

Topical amethocaine gel in the newborn infant: how soon does it work and how long does it last?

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Abstract

Aim—To explore the time of onset and duration of action of topical amethocaine gel in the newborn infant.

Design—A randomised double blind placebo controlled trial.

Subjects—Thirty six infants were studied after 30 minutes application and 36 after 60 minutes application. A total of 56 infants (gestation 27–42 weeks, weight 0.79–4.1 kg) were studied in the first two weeks after delivery.

Method—1.5 g amethocaine or placebo was applied to the dorsum of either foot, occluded, and then left for 30 or 60 minutes. Local anaesthesia was assessed by observing the cutaneous withdrawal response to graded nylon filaments (von Frey hairs). If there was a difference between feet in filament thickness required to elicit a response, the infant was studied in an identical manner at hourly intervals until the difference had disappeared.

Results—Evidence of local anaesthetic action of amethocaine was seen in 23 of 36 (64%) infants after 30 minutes and 26 of 36 (72%) infants after 60 minutes application (no significant difference). Evidence of local anaesthetic action was independent of gestation and order of testing. Amethocaine responders showed a significantly deeper anaesthetic action than placebo responders. The median duration of action was 1.5 hours (range 0.5–3.5) after 30 minutes and three hours (range 1–5) after 60 minutes ($p < 0.001$).

Conclusion—Topical amethocaine gel has a local anaesthetic action after 30 minutes application, but application for 60 minutes results in longer duration of action.

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Keywords: anaesthesia; amethocaine; pain

Painful and invasive procedures are commonly performed in the newborn, particularly in neonatal intensive care units. Heel prick blood sampling and venepuncture are the commonest procedures that pierce the skin and are necessary for the routine care of healthy term and sick premature infants alike.¹ Venepuncture is probably less painful than unmodified heel lancing,^{2,3} and the pain can be further reduced by non-pharmacological means.^{4–6} Nevertheless, it is still a painful procedure. Topical local anaesthetics are effective and widely used to relieve the pain of venepuncture

in children, but their use in the newborn has been less successful.

The ideal topical local anaesthetic should be quick acting, effective, safe, and should not interfere with the procedure involved. Studies on lignocaine and lignocaine/prilocaine eutectic mixture (EMLA) in the newborn have been disappointing.^{7–12} Amethocaine is an alternative. It is a local anaesthetic of the ester group, available as a 4% (w/w) topical gel, which has been shown to provide effective and safe surface local anaesthesia in children.^{13–16}

We have recently shown that topical amethocaine gel has a local anaesthetic action on the newborn skin after application for one hour.¹⁷ Two further pieces of information would be useful before examining amethocaine gel in a clinical setting: the time to onset and the duration of action. We therefore designed a study to answer the following questions: does topical amethocaine gel have a local anaesthetic action when applied for 30 minutes, and, if so, how does this compare with the action after 60 minutes application? If a local anaesthetic action can be shown, how long does it last?

Methods

We conducted a randomised double blind controlled trial comparing 4% (w/w) amethocaine gel (Ametop, Smith and Nephew, Hull, UK) with placebo. Surface local anaesthesia was assessed by eliciting the cutaneous withdrawal reflex in response to stimulation of the dorsum of the foot. To provide a range of stimuli, we used a series of 20 graded nylon filaments, von Frey hairs. Each hair consists of a flexible nylon filament attached at right angles to one end of a perspex holder. Each filament has a different thickness, ranging from very fine to thick. The nylon filament is placed on to the dorsum of the foot and deformed by downward pressure. A measurable and reproducible weight is required to deform the filament. When the stimulus exceeds the threshold of the reflex, the cutaneous withdrawal reflex is elicited. This reflex consists of fanning of the toes, followed by flexion of the ankle, knee, and hip and withdrawal of the leg.

We applied a marker ring to the dorsum of each foot. This defined and exposed a circular area of skin 1 cm in diameter that was used for testing. Within the marker ring, we applied 1.5 g 4% (w/w) amethocaine gel to one foot and 1.5 g placebo to the other foot. The placebo was identical in every way except for the absence of amethocaine. We covered each foot with an occlusive dressing and left the baby alone. The occlusive dressings were removed and the excess gel wiped from each foot after

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either 30 minutes or 60 minutes. The foot to be tested first (left or right foot) and the order of testing (amethocaine/placebo or placebo/amethocaine) were determined by randomisation in order to control for habituation to repeated stimulation which we had noted previously.¹⁷

Filament thickness was increased until the cutaneous withdrawal reflex was elicited from the first foot. The filament thickness and its corresponding deforming weight were recorded. This was repeated in an identical fashion on the second foot until the reflex was again elicited. The thickness of filament and corresponding deforming weight required to elicit the reflex were recorded. If there was no difference, the baby was not studied again. Otherwise the baby was studied in an identical manner at one hourly intervals until the difference disappeared. A difference in thickness of filament required to elicit the cutaneous withdrawal reflex from the two feet was taken as evidence of a local anaesthetic action. The difference in corresponding deforming weights was used as a measure of the strength of this action. The duration of action was recorded as the time from application of the gels to the last time when a local anaesthetic action could still be shown.

