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Clinical experiences with a novel percutaneous amethocaine preparation: prevention of pain due to venepuncture in children

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1 The efficacy and safety of a novel percutaneous anaesthetic preparation based on amethocaine has been investigated in the paediatric clinical environment.
2 There were 1241 recorded applications on a named patient basis made to patients from infant to age 16 years. Of these, 88.7% had satisfactory anaesthesia to venepuncture challenge, rising to approximately 90% when the infant group was excluded.
3 A 30 min application time was found to be adequate for reliable topical anaesthesia.
4 There were no serious adverse reactions to the preparation. Of the total 6.9% recorded reactions, 6.3% were of a mild, transient erythema later identified as due to the vasodilator action of the drug.
5 A total of 123 patients received more than one application of the preparation. There was no evidence of sensitisation on subsequent exposure to the preparation.
6 The short application time required was found to be advantageous to ward and clinic routines.

Keywords percutaneous anaesthesia amethocaine venepuncture paediatrics

Introduction

The relief of the pain associated with routine venepuncture can do much to reduce the stress suffered by children on admission to hospital (Blom, 1958). Administration of anaesthetics to the skin via the topical route presents a particular problem since the nociceptors lie just below the stratum corneum which offers an effective barrier to most drugs (Stuttgen, 1982) unless specific formulation procedures are adopted. However, a percutaneous anaesthetic formulation based on a eutectic mixture of lignocaine and prilocaine (EMLA) is now commercially available (Ehrenstrom-Reiz & Reiz 1982), though prolonged application times are required.

Amethocaine has been identified as a particularly useful drug for topical application to intact skin (McCafferty *et al.*, 1988). A novel amethocaine percutaneous anaesthetic preparation developed by us (Woolfson *et al.*, 1988) has been shown to produce profound cutaneous anaesthesia to pinprick challenge in double-blinded adult volunteer trials (Woolfson *et al.*, 1988). In a double-blinded comparison with EMLA (McCafferty *et al.*, 1989) the amethocaine preparation was distinguished by a faster onset time and a significantly increased duration of anaesthesia, extending to several hours. It has now been suggested (Coley, 1989) that clinical results, particularly in children, obtained with

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this preparation would be of interest. We therefore report on the use of this preparation (on a named patient basis) for the prevention of pain associated with venepuncture in children. It is now well-established that such pain results directly from puncture of the skin by the needle (Clarke & Radford, 1986; Hopkins *et al.*, 1988). Percutaneous anaesthesia alleviates or prevents this pain by inactivation of cutaneous nociceptors and consequent production of a profound topical anaesthesia.

Methods

Formulation

The amethocaine preparation (4% w/w) was prepared as described previously (Woolfson *et al.*, 1988). The preparation was dispensed in 25 g lacquered ointment tubes.

Application instructions

Approximately 500 mg of the preparation was applied to the site and covered with Op-Site i.v. (Smith & Nephew Ltd, Hull, UK). Following a 30 min contact period the preparation was removed and the site wiped clean. If required, the presence of anaesthesia was confirmed by pinprick prior to commencement of the procedure.

Subjects and clinical units

Approval for use of the amethocaine preparation was given by the local ethics committee. Subjects receiving the anaesthetic preparation were children up to the age of 16 years who were either in hospital or attending as out-patients. The participating hospitals were the Royal Belfast Hospital For Sick Children and the Belfast City Hospital. Specifically, the following units were involved and were coded for subsequent data processing: two general paediatric wards (G1, G2), an E.N.T. department (ENT), a theatre (T), an X-ray department (X-RAY) and a paediatric medical outpatients' department (OPD).

Records

Units were issued with a book to record each application of the preparation on a named patient basis. The following information was recorded: patient name, age and sex; date and duration of application; clinical procedure; pain score; adverse reactions or other general comments.

Procedures

In all recorded cases the clinical procedure involved was venepuncture. The site was either the forearm (ventral surface at or just below the anterior cubital fossa) or the back of the hand.

Pain scores

Following treatment with the preparation a subjective determination of pain due to the clinical procedure was made and a pain score of 1–4 allocated. A pain score of 1 indicated a completely painfree procedure, 2 represented minimal sensation but no discomfort, 3 represented moderate pain and 4 corresponded to no apparent anaesthesia. For statistical analysis pain scores of 1 and 2 were grouped together as indicating successful anaesthesia. Pain scores of 3 and 4 were taken as failure of the technique.

