PHARMACOKINETICS OF LIGNOCAINE IN CHILDREN FOLLOWING CAUDAL ANAESTHESIA

C. ECOFFEY, J. DESPARMET, A. BERDEAUX, M. MAURY, J. F. GIUDICELLI AND C. SAINT-MAURICE

SUMMARY

The time course of the plasma lignocaine concentration, following caudal anaesthesia, was studied in 11 healthy children (3.5–9 yr). Plasma lignocaine concentrations were measured for up to 6 h after administration (5 mg kg$^{-1}$). Peak plasma concentration was 2.05 ± 0.08 µg ml$^{-1}$ and occurred at 28.2 ± 2.9 min after administration. Pharmacokinetic parameters determined from a two-compartmental model were similar to those observed after the i.v. or extradural administration of lignocaine in adults, except for a longer half-life of elimination (155 ± 32 min). Since the total body clearance of lignocaine was similar in children (15.4 ± 1.2 ml min$^{-1}$ kg$^{-1}$) to that in adults, the longer half-life of elimination was attributed to a larger volume of distribution in the children (3.05 ± 0.40 litre kg$^{-1}$).

Although caudal anaesthesia is used widely in children (Fortuna, 1967; Schulte-Steinberg and Rahlfs, 1970; Armitage, 1979), few studies have considered the pharmacokinetic analysis of the local anaesthetic drugs administered by this route. To date, the only available data relate to mean plasma concentrations following the caudal injection of lignocaine and bupivacaine (Eyres et al., 1978). The present study determined the time course of the plasma concentrations of lignocaine, its initial vascular absorption rate and its elimination characteristics following caudal anaesthesia in healthy children.

PATIENTS AND METHODS

Eleven children (six boys) aged 5.3 ± 0.5 yr, weighing 19.5 ± 1.8 kg were studied. They were free of cardiac, renal or hepatic disease, and were about to undergo lower abdominal or genito-urinary surgery. The study was approved by the Human Investigation Committee and parental consent was obtained. All patients had fasted for 6 h before anaesthesia and were premedicated with atropine 0.02 mg kg$^{-1}$ and diazepam 0.3 mg kg$^{-1}$ i.m. 1 h before surgery. Heart rate was recorded continuously from the electrocardiogram and arterial pressure measured by standard sphygmomanometry every 5 min. Anaesthesia was induced by the inhalation of 70% nitrous oxide plus 1% halothane in oxygen using a partial rebreathing system while patients were lying on their side. Halothane was inhaled for a short period which was always less than 10 min. Once the lid reflex had disappeared, a 22-gauge needle was inserted to the caudal extradural space, and the halothane discontinued. One percent lignocaine 5 mg kg$^{-1}$ (98.4 ± 9.4 mg) was injected at a rate of about 1 ml s$^{-1}$. Venous blood samples (0.5 ml) were drawn from a cannula placed in an antecubital vein. Samples were collected before and at 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 60, 90, 120, 240 and 360 min after the end of the injection of lignocaine. Plasma was separated by centrifugation at 4°C and stored at −20°C for further analysis. Plasma lignocaine concentrations were assayed in duplicate by the specific EMIT homogenous enzyme immunoassay (Syva Biomérieux Laboratories), which measured the concentration of lignocaine between 1 and 12 µg ml$^{-1}$ with a coefficient of variation of less than 10%. Studies in our laboratory showed no cross reactivity between lignocaine and its two major metabolites, monoethylglycinxylidide and glycinxylidide. The pharmacokinetic parameters of lignocaine following caudal anaesthesia were calculated using a two-compartment open model. For each child the lignocaine concentration v. time data were fitted by the non-linear least-squares method using an iterative GRAPHAHIN program. A Tektronix 4052 computer was used in the calculations. Pharmacokinetic parameters were calculated as maximum concentration ($C_{p_{\text{max}}}$), time to $C_{p_{\text{max}}}$ ($t_{p_{\text{max}}}$), vascular absorption and elimination half-lives ($T_{a}^{\text{abs}}$ and $T_{e}^{\text{abs}}$), volume of distribution ($V$), total body clearance ($C_{b}^{\text{clear}}$), and the area under the plasma concentration–time curve.
extrapolated from zero time to infinity according to the trapezoidal rule.

