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Safety of lidocaine-prilocaine cream application four times a day in premature neonates: a pilot study

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Abstract Although safety is established for lidocaine-prilocaine cream application to the heel once a day in neonates, it is often necessary to repeat heel lances several times a day in the clinical situation. A pilot safety study applying 0.5 g lidocaine-prilocaine cream to the heel covering an area of 5 cm^2 with an occlusive dressing during 30 min four times a day was carried out. Twelve neonates (5 male, 7 female) with a gestational age of 30.1–36.3 weeks (mean 31.6 weeks) and a birth weight of 1100–2910 g (mean 1665 g) were enclosed. To establish safety, methaemoglobin levels and plasma concentrations of lidocaine, prilocaine and o-toluidine were measured until 24 h after the final application. Methaemoglobin levels were no different from baseline measurements, ranging from 0.2–1.1% and 0.1–0.7% respectively. Plasma concentrations of lidocaine and prilocaine were very low, maxima at 0.230 and 0.223 mg/l respectively. Plasma o-toluidine concentrations remained below the detection limit (0.025 mg/l).

Conclusion Application of 0.5 g lidocaine-prilocaine cream to the heel under occlusion four times a day during 30 min is safe in preterm neonates. Establishing safety by measuring the methaemoglobin level by daily application is recommended.

Key words Local anaesthetics · Methaemoglobin · Neonates · Safety

Introduction

An eutectic mixture of lidocaine and prilocaine (EMLA cream) for local anaesthesia of the skin, has proven its safety and efficacy in children and adults [6, 10]. Since fear of methaemoglobinaemia exists due to an immature enzyme system and immaturity of the skin, its use is restricted to children over 3 months of age.

Recent studies in neonates and newborn infants however, established safety of 0.5 g lidocaine-prilocaine cream applied once a day for minor interventions such as venipuncture or heel lance [5, 9, 11]. Since heel lances are often performed several times a day, the use of lidocaine-prilocaine cream once daily was not considered acceptable in our Department of Neonatology. A safety study in neonates applying 0.5 g lidocaine-prilocaine cream to the heel four times a day was therefore carried out.

Patients and methods

Patient group

The study was approved by the Ethics Committee of the University Hospital of Nijmegen. All parents were informed and written consent obtained. Neonates from the Department of Neonatology were eligible to participate when they had a gestational age of 30–

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40 weeks, were in stable haemodynamic condition and an intravascular access was available (arterial catheter). An extra burden by performing heel lances was thus avoided.

Exclusion criteria were: anaemia (Hb <8 mmol/l), metabolic acidosis, sepsis, congenital or idiopatic methaemoglobinaemia, methaemoglobin level over 2%, weight not in correspondence with age and treatment with agents inducing methaemoglobinaemia. A patient dropped out of the study when his methaemoglobin level was over 5%, serious skin reactions occurred (allergic reactions, redness etc.), or when treatment with agents inducing methaemoglobinaemia was started. Finally, if the vital signs of the patient worsened, the patient was excluded from the study protocol.

Study procedure

Prior to the first application of lidocaine-prilocaine cream a baseline methaemoglobin level was measured twice, 10–24 h before and just preceding the first application. If the methaemoglobin level did not exceed 2%, the study was started. Lidocaine-prilocaine cream (0.5 g = 0.5 ml) was applied to a heel using a syringe, covering an area of 5 cm^2, four times daily ($t = 0$, 6, 12 and 18 h). The skin was covered with an occlusive dressing (Tegaderm). After 30 min the dressing was removed and the cream was wiped away with a gauze presoaked in water.

Safety was examined measuring the following parameters: (1) methaemoglobin level, considering a level $>5\%$ clinically relevant (normal methaemoglobin levels are between 0%–2%; University Hospital St. Radboud), (2) plasma concentration of lidocaine <0.5 mg/l, (3) plasma concentration of prilocaine <0.5 mg/l. These concentrations are 10 fold lower than that at which CNS effects are to be expected (5 mg/l) [12], (4) plasma concentration of o-toluidine below the detection limit. O-toluidine is the toxic metabolite of prilocaine, suspected to be the cause of methaemoglobinaemia.

Blood samples

Blood samples were obtained from the arterial catheter at $t = 0$ and just after removal of the cream at $t = 0.5$, 6.5, 12.5, 18.5 h and at $t = 24$, 36 and 48 h. Each sample was collected into a specimen tube containing the anticoagulant lithium heparin and taken to the laboratory for analysis.

Plasma analysis

The methaemoglobin level was measured within the hour after sampling using a co-oximeter (type 270 Chiron Diagnostics) and given as a percentage of the total haemoglobin concentration.

The blood samples for analysis of lidocaine, prilocaine and o-toluidine were centrifuged and the plasma stored at $-20°C$ until required for analysis by high performance liquid chromatography using a method based on the assay described by Klein et al. [8]. Separation was achieved using a 250×4 mm Spherisorb RP18 column with a 75×2 mm RP-guard column (Chrompack BV, Bergen op Zoom, The Netherlands). Detection was at 210 nm with a flow rate of 1.5 ml min^{-1} using an isocratic mode (Thermo Quest, Breda, The Netherlands). The internal standard was bupivacaine (Astra, Zoetermeer, The Netherlands). The mobile phase was prepared from acetonitrile and disodium phosphate (Na_2HPO_4) buffer (55:45 v/v). The buffer was composed of 8.9 g Na_2HPO_4 and 0.4 g tetramethylammonium chloride (as modifier) per liter demineralised water and adjusted to pH 5.4 with 50% phosphoric acid.