Adverse reactions

Three possible classes of reaction were defined. Class A was a severe reaction including an overt sensitisation, precluding further use of the preparation. Class B was an urticarial reaction, generally presenting with localised oedema and itch. This type of reaction spontaneously disappeared within about 2 h with no subsequent sensitisation. Further use of the preparation was not precluded. Finally, a class C reaction was defined as a slight, transient erythema of the treated site. Since no Class A and very few Class B reactions were experienced throughout the study all reactions were counted together for the purposes of statistical analysis.

Statistical analysis and data processing

Data were collated using a BBC microcomputer and a database manager (Viewstore). Patient names were not stored in the database but repeat applications were flagged in the records. Statistical analysis of the results from this study was made using the chi-square procedure on single applications, and also on the total of all applications of the preparation, including repeat applications to the same patient.

Results

There were 1241 complete records. Of these, 879 cases (70.8%) experienced no pain (class 1) and 222 cases (17.9%) reported a minimal sensation (class 2). Thus, satisfactory anaesthesia was achieved in 88.7% of all cases. Of the re-

mainder, 86 (6.9%) experienced moderate pain (class 3) and 54 (4.4%) had no apparent pain relief (class 4).

In 1155 cases (93.1%) no adverse reactions were noted. Class C reactions (transient erythema) occurred in 78 cases (6.3%) and class B reactions in 8 cases (0.6%). There were no Class A reactions.

A detailed analysis of the data in respect of both efficacy and adverse reactions was made relative to the following factors: sex of patient (Tables 1 and 2), age (Tables 3 and 4), application period (Tables 5 and 6) and hospital unit (Tables 7 and 8). Table 9 analyses the incidence of adverse reactions with respect to the incidence of satisfactory anaesthesia. Tables 10 and 11 present a specific analysis of those cases which received more than one application of the preparation and Table 12 gives the overall statistical analysis of the results in Tables 1–9.

Table 1 Influence of the sex of the patient on the efficacy of percutaneous absorption

Sex	*Number of applications*	*Cases of satisfactory anaesthesia (Pain = 1 and 2)*	
		Number	*%*
Male	705	622	88.2
Female	536	479	89.4
Totals	1241	1101	88.7

Table 2 Influence of the sex of the patient on the incidence of adverse reactions

Sex	*Number of applications*	*Severity of reaction*					
		A		*B*		*C*	
		Number	*%*	*Number*	*%*	*Number*	*%*
Male	705	0	0	7	1.0	39	5.5
Female	536	0	0	1	0.2	39	7.3
Totals	1241	0	0	8	0.6	78	6.3

Table 3 Influence of patient age on the efficacy of percutaneous anaesthesia

Age (years)	*Number of applications*	*Cases of satisfactory anaesthesia (Pain = 1 and 2)*	
		Number	*%*
0–2	68	56	82.4
3–5	405	349	86.2
6–10	499	449	90.0
>10	269	247	91.8
Totals	1241	1101	88.7

Discussion

The complex mechanisms of pain perception often result in a specific pain seeming severe at one time but relatively minor at another. Thus, a given pain stimulus may record different levels of severity depending on the level of higher control blocking the afferent impulses. This makes comparison and quantification of pain highly subjective in adults, and particularly difficult in children. Given the open nature of the present study, and the widespread clinical use of the novel percutaneous anaesthetic preparation, a comparatively simple regimen of pain assessment was required. Pain assessment, particularly

Table 4 Influence of patient age on the incidence of adverse reactions

Age (years)	*Number of applications*	*Severity of reaction*					
		A		*B*		*C*	
		Number	*%*	*Number*	*%*	*Number*	*%*
0–2	68	0	0	0	0	3	4.4
3–5	405	0	0	4	1.0	15	3.7
6–10	499	0	0	2	0.4	32	6.4
>10	269	0	0	2	0.7	28	10.4
Totals	1241	0	0	8	0.6	78	6.3

Table 5 Influence of application period on the efficacy of percutaneous anaesthesia

Application time (min)	Number of applications	Cases of satisfactory anaesthesia (Pain = 1 and 2) Number	%
0–20	52	36	69.3
21–40	363	322	88.7
41–60	445	396	89.0
61–120	342	310	90.6
>120	39	37	94.9
Totals	1241	1101	88.7