RESULTS

Neither heart rate nor arterial pressure were affected by the institution of caudal anaesthesia. Figure 1 shows the mean time course of the plasma lignocaine concentration following caudal anaesthesia and table I summarizes individual pharmacokinetic parameters. After the injection of lignocaine, the maximum concentration of the drug in the plasma was achieved between 15 and 40 min ($t_{max} = 28.2 \pm 2.9 \text{ min}$) and the concentration ranged from 1.6 to $2.5 \mu g \text{ ml}^{-1}$ ($C_{p max} = 2.05 \pm 0.08 \mu g \text{ ml}^{-1}$). The half-life of vascular absorption was $8.9 \pm 1.0 \text{ min} (T_{1/2}^{abs}) (K_{1/2}^{abs} = 0.09 \pm 0.01)$ and the half-life of the elimination phase was $155 \pm 32 \text{ min}$. The total plasma clearance of lignocaine was $15.4 \pm 1.2 \text{ ml min}^{-1} \text{ kg}^{-1} (Cl)$ and $V$ was $3.05 \pm 0.40 \text{ litre kg}^{-1}$. The area under the plasma concentration–time curve (AUC) was $347 \pm 27 \mu g \text{ min ml}^{-1}$.

DISCUSSION

The present results confirm the views expressed previously (Fortuna, 1967; Schulte Steinberg and Rahlfs, 1970) that caudal anaesthesia with lignocaine is an effective and safe technique in children since no adverse cardiovascular or central nervous effects were observed. $C_{p max}$ was similar to that reported previously (Eyres et al., 1978) in children following caudal injection of 1% lignocaine $4 \text{ mg kg}^{-1}$ and by Freund and colleagues (1982) in adults following the caudal injection of 2% lignocaine $6 \text{ mg kg}^{-1}$ with adrenaline 1:200000; $C_{p max}$ was well below the value of $5 \mu g \text{ ml}^{-1}$ considered as toxic in adults (Foldes et al., 1960). According to Eyres and colleagues (1978), the short initial half-life of vascular absorption of lignocaine ($T_{1/2}^{abs}$) confirms that this local anaesthetic drug is absorbed rapidly through the caudal extradural space in children. However, the half-life of elimination ($T_{1/2}^{b}$) of lignocaine after caudal administration was slightly longer than the corresponding values reported in adults following the i.v. (Benowitz and Meister, 1978) or extradural injection of lignocaine (Tucker and Mather, 1975). Although this pharmacokinetic parameter has not been reported previously in chil-

### Table I. Pharmacokinetic parameters of each child, and mean ± SEM for the group

<table>
<thead>
<tr>
<th>Patient</th>
<th>Weight (kg)</th>
<th>Age (yr)</th>
<th>$C_{p max}$ (µg ml$^{-1}$)</th>
<th>$t_{max}$ (min)</th>
<th>$T_{1/2}^{abs}$ (min)</th>
<th>$K_{1/2}^{abs}$ (min)</th>
<th>$T_{1/2}^{b}$ (min)</th>
<th>AUC ($µg$ min ml$^{-1}$)</th>
<th>$V$ (litre kg$^{-1}$)</th>
<th>$Cl_{max}$ (ml min$^{-1}$ kg$^{-1}$)</th>
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<td>103</td>
<td>369</td>
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<td>1.6</td>
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<td>0.10</td>
<td>153</td>
<td>461</td>
<td>2.39</td>
<td>10.8</td>
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(Mean $19.5 \pm 1.8$ | Age $5.3 \pm 0.5$ | $C_{p max} = 2.05 \pm 0.08$ | $t_{max} = 28.2 \pm 2.9$ | $T_{1/2}^{abs} = 8.9 \pm 1.0$ | $K_{1/2}^{abs} = 0.09 \pm 0.01$ | $T_{1/2}^{b} = 155 \pm 32$ | AUC $347 \pm 27$ | $V = 3.05 \pm 0.40$ | $Cl_{max} = 15.4 \pm 1.2$ |
In conclusion, pharmacokinetic parameters of lignocaine after caudal anaesthesia in children were similar to those reported after the injection of lignocaine in adults, except for $T_{1/2}$, which was slightly longer.

