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Evaluation of an amethocaine gel preparation for percutaneous analgesia before venous cannulation in children

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Summary

We have evaluated the efficacy and safety of a preparation of 4 % amethocaine gel in alleviating the pain of venous cannulation in children. In an initial open study of 148 children, clinically acceptable anaesthesia was achieved in 92 % of cases. The preparation was then compared with 5 % EMLA cream in a single-blind study in 94 patients using an application time of 40 min. We found clinically acceptable conditions in 85 % of patients receiving amethocaine gel compared with 66 % in the EMLA group. There were no significant adverse effects noted in each group, although 37 % of those children treated with amethocaine gel showed localized erythema at the application site. The results suggest that amethocaine gel has greater efficacy and a faster onset time than EMLA cream when used for this purpose in children. (*Br. J. Anaesth*. 1995; **75**: 282–285).

Key words

Anaesthetics local, amethocaine. Anaesthetics local, EMLA. Children.

Percutaneous local anaesthesia before venepuncture and venous cannulation is now regarded as the standard of care in children. The local anaesthetic formulation should provide rapid, deep and relatively long-lasting anaesthesia of both the skin and underlying tissues. In addition, the drug used should have low toxicity [1]. Recent studies have suggested that amethocaine has advantageous pharmacological properties for the provision of percutaneous local anaesthesia; there include high lipid solubility and high affinity for neural tissue [2, 3]. A high protein-binding capacity maintains the drug at the receptor site with formation of a long-lasting depot in the stratum corneum and clearance by esterases in the skin and bloodstream.

The efficacy of EMLA cream (eutectic mixture of local anaesthetics) has been proved but requires a minimum application time of 60 min and has an average duration of action of 30–60 min [3, 4]. A preparation with a more rapid onset and longer duration of effect is potentially advantageous in clinical practice.

In addition to the drug used, the delivery system may also play a part in the overall efficacy of a preparation. For example, a patch formulation of amethocaine was shown to be useful in children [5]. In this study we evaluated the safety and efficacy of a gel formulation of amethocaine in an open study and then in a comparative study with EMLA cream.

Patients and methods

The amethocaine gel contained 4 % w/w amethocaine base and was supplied in tubes containing 1.5-g unit doses. This gave one topical application of 1 g of amethocaine gel. EMLA cream 1 g contains lignocaine base 25 mg and prilocaine base 25 mg in a eutectic mixture. The standard dose of 2 g was used. All applications were occluded with a flexible dressing (OpSite Flexigrid, Smith and Nephew Medical Ltd) and left in place for 40–60 min (open study) and 40 min (comparative study).

After obtaining Ethics Committee approval and informed consent from the parent or guardian, we studied 150 patients in the open study and 110 in the comparative trial. All children were between the ages of 3 and 12 yr, weighed more than 10 kg and had the ability to speak. Exclusion criteria included known sensitization to local anaesthetics, broken skin at the intended site of cannulation and use of analgesia within the previous 24 h. Patients who were crying or agitated before application of the preparation were also excluded as this would make subsequent assessment difficult. All patients were unpremedicated and parents were present at all times.

Weight, height, heart rate and arterial pressure were recorded before application of each preparation, and heart rate and arterial pressure were measured again after removal of the gel before cannulation.

OPEN STUDY

All patients had the contents of one tube of amethocaine gel applied to the dorsum of the hand, and the absence or degree of pain on cannulation with a 22-gauge cannula was assessed subsequently by one of two investigators. The time at which

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Table 1 Assessment scores for pain and skin signs after application of amethocaine gel (open study). Totals for pain assessment are of protocol-compliant patients. Totals for skin signs are of all evaluable patients where data were complete

	Pain score				
	0 68 (61.3 %)	1 34 (30.6 %)	2 9 (8.1 %)		
	Skin signs				Total 111
	None (0)	Slight (1)	Moderate (2)	Severe (3)	
Erythema	113 (77.4 %)	24 (16.4 %)	8 (5.5 %)	1 (0.7 %)	146
Oedema	141 (95.3 %)	5 (3.4 %)	1 (0.6 %)	1 (0.6 %)	148
Itching	144 (97.3 %)	2 (1.2 %)	2 (1.2 %)	0 (0.0 %)	148

cannulation occurred was recorded. Pain was assessed using the following scale: 0 = no sensation of pain, 1 = some sensation, no obvious discomfort, and 2 = painful (including withdrawal of the hand).

