methyl salicylate.

Product	Methyl salicylate (%)	k_p (cm/h)	F	C_{ss} (mg/l)
Metsal	25	1·9±0·5*	0·17±0·04*	7·2†
Thermorub	25	1·5±0·5	0·18±0·08	6·8
Dencorub	12	1·5±0·7	0·17±0·09	2·7
Deep Heat	12·8	1·3±0·6	0·20±0·14	2·5
Ung. Methyl Sal. B.P.C.	50	1·0±0·4	0·12±0·05	7·6

* mean ± S.D.
† based on a mean salicylate clearance of 3 l/h.[9,10]

continuous application of product to skin area (A) was determined using Equation 1.

$$c_{ss} = \frac{k_p.A.C}{Cl} \qquad (1)$$

where C is the concentration of methyl salicylate in the product (expressed as equivalent salicylate) and Cl is the total body clearance of salicylate.

Table 1 shows the mean permeability coefficients, percentage of methyl salicylate absorbed and estimated steady-state salicylate concentrations. Similar skin permeability coefficients were observed for each of the products evaluated. Only about 12 to 20% of the amount of salicylate applied to the skin is absorbed into the systemic circulation after 10 hours of application. All subjects experienced pain and redness at the site of application for all products. The steady-state salicylate plasma concentrations estimated from the permeability coefficients obtained in this study are extremely low (Table 1) and, even with increases in application area or amount applied, unlikely to result in any real systemic effect. Plasma salicylate concentrations of 150 to 300 μg/ml (1 to 2 μmol/l) are usually required to manage rheumatoid arthritis.[8, 10] As all salicylate penetrating the skin would be removed by the cutaneous blood supply, it is also unlikely that clinically significant amounts of salicylate would be found in joints to which methyl salicylate had been topically applied.

Figure 1 shows urinary salicylate time profiles obtained for subject WF after application of the product Metsal to different areas of the body. The skin permeability coefficient for methyl salicylate and percentage of salicylate absorbed from this product applied to different areas of the body were in the rank order-abdomen > forearm > instep > heel > plantar for all subjects. All subjects also reported that the extent of pain associated with application of these products to these different sites followed this same rank order. The slower absorption from the regions of the foot relative to the forearm and abdomen may reflect the fewer hair follicles in this region and a thicker stratum corneum. As limited information is available

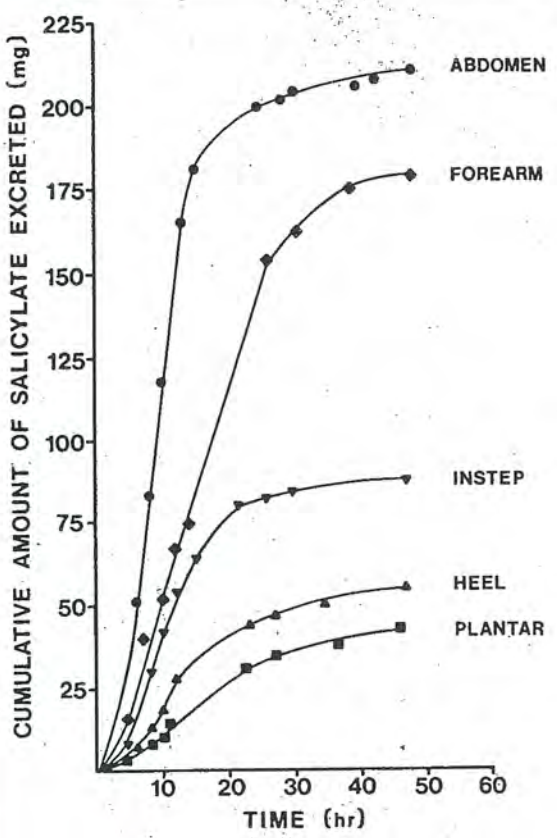

FIGURE 1. Cumulative urinary salicylate recovery showing influence of skin site on percutaneous absorption rate of methyl salicylate from 5 g Metsal applied to a 50 cm² area for 10 hours.

about the *in vivo* permeability coefficients of drugs from different application sites on the body[11], this rank order for methyl salicylate absorption may be relevant in optimising the topical bioavailability of other medicaments being administered for a systemic effect.

The present study shows that low plasma salicylate concentrations are likely to be achieved from the topical application of commercially available products containing methyl salicylate. The usefulness of these products in drug therapy is therefore mainly limited to their local effects. In designing topical dosage forms for systemic effects it would appear to be desirable to use medicaments with reasonable skin permeability coefficients and which require relatively low plasma concentrations for their therapeutic efficacy. Although methyl salicylate does not fulfil these criteria, it is likely that drugs other than nitroglycerin and hyoscine will also be

shown to exert a desirable systemic effect when administered by topical application.

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LETTER TO THE EDITOR

CHEMICAL LEACHING FROM TERUMO SYRINGE SEALS

Sir,

Petersen, Vine, Ashley and Nation[1] reported that the black rubber seals on the plungers of Monoject (Sherwood) and Terumo (Terumo) syringes may release 2-(2-hydroxyethyl-mercapto) benzothiazole (HMBT). HMBT is thought to be a reaction product of the rubber vulcanizer, 2-mercaptobenzothiazole (MBT) and ethylene oxide (ETO) which is used to sterilise the syringes.[2]

The National Biological Standards Laboratory examined the problem of leaching from the seals of Terumo syringes by measuring if the seals, or extracts thereof, released substances which affected cultured mammalian cells. Terumo supplied seals for testing which had been subject to the experimental treatments outlined in the Table.

Two cell culture methods were used, an agarose overlay method and an endpoint titration method. The agarose overlay method was similar to that of Guess, Rosenbluth, Schmidt and Autian.[3] A sterile 1 cm disc cut from the seal was placed on a layer of medium solidified with agarose covering a monolayer of

TABLE 1

Experimental treatments, and *in vitro* cytotoxicity, of rubber seals used in Terumo syringes. Sample 6 differed from samples 1–5 in that its formulation did not include MBT. The number of samples tested is shown in brackets

	Sample					
	1	2	3	4	5	6
Sequential treatment						
Wash*		+	+	+	+	+
Ethylene oxide†			+	+	+	+
Wash*				+	+	
Ethylene oxide†					+	
In vitro cytotoxicity						
Overlay method (average diameter, in cm, of dead cell zone)	3·5 (4)	3·5 (2)	2·3 (4)	2·2 (4)	1·9 (4)	non-toxic (4)
Titration method (% concentration of extract first producing toxicity)	10–30 (2)	10–30 (2)	70 (2)	60–80 (2)	90–100 (2)	non-toxic (1)

*rubber seals washed 10 minutes in water containing detergent (40°C), followed by three 5 minute cycles in water (40°C) and then tumble dried.
†rubber seals sterilised with ethylene oxide for 3 hours.