Table 6 Influence of application period on the incidence of adverse reactions

Application time (min)	Number of applications	Severity of reaction A Number	%	B Number	%	C Number	%
0–20	52	0	0	1	1.9	2	3.8
21–40	363	0	0	2	0.6	29	8.0
41–60	445	0	0	3	0.7	31	7.0
61–120	342	0	0	2	0.6	13	3.8
>120	39	0	0	0	0	3	7.7
Totals	1241	0	0	8	0.6	78	6.3

Table 7 Influence of the hospital unit on the efficacy of percutaneous anaesthesia

Unit	Number of applications	Cases of satisfactory anaesthesia (Pain = 1 and 2) Number	%
G1	275	252	91.6
T	120	97	80.8
G2	74	56	75.7
ENT	264	236	89.4
OPD	362	335	92.5
X-RAY	146	125	85.6

Table 8 Influence of the hospital unit on the incidence of adverse reactions

Unit	Number of applications	Severity of reaction A Number	%	B Number	%	C Number	%
G1	275	0	0	1	0.4	27	9.8
T	120	0	0	1	0.8	2	1.7
G2	74	0	0	0	0	1	1.4
ENT	264	0	0	0	0	0	0
OPD	362	0	0	6	1.7	38	10.5
X-RAY	146	0	0	0	0	10	6.8

Table 9 Incidence of adverse reactions in cases of satisfactory and unsatisfactory anaesthesia

Anaesthetic effect	*Number of applications*	*Severity of reaction* A Number	%	B Number	%	C Number	%
Satisfactory (Pain = 1 and 2)	1101	0	0	7	0.6	68	6.2
Unsatisfactory (Pain = 3 and 4)	140	0	0	1	0.7	10	7.1

Table 10 Influence of repeated applications on the efficacy of percutaneous anaesthesia

Number of successive repeat applications	*Number of subjects*	*Cases of satisfactory anaesthesia (Pain = 1 and 2)* Number	%
1	123	106	86.2
2	123	113	91.9
3	59	55	93.2
4	37	35	94.6
5	21	21	100
6	1	11	100
≥6	2	2	100

Table 11 Influence of repeated applications on the incidence of adverse reactions

Number of successive repeat applications	*Number of subjects*	*Severity of reaction* A Number	%	B Number	%	C Number	%
1	123	0	0	0	0	7	5.7
2	123	0	0	1	0.8	12	9.8
3	59	0	0	2	3.4	7	11.9
4	37	0	0	0	0	4	10.8
5	21	0	0	1	4.8	4	19.0
6	11	0	0	0	0	0	0
≥6	2	0	0	0	0	1	50.0

Table 12 Statistical analysis of the results in Tables 1–9

Test	*Significance (Chi-square)* *Inclusion of repeat applications*	*Exclusion of repeat applications*
Efficacy *vs* sex	$0.5 < P \leq 0.7$	$0.7 < P \leq 0.8$
Reactions *vs* sex	$0.5 < P < 0.7$	$0.95 < P$
Efficacy *vs* age	$0.02 < P \leq 0.05$	$0.05 < P \leq 0.1$
Reactions *vs* age	$0.01 < P \leq 0.02$	$0.05 < P \leq 0.1$
Efficacy *vs* contact time	$P \leq 0.001$	$0.001 < P \leq 0.01$
Reactions *vs* contact time	$0.1 < P \leq 0.2$	$0.02 < P \leq 0.05$
Efficacy *vs* ward	$P \leq 0.001$	$P \leq 0.001$
Reactions *vs* ward	$P \leq 0.001$	$P \leq 0.001$
Efficacy *vs* reactions	$0.5 < P \leq 0.7$	$0.5 < P \leq 0.7$

in younger children, was necessarily made in conjunction with experienced nursing and medical staff. There were rather more male than female participants in the study (Tables 1 and 2). However, statistical analysis (Table 12) indicated no significant difference between the sexes with respect to either the efficacy or safety of the anaesthetic preparation. However, Table 12 did indicate a significant relationship between age and these two variables (Tables 3 and 4). Subsequent investigation demonstrated that this was due entirely to the inclusion of results from the 0–2 years age group, numerically the smallest group considered. There was no significant difference between the other groups in either respect when this youngest age band was omitted. It is perhaps not surprising that very young children apparently benefit less from this type of percutaneous anaesthetic preparation, given the psychological trauma of hospitalisation and also the inherent difficulties in pain assessment. Nevertheless, even in this very young age group, 82% of applications were judged to have produced satisfactory anaesthesia to venepuncture.