The degree of erythema and oedema under the application site was assessed immediately after removal of the gel and child was also asked to report any itching felt and its severity. The skin signs were graded as: none = 0, slight = 1, moderate = 2, severe = 3.

COMPARATIVE STUDY

This was designed as a randomized, single-blind, between-patient comparison. Each patient was allocated randomly to receive either amethocaine gel or EMLA cream which was applied by the nursing staff so that the investigator was blinded to the treatment. After 40 min the preparation was removed by the nurse before assessment for cannulation by the investigator. The precise times at which treatments were applied and removed were recorded.

As in the open study, the area of skin used was assessed for erythema, oedema or itching immediately before application and immediately after removal but before venepuncture, and any skin signs graded 0–3, as described above. One of three investigators then performed venous cannulation using a 22-gauge cannula on the dorsum of the hand. Assessment of pain at the time of puncturing the skin (not during insertion of the cannula) was reported by the child and graded according to the self report score used in the open study. After cannulation, the material used to secure the cannula was recorded and the skin site inspected after removal.

The results of the open study were recorded as percentages and those of the comparative study were analysed statistically using Fisher's exact test, an extension to McNemar's test, and the paired *t* test method, where appropriate.

Results

OPEN STUDY

We studied 150 patients (116 male). Ages ranged from 3 to 12 yr (mean 6.4 yr) and weights from 12.3 to 67.5 kg (mean 23.4 (SD 9.1) kg). No adverse events or reactions to the test substances were reported but two patients were excluded from the study (operations cancelled) which was completed by 148 patients.

Table 2 Pain scores from comparative study of amethocaine gel and EMLA cream

Pain score	Amethocaine gel	EMLA cream	Across treatments total
0	29 (61.7 %)	15 (31.9 %)	44
1	11 (23.4 %)	16 (34.0 %)	27
2	7 (14.9 %)	16 (34.0 %)	23
Total	47	47	94

Amethocaine gel was applied for a mean time of 44.1 (SD 4.0) min, although the application time did exceed the maximum specified in the protocol (60 min) in two of the 150 patients starting the study and was less than the minimum specified (40 min) in 35 patients. Data from these 37 patients were excluded from analysis of pain score data, but were included for all safety assessments. Scores for degree of erythema were missing in two patients. The results of pain scores and assessments of erythema, oedema and itching are shown in table 1.

Recordings of heart rate and arterial pressure revealed no statistically or clinically significant differences between measurements before application and on removal of the gel.

COMPARATIVE STUDY

We studied 110 patients (55 per treatment group—34 female). Ages ranged from 3 to 12 yr (mean 7.3 yr) and weights from 11.2 to 68.7 kg (mean 26.6 (SD 11.9) kg). No adverse reactions to the test substances were reported but six patients had their operations cancelled (three from each treatment group) and were excluded from the analysis.

The mean application time of the amethocaine gel was 40.5 (SD 1.9, range 35–45) min and for the EMLA cream 41.4 (2.4, 35–45) min. Ten patients (five from each group) had application times greater than 45 min and were excluded from analysis of the pain score data, but were included for all safety assessments.

A total of 62 % of children in the amethocaine treatment group in comparison with 32 % in the EMLA group reported no pain ($P < 0.05$) (pain score = 0); 85 % in the amethocaine group experienced acceptable anaesthesia (pain score = 0 + 1) in comparison with 66 % in the EMLA group ($P < 0.05$) (table 2).