SUBJECTS

We studied 36 infants after amethocaine and placebo had been applied for 30 minutes and 36 after the gels had been applied for 60 minutes (table 1). Subjects were studied in the first two weeks after birth by a single observer. In total, we studied 56 babies; 16 were studied twice, the two investigations being a week apart. In each study, subjects were stratified by gestation into three groups of 12: term (>37 weeks), mildly preterm (33–36 weeks), and moderately preterm (< 32 weeks). Infants on the neonatal intensive care unit or postnatal wards at Nottingham City Hospital were eligible for entry, but we excluded those who were unwell, ventilated, or sedated. The study was approved by the hospital research ethics committee. Infants were studied with the informed written consent of one or both parents. We obtained exemption from the restrictions of the drug's product licence from the Medicines Control Agency.

Table 1 Details of infants to whom amethocaine was applied for either 30 or 60 minutes

	30 minutes	60 minutes	p Value
Gestation (weeks)	33.5 (27–40)	34 (27–42)	0.85
Birth weight (g)	2.01 (0.79–4.1)	1.9 (0.79–3.93)	0.95

Values are median (range). p Value calculated using the Mann-Whitney U test.

Table 2 Evidence of local anaesthetic action of amethocaine after 30 or 60 minutes application

	Amethocaine responders	Placebo responders	Non-responders	p Value
30 minutes application	23/36 (64)	6/36 (17)	7/36 (19)	<0.001
60 minutes application	26/36 (72)	8/36 (22)	2/36 (2)	<0.001

Values in parentheses are percentages. The p values are for the results of amethocaine *v* all others.

RANDOMISATION

Placebo and amethocaine were packaged into identical tubes by the hospital pharmacy who randomised and coded them. Packages and codes for the studies of 30 minutes or 60 minutes application were generated independently. The codes were kept in the pharmacy and broken on completion of the study. Within each gestational age group, infants were assigned to one of four equal groups:

- (1) amethocaine applied to right foot, placebo applied to left foot; right foot tested first;
- (2) amethocaine applied to right foot, placebo applied to left foot; left foot tested first;
- (3) placebo applied to right foot, amethocaine applied to left foot; right foot tested first;
- (4) placebo applied to right foot, amethocaine applied to left foot; left foot tested first.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS 8.0 software. The data were not normally distributed and therefore non-parametric statistical tests were used. Comparison of the median von Frey hair thickness in each group and the proportions within the amethocaine and placebo groups who showed a local anaesthetic action were made by Mann-Whitney U and Wilcoxon signed ranked tests respectively. Intergroup differences were tested using the Kruskal-Wallis test. The difference in mean deforming weight required to elicit the reflex from the amethocaine and placebo groups and the duration of effect were analysed by the Mann-Whitney U test. Logistic regression was used to test the association between the presence of a local anaesthetic action and other confounding variables.

Results

DEMONSTRATION OF A LOCAL ANAESTHETIC ACTION

After 30 minutes, 23 of 36 (64%) babies showed evidence of local anaesthetic action on the amethocaine treated foot (amethocaine responders) compared with six of 36 (17%) on the placebo treated foot (placebo responders) and seven of 36 (19%) who showed no difference between feet (non-responders) (difference between amethocaine responders and the rest, $p < 0.001$) (table 2). After 60 minutes, 26 of 36 (72%) babies were amethocaine responders compared with eight of 36 (22%) placebo responders and two of 36 (6%) non-responders (difference between amethocaine responders and the rest, $p < 0.001$).

Amethocaine responders differed from placebo responders. After 30 minutes, the median difference in grade of filament thickness was 3 in the amethocaine responders and 2 in the placebo responders ($p < 0.001$). After 60 minutes, the median difference was 4 in amethocaine responders and 2 in placebo responders ($p < 0.001$). We compared the strength of local anaesthetic action in the two groups by recording the difference in corresponding deforming weight required to elicit the reflex between feet. After 30 minutes, the median weight difference was 21.0 g (interquartile range (IQR) 8.6–52.5) in amethocaine responders and 7.5 g

convenient objective way of testing local anaesthetic action in the newborn without inflicting pain.^{7 23-25} To minimise the known influence of habituation to the stimulus, we randomised the order of stimulation of the feet with respect to right or left and whether the amethocaine or placebo treated foot was tested first.

Our original study of amethocaine showed that it was effective after application for 60 minutes. There is evidence that an application time of 30 minutes can provide satisfactory anaesthesia in up to 71% of children.^{13 18} We have shown that 64% of newborn infants show a positive response to amethocaine after 30 minutes. Although the response rate was not significantly longer after 60 minutes application, the duration of effect was. The median duration of action was three hours, twice as long as after 30 minutes application. This suggests that there is some choice if topical amethocaine is to be used in this age group, depending on whether speed of onset or duration of effect are needed.

We conclude that topical amethocaine gel has a local anaesthetic action when applied to the dorsum of the foot in the newborn infant. The effect after 30 and 60 minutes application is similar in terms of rate of local anaesthetic action and strength. Application for 60 minutes results in a duration of action that is twice as long. A clinical study of efficacy is now justified.

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