The importance of application time of the preparation to the skin, and its possible relationship to both efficacy and adverse reactions, was investigated. The recommended regimen involved a 30 min contact period, based on adult volunteer studies, and also on monitoring with laser-Doppler velocimetry blood flow in the cutaneous microcirculation (in which the vasodilator action of amethocaine is used to follow drug penetration through the skin) following application of the preparation (Woolfson *et al.*, 1989). Nevertheless, the practical requirements of the clinical situation often resulted in a variation from the recommended application regimen in respect of application time, with periods from < 20 min to > 120 min being used (Tables 5 and 6). Statistical analysis (Table 12) indicated that the effect of application time was significant in respect of efficacy, and marginally so in respect of adverse reactions (in the single application group only). However, this was found to be due entirely to inclusion of the application time group < 20 min. Further analysis excluding this time group showed no significant difference between any of the other groups either in terms of efficacy or adverse reactions, both for single and repeated applications. Although 20 min is less than the recommended application period it is interesting to note that almost 70% of applications in this group produced successful anaesthesia of the site. This suggests that, as might be expected, the preparation acts more rapidly in children than in adults, the mean onset time for anaesthesia in the latter being about 40 min (McCafferty *et al.*, 1989). Although it was impractical to monitor the duration of anaesthesia during this study, previous investigations (Woolfson *et al.*, 1988; McCafferty *et al.*, 1989) have clearly demonstrated that the main effect of increasing the application time of the preparation is to increase the duration of anaesthesia.

The analysis of the results obtained during use of the percutaneous anaesthetic preparation was extended to variations observed between different hospital units. This was designed to allow for the different numbers of applications made in each of the units, and therefore differences in the experience gained by nursing staff in both using and assessing the preparation. Table 7 indicates a trend towards greater efficacy as the number of applications, and therefore experience, increased in a unit. The differences noted were statistically significant. Age distributions were similar in each of the units and the number of applications made to children below 2 years of age was, in any case, a small proportion of the total (5.5%). Differences in observed adverse reactions were also statistically significant between units. However, this result must be interpreted with care since the numbers of all such reported reactions are low. The chi-square test loses power when the number in any cell of the contingency table falls below 5. In this case the ENT unit reported no adverse reactions whatsoever (Table 8). Since all other units observed some degree of mild, transient erythema (Class C) it is likely that this minor reaction was simply not recorded by staff in this unit. Interestingly, there was no significant relationship between the number of adverse reactions reported and the efficacy of the preparation (Table 9). Since a Class C erythematous reaction indicates that the anaesthetic has penetrated to the cutaneous microcirculation (Woolfson *et al.*, 1989) an effect on the cutaneous nociceptors would reasonably be expected. In previous trials on adult volunteers (McCafferty *et al.*, 1989) the amethocaine preparation was reliably 100% effective at producing complete anaesthesia of the treated site compared with an overall efficacy of about 90% in this study. It is likely, given the trauma and anxiety associated with hospital, and the use of equipment such as needles, that there will always be a finite percentage failure with this type of preparation in the paediatric clinical situation.

Anaesthetics of the ester type, including amethocaine, generally raise concern about toxicity and, in particular, sensitisation. It was therefore important to look closely at those patients who received more than one application

of the preparation. Most repeat applications took place in the OPD unit and involved juvenile diabetics. Table 10 indicates an increase in efficacy with an increasing number of applications. Since these repeat applications often occurred several weeks apart in an individual it is unlikely that a carry over of the drug was responsible. Rather, this observation probably reflects increasing familiarity with, and confidence in, percutaneous anaesthesia.

With respect to adverse reactions, there was no evidence of sensitisation or toxicity associated with repeat applications of the preparation (Table 11). Although 123 patients received more than one application of the preparation, clearly further controlled trials will be necessary to establish fully confidence in this respect. Nevertheless, the results reported here are encouraging, particularly when taken in association with earlier work, including clinical use with adult patients (Small *et al.*, 1988).

Throughout the study, almost all reactions reported were of a mild, transient erythema. Recent investigations using laser Doppler velocimetry (Woolfson *et al.*, 1989) have established that this effect is due to increased blood perfusion in the cutaneous microcirculation caused by the direct vasodilator action of amethocaine. It is therefore probably incorrect to classify this effect as an adverse reaction. Certainly, it was of no clinical significance.

It was clearly our experience that percutaneous anaesthesia with the novel amethocaine preparation gained rapid and enthusiastic acceptance by patients, nursing and medical staff. The comparatively short application period was perceived as advantageous to ward and clinic routines. Anaesthesia was reliable, profound and free from significant adverse reactions.

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