A statistically significant difference in the incidence of erythema was seen between the two treatment groups; 37 % of patients (18 slight and two moderate) showed erythema in the amethocaine treatment group compared with 4 % (two slight) in the EMLA group ($P < 0.05$). There was no significant difference ($P > 0.05$) in oedema between the two groups. There was no significant difference ($P > 0.05$) in itching between the two groups, although the three cases of slight itching that did occur were in the amethocaine gel group.

There were no clinically or statistically significant effects of each treatment on systolic or diastolic arterial pressure or heart rate.

Discussion

The aim of the open study was to investigate the efficacy and safety of a new preparation of amethocaine gel in children. The subsequent study assessed the comparative efficacy and safety of amethocaine gel compared with EMLA cream in a similar patient population.

In the open investigation, clinically acceptable anaesthesia (pain score 0 to 1) was achieved in 92 % of all patients, and there were no significant adverse effects either locally or systemically. Thus it can be concluded that amethocaine gel applied topically for 40–60 min is a safe and effective percutaneous local anaesthetic for use in children undergoing venous cannulation. In comparison with EMLA cream, where clinically acceptable anaesthesia was produced in 66 % of patients, amethocaine gel gave acceptable conditions in a significantly higher proportion of children (85 % ($P < 0.05$)) when applied for a mean time of 40 min. The faster onset time of amethocaine appears to be confirmed by these results and can be explained on the basis of the pharmacological characteristics of amethocaine.

Lipophilic drugs penetrate the stratum corneum layer of the skin more readily and amethocaine has been shown in several *in vitro* and *in vivo* studies to be relatively lipophilic [2, 3]. In contrast, the constituents of EMLA cream (lignocaine and prilocaine) are relatively hydrophilic and therefore less efficacious in penetrating the stratum corneum and thus nerve endings in the dermis.

A previous study comparing an amethocaine formulation with EMLA in adults [3] commented on the difficulty of designing a study where recommended application times differed for the two preparations being studied. They used placebo groups for comparison in the first instance. However, the efficacy of EMLA cream is well documented and it was considered unethical to include a placebo group in this paediatric study.

As the comparative study was designed to test the claim that amethocaine produced anaesthesia more rapidly than EMLA, it was considered acceptable to use the shorter application time in both groups. It was also explained to the parents that there was a chance that there may not be full percutaneous analgesia with both preparations. An application time of 30 min for EMLA cream has been used in a previous study in comparison with amethocaine cream in adults [6]. In contrast with earlier work, this study revealed no significant differences between the two preparations. This may be because the authors made no differentiation between venous cannulation and venepuncture when measuring pain scores. Assessment of pain is always more difficult in children than adults. This study took place on an open day surgery ward where it was possible for the children to be in contact with each other before and after cannulation. The self-report pain score chosen was simple, effective and validated in previous investigations [5, 7].

The erythema noticed in a significant number of patients receiving amethocaine gel is a consequence of the known vasodilator action of amethocaine at the site of dermal application [8]. This may be an advantage in making small veins on the dorsum of the hand more prominent.

There appears to be no evidence of toxicity with topical amethocaine preparations applied to intact skin. The lack of toxicity may be explained in part by the ester local anaesthetic being metabolized by non-specific esterases both in the skin and systemically. In addition, amethocaine preparations appear to form a depot in the stratum corneum which is slowly depleted and thus minimizes the risk of sudden systemic toxicity.

Repeated application of the ester preparation might also be expected to result in localized problems such as dermatitis. However, there was no evidence of this in a large series of children studied in Belfast [7]. The formation of a reservoir of local anaesthetic may also explain why amethocaine preparations have a prolonged action in comparison with other percutaneous local anaesthetics. Our study was not designed to demonstrate a prolonged action, but this property has been confirmed in a study using amethocaine at the site for split skin graft sites in patients undergoing plastic surgery [9]. Thus, the formulation has potential for providing prolonged analgesia for surface wounds.

A recent *in vitro* and *in vivo* comparison between an amethocaine patch and amethocaine gel in adult volunteers showed that the patch was more efficient [10]. However, if the wider uses of percutaneous anaesthesia are considered, such as in plastic surgical procedures, a gel preparation would seem useful in being accessible to several different sites in varying doses [11].

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