Amethocaine gel for percutaneous local anaesthesia

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Amethocaine gel is a recently developed formulation of amethocaine, designed to provide percutaneous local anaesthesia. Its pharmacological characteristics coupled with a phase-change gel formulation may confer therapeutic advantages over existing preparations. Percutaneous local anaesthesia has increasing relevance in analgesia for paediatric procedures and superficial surgical operations.

In this article, the place of amethocaine (Ametop, Smith & Nephew, Hull) as a gel formulation in the provision of percutaneous anaesthesia is considered. The pharmacological characteristics and mechanism of action are reviewed along with studies of clinical efficacy, toxicity and safety. We will also cover the use of amethocaine gel in different clinical settings such as venepuncture in children and minor surgical procedures.

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RELEVANT ANATOMY

In order to achieve percutaneous analgesia, a drug must first penetrate the epidermal barrier of the skin (stratum corneum) to reach nociceptors situated near the dermo-epidermal junction. The ideal preparation should diffuse easily across the stratum corneum and spend maximal time at the nerve endings. There should then be a slow diffusion through the deeper dermis to ultimately reach the circulation, thus minimizing acute toxic effects (*Figure 1*).

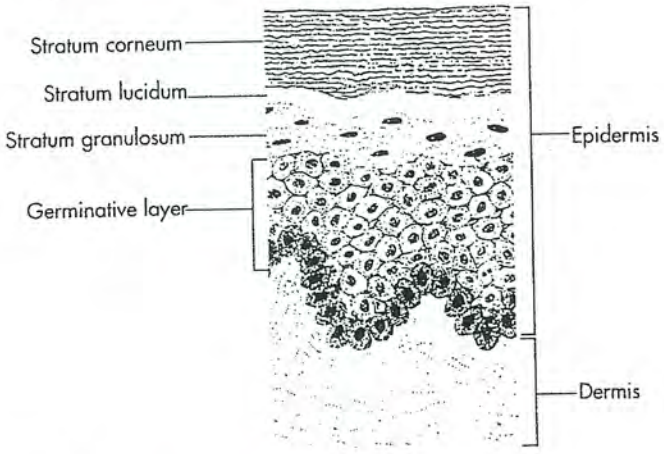

Figure 1. The skin showing the main layers of the epidermis.

The ideal preparation should achieve:

- Profound anaesthesia of the skin surface and surrounding tissues
- Rapid onset of action
- Prolonged duration
- Minimum necessary concentration of local anaesthetic
- No systemic toxicity
- No significant local reactions.

Pharmacological characteristics concurring with these ideals include high lipophilicity for stratum corneum penetration, a potent local anaesthetic drug for rapid action and long-lasting effect and rapid breakdown once the systemic circulation is reached.

PHARMACOLOGY

Amethocaine is a potent local anaesthetic of the amino-ester type.

In the free base (i.e. un-ionized form), it is highly lipophilic and binds strongly to neuronal receptor sites. These properties mean that a lower concentration of drug will produce a rapid and longer-lasting effect than more hydrophilic local anaesthetics. As an ester, amethocaine is rapidly metabolized by non-specific esterases in the skin and blood. Both the relatively low drug concentration and rapid breakdown minimize the risk of systemic toxicity. In addition, amethocaine is known to have a local vasodilatation effect in common with other ester-type local anaesthetics which may be of use in the cannulation of small vessels (Willats and Reynolds, 1985).

PREPARATION

Following work undertaken in Belfast (Woolfson and McCafferty, 1993a; McCafferty et al, 1988), the formulation contains 4% w/w

amethocaine as the free base in an aqueous gel; 1 gram of the gel provides a dose of 40 mg amethocaine.

Current recommended application time is 30 minutes for venepuncture and 45 minutes for venous cannulation with an expected duration of effect of 4–6 hours. Recommended maximum doses for topical areas capable of substantial absorption of amethocaine are 300 mg for an adult and 75 mg for a child in a 24-hour period (American Medical Association, 1986). These guidelines should be interpreted with care as it is likely that only a small proportion of the drug content will be absorbed through intact healthy skin.