The assay was validated determining the following parameters: detection limit, lower and upper limit of quantitation, accuracy, intra-assay and inter-assay precision and recovery. Specificity was determined by analysing blank plasma and the usual co-medication. No interference with the analytical method was observed.

Results

Twelve neonates (5 males and 7 females) entered the study with a median gestational age of 31 weeks and 6 days (range 30.1–36.3 weeks) and a median birth weight of 1665 g (range 1100–2910 g) at a postnatal age of 6 days (range 4–8 days). One patient was excluded from the study after analysis of plasma concentrations of lidocaine, prilocaine and o-toluidine because of inconsistent results. Blood sampling was probably inadequate. No significant difference in methaemoglobin levels and baseline measurements was observed, levels ranging from 0.2 to 1.1% and 0.1 to 0.7% respectively (Fig. 1).

Low plasma concentrations of lidocaine and prilocaine were measured on the day that lidocaine-prilocaine cream was applied with a maximum at 6 and 12 h after the first application respectively (Fig. 2). The highest concentration of lidocaine and prilocaine measured in one patient was 0.230 and 0.223 mg/l. Eighteen hours after the final application of lidocaine-prilocaine cream low plasma concentrations of lidocaine and prilocaine were detected in one and six patients respectively. All plasma o-toluidine concentrations were below the de-

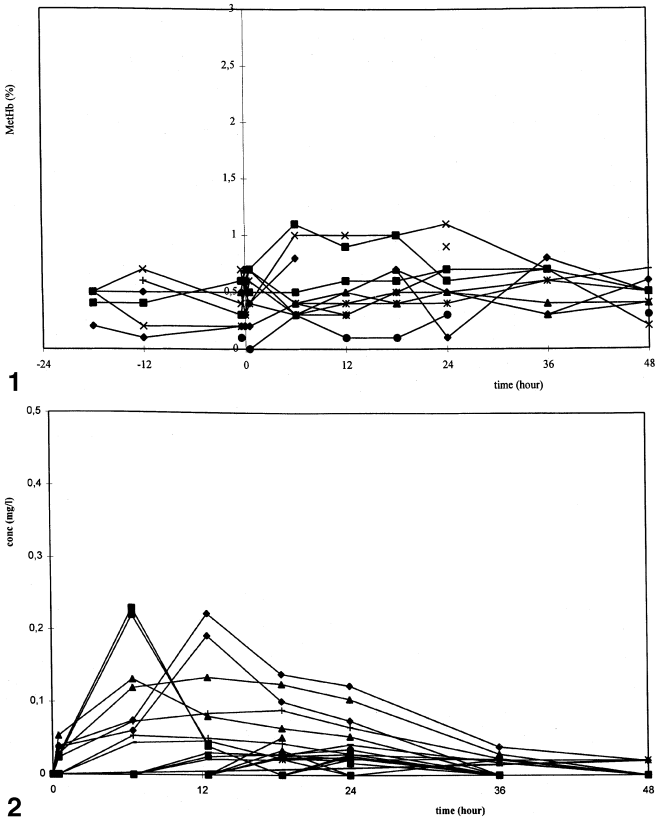

Fig. 1 Methaemoglobin levels in 12 neonates before and after application of lidocaine-prilocaine cream at $t = 0$, 6, 12 and 18 h until 24 h after the final application

Fig. 2 Plasma concentrations of lidocaine and prilocaine in 11 neonates after application of lidocaine-prilocaine cream at $t = 0$, 6, 12 and 18 h until 24 h after the final application

tection limit (0.025 mg/l). No systemic or local adverse reactions were reported.

Discussion

A minimal application time of 1 h of lidocaine-prilocaine cream on intact skin is recommended by the manufacturer. In our study lidocaine-prilocaine cream was applied to the heel of the neonate for 30 min. The shorter application time is justified because immaturity of the neonatal skin will result in a more rapid uptake and a shortened effect compared to children and adults [1–4, 7].

Blood sampling was continued after the final application for 24 h in order to detect a possible cumulative effect of methaemoglobin, or plasma lidocaine, prilocaine or o-toluidine concentrations. All methaemoglobin levels remained below the defined safety parameter of 5%. Also all drug concentrations remained below the defined safety parameters. The plasma concentrations of lidocaine and prilocaine were extremely low and therefore no central effects were to be expected.

A large variation in plasma lidocaine and prilocaine concentrations between patients exists. However, even the maximum plasma concentrations were well below toxic levels. Comparing our results with those of Taddio et al. [11] (single application for 1 h of 0.5 g lidocaine-prilocaine cream) the differences between the maximum plasma concentrations of lidocaine and prilocaine (0.230 and 0.223 vs 0.295 and 0.098) were not clinically relevant. Eighteen hours after the final application, very low plasma concentrations of lidocaine and prilocaine were detectable in a number of patients, while Taddio et al. [11] found a low plasma lidocaine concentration in only one patient 12 h after application. This might suggest a mild cumulative effect, despite the absence of the toxic metabolite o-toluidine.

No correlation was found between maximum methaemoglobin levels and maximum plasma drug concentrations of the local anaesthetics. Since methaemoglobin appears to be the toxic substance it therefore seems adequate to measure the methaemoglobin level as the sole safety parameter in future studies.

Based on these results we conclude that lidocaine-prilocaine cream is safe in preterm, healthy neonates when applied to the heel four times a day in the advised dosage. Future studies on safety of liodcaine-prilocaine cream application several times a day in neonates during an interval exceeding 24 h is mandatory. However, establishing safety by measuring the methaemoglobin level in case of daily application is recommended.

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