ACKNOWLEDGEMENT

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REFERENCES


PHARMACOCINETIQUE DE LA LIGNOCAINE CHEZ LES ENFANTS A LA SUITE D'UNE ANESTHESIE SACREE

RESUME

Chez 11 jeunes patients (3,5 à 9 ans), on a étudié le parcours temporel des concentrations de lignocaine dans le plasma à la suite d'une anesthésie sacrée. Les concentrations de lignocaine dans le plasma ont été mesurées jusqu'à 6 h après l'administration de l'anesthésique (5 mg·kg⁻¹). Les concentrations maximales dans le plasma étaient de 2,05 ± 0,08 µg·ml⁻¹ et ne sont produites que 28,2 ± 2,9 min après administration. Les paramètres pharmacocinétiques déterminés à partir d'un modèle à deux compartiments étaient analogues à ceux observés après l'administration i.v. ou extradurale de lignocaine chez des adultes, sauf en ce qui concerne la demi-vie d'élimination qui était plus longue (155 ± 32 min). Etant donné que l'élimination totale de la lignocaine du corps était analogue chez les enfants (15,4 ± 1,2 ml·min⁻¹·kg⁻¹) et chez les adultes, on a attribué la demi-vie d'élimination plus longue au plus grand volume de distribution chez les enfants (3,05 ± 0,40 litre·kg⁻¹).

PHARMAKOKINETIK VON LIGNOCAIN BEI KINDERN NACH KAUDALANÄSTHESIE

ZUSAMMENFASSUNG

Bei 11 gesunden Kindern (3,5 bis 9 Jahre alt) wurde der zeitliche Verlauf der Plasma-Lidocainkonzentration nach Kaudalanästhesie untersucht. Die Konzentration wurde bis zu 6 h nach der Verabreichung von 5 mg·kg⁻¹ Lignocain gemessen. Die Plasma-Spiegellagenkonzentration von 2,05 ± 0,08 µg·ml⁻¹ fand sich 28,2 ± 2,9 Minuten nach der Injektion. Die nach dem Zweikompartiment-Modell abgeleiteten pharmacokinetischen Parameter stimmen mit denen nach intravenöser oder extraduraler Verabreichung von Lignocain bei Erwachsenen gefundenen Werten überein, mit Ausnahme der längeren Eliminationshalbwertszeit (155 ± 32 Minuten). Da die Gesamtkörperclearance von Lignocain bei Kindern (15,4 ± 1,2 ml·min⁻¹·kg⁻¹) der von Erwachsenen gleich, wurde die längere Eliminationshalbwertszeit einem größeren Verteilungsvolumen bei Kindern (3,05 - 0,40 litre·kg⁻¹) zugeschrieben.
FARMACOCINETICA DE LA LIGNOCAINA EN NIÑOS DESPUÉS DE ANESTESIA CAUDAL

SUMARIO
En 11 niños sanos (3,5–9 años), se estudió el curso de tiempo de las concentraciones de lignocaina en el plasma después de una anestesia caudal. Se midieron las concentraciones de lignocaina en el plasma durante hasta 6 h después de la administración (5 mg·kg⁻¹). La concentración máxima en el plasma era de 2,05 ± 0,08 µg·ml⁻¹ y ocurrió a los 28,2 ± 2,9 min después de la administración. Los parámetros farmacocinéticos determinados mediante un modelo de dos compartimentos eran similares a los observados después de la administración i.v. o extradural en adultos, salvo en lo que se refiere a la mayor media-vida de eliminación (155 ± 32 min). Puesto que la eliminación corporal total de la lignocaina era similar en los niños (15,4 ± 1,2 ml·min⁻¹·kg⁻¹) y en los adultos, se atribuyó la mayor media-vida de eliminación a un mayor volumen de distribución en los niños (3,05 ± 0,40 litro·kg⁻¹).