CLINICAL EFFICACY

Assessment of drug formulation

Amethocaine as a topical preparation has been assessed in adults and children in both open and comparative studies. In a preliminary study, Mazumdar et al (1991) reported no pain in 10 adult patients treated with amethocaine cream undergoing cannulation with a 16G cannula.

When amethocaine gel was compared to placebo in a study of 42 adults, 90% of those receiving gel reported clinically acceptable analgesia compared to 52% in the placebo group (O'Connor and Tomlinson, 1995). Clinically acceptable analgesia was defined as a pain score of 0 or 1 (no pain (0) or sensation but no obvious discomfort (1)).

It has been considered unethical to perform comparisons with a placebo in children; however, there have been several open studies, again looking at efficacy and safety, and amethocaine has also been studied as a patch formulation in children (Doyle et al, 1993; Lawson et al, 1995).

Comparison with EMLA cream

In an adult volunteer study, amethocaine gel was shown to have greater efficacy in terms of speed of onset and duration of action than EMLA cream (Eutectic Mixture of Local Anaesthetic, Astra Pharmaceuticals Ltd, Corby) (McCafferty et al, 1989). It has also been shown to give effective anaesthesia to pinprick in adult volunteers with negroid skin type and have greater clinical efficacy in this group compared to EMLA (SR Dunnett, unpublished observations, 1996).

When amethocaine gel was compared to EMLA cream in children undergoing venous cannulation, clinically acceptable analgesia as defined above was obtained in 85.1% receiving amethocaine for 40 minutes compared to 65.9% treated with EMLA ($P<0.05$) (Lawson et al, 1995) (*Figure 2*).

Local vasodilatation with amethocaine as opposed to local vasoconstriction with EMLA helps to delineate the site of application.

ADVERSE REACTIONS, POTENTIAL TOXICITY AND SAFETY

Adverse reactions

In the above studies, adverse reactions to amethocaine gel were reported as localized erythema, oedema and itching. Erythema was by far the most prevalent topical reaction with an average incidence of 30% and this can be explained by the intrinsic vasodilator property of amethocaine. Oedema and itching at the site of application were much less common occurrences (less than 5%). No clinically significant changes in cardiovascular parameters have been documented in any study.

Toxicity

When plasma concentrations of amethocaine were assayed in 10 adults after prolonged application, little or no systemic absorption was found with no evidence of clinical toxicity (Mazumdar et al, 1991). The repeated use of amethocaine gel in a large series of children in Belfast has not led to sensitization reactions (Woolfson et al, 1990).

Safety

As with any percutaneous drug, amethocaine gel is not recommended for use on broken or inflamed skin or mucosal surfaces. In addition, because drug transfer is dependent on penetration of the epidermal layers, its use is contraindicated in psoriasis where there is a high rate of

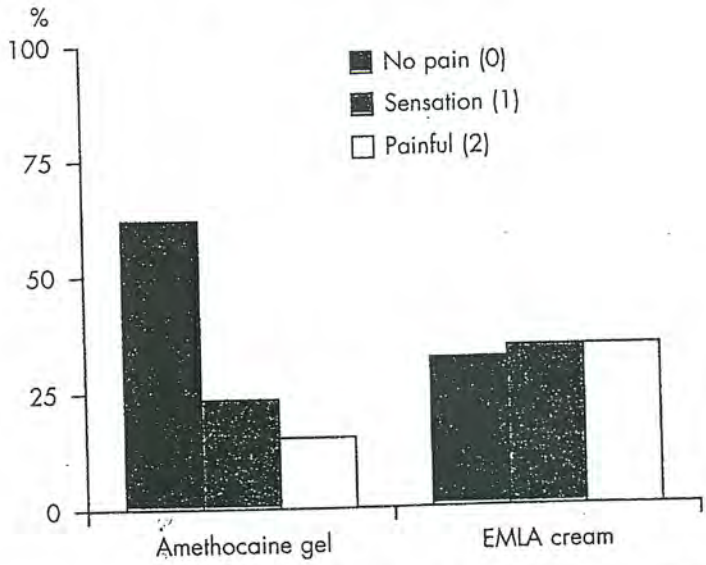

Figure 2. Pain scores from comparative study of amethocaine gel with EMLA cream in children. From Lawson et al (1995).

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