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Clonidine and or adrenaline decrease lignocaine plasma peak concentration after epidural injection

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Clonidine is an α_2-adrenoceptor agonist increasingly used in combination with lignocaine for spinal or epidural anaesthesia because of a prolonged analgesic effect. Like adrenaline, it may decrease lignocaine peak concentration (C_{max}), thus leading to decreased toxicity. However, the effects of clonidine on resorption of lignocaine into the systemic circulation from the epidural space remain to be established. We studied the pharmacokinetics of lignocaine after epidural injection of lignocaine with or without clonidine, adrenaline and both drugs. Total body clearance and apparent volume of distribution were similar in the four groups, but the maximum observed concentration (C_{max}) was markedly increased in the plain solution group as compared with the other groups: (plain lignocaine: 7.15 ± 2.04 μg ml^{-1}, lignocaine + adrenaline: 3.11 ± 136 μg ml^{-1}, lignocaine + clonidine: 4.48 ± 1.26 μg ml^{-1}, lignocaine + adrenaline + clonidine: 4.06 ± 1.42 μg ml^{-1} [mean ± s.d.]). Our results show that, clonidine decreases lignocaine C_{max} to the same extent as adrenaline.

Keywords local anaesthetics lignocaine epidural anaesthesia clonidine peak concentration pharmacokinetics regional anaesthesia

Introduction

Clonidine is an α_2-adrenoceptor agonist increasingly used in combination with local anaesthetics for spinal or epidural analgesia [1, 2]. Adrenergic agonist agents exert a direct antinociceptive effect at the spinal cord level by activating the descending noradrenergic pathway [3, 4]. In addition to this direct effect, it has been postulated that clonidine might prolong the duration of action of local anaesthetics by a mechanism similar to that observed with adrenaline [5, 6]. In fact, although it is well established that spinally injected clonidine decreases spinal cord blood flow in various animal species [7, 8], it has not been possible to demonstrate a decrease in systemic resorption of bupivacaine after spinal injection of bupivacaine and clonidine [9]. Since clonidine decreases regional blood flow [10, 11], its seems reasonable to expect that this drug may decrease resorption of epidurally injected drugs in a similar manner to that encountered with adrenaline [5]. This decreased resorption from the epidural space into the systemic circulation leads to a lower peak concentration than usually observed and therefore to decreased toxicity, whereas any phenomenon leading to an increased peak concentration may favour toxic reactions. However, neither fentanyl [12] nor lignocaine [13] resorption from the epidural space seem to be decreased by the concomitant injection of clonidine. In the latter case (lignocaine), it appears that an increased peak concentration might be observed [13]. Because such a potential increase in local anaesthetic toxicity may lead to modified dosage, we present the results of a study of the pharmacokinetics of lignocaine after epidural injection of lignocaine and clonidine in surgical patients.

Methods

Subjects and anaesthesia

After institutional approval, 24 ASA physical status I patients scheduled for minor general or orthopaedic surgery gave their informed consent to this controlled blind study. After 1.5 μg kg^{-1} i.v. fentanyl and 15 μg kg^{-1} i.v. midazolam, an epidural catheter was inserted at the L3–L4 interspace. Patients were randomly assigned to one of the following groups. Group 1

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patients received 20 ml of plain lignocaine 2% (400 mg) + 2 ml of saline; group 2 patients received 20 ml of lignocaine 2% with adrenaline 1/200,000 + 2 ml of saline; group 3 patients received 20 ml of plain lignocaine 2% + clonidine 300 μg in 2 ml; group 4 patients received 20 ml of lignocaine 2% with adrenaline 1/200,000 + clonidine 300 μg in 2 ml. Before lignocaine injection, all patients received a 500 ml fluid load with Ringer lactate solution.

Sampling and analytical procedure

Venous blood was sampled in glass tubes (Vacutainer®) from an indwelling catheter inserted in a forearm vein before and 5, 10, 15, 20, 30, 40, 60, 90, 120, 180, 240 and 360 min after epidural injection. After centrifugation, serum was removed and kept at −20°C until assayed for lignocaine. Lignocaine was determined by gas chromatography with a nitrogen specific detector, using mepivacaine as internal standard [14].

Data analyses

Maximum peak lignocaine concentration (C_{max}) and the time to reach the peak (t_{max}) were measured and the following parameters were calculated: terminal half-life ($t_{1/2}$) was obtained by log-linear regression of the terminal phase of the concentration–time curve; area under the curve (AUC) was calculated by the trapezoidal rule and extrapolated to infinity, total body clearance (CL) was calculated as the ratio between the injected dose (400 mg) and AUC, and the apparent volume of distribution (V) as $t_{1/2} \times CL/0.693$. Statistical analysis used one way factorial ANOVA for demographic data comparison and Kruskal–Wallis test for comparison of pharmacokinetic parameters. The latter was followed by a Mann–Whitney test as appropriate. Data are reported as the mean ± s.d. Geometric mean ratios of significant differences between kinetic parameters are also reported together with their 95% confidence intervals (CI). $P < 0.05$ was considered as significant.

Results

The four groups were similar for demographic data (Table 1). Patients did not experience a decrease in their systolic blood pressure greater than 25% of basal value and therefore none of them required the injection of ephedrine or any other vasoactive agent. C_{max} was significantly higher in group 1 (plain lignocaine) than in the other three groups (Table 1 and Figure 1) as shown by the fact that the geometric mean ratio and (95% CI) between group 1 and the three other groups is always greater than one: 2.43 (1.60–3.25), group 1/group 2; 1.60 (1.15–2.23) group 1/group 3; 1.80 (1.37–2.35), group 1/group 4. In contrast, the 95% CI of the mean ratio between the other three groups is entirely on both sides: 0.66 (0.42–1.51), group 2/group 3; 0.74 (0.29–1.89), group 2/group 4; 1.12 (0.43–1.83), group 3/group 4. All other parameters were not statistically different between the groups (Table 1).

Discussion

We observed a significant decrease in lignocaine C_{max} when clonidine 300 μg or adrenaline 100 μg were added

Table 1 Demographic data and pharmacokinetic parameters

Parameter	*L* *(group 1)*	*L+A* *(group2)*	*L+C* *(group 3)*	*L+A+C* *(group 4)*
Sex (M/F)	3/3	2/4	3/3	3/3
Age (years)	44 ± 22 (16–70)	43 ± 18 (19–64)	31 ± 13 (18–53)	37 ± 10 (22–64)
Weight (kg)	71 ± 10 (57–84)	70 ± 12 (60–89)	65 ± 13 (52–85)	57 ± 12 (41–72)
C_{max} (μg ml^{-1})	7.15 ± 2.04* (5.47–10.96)	3.11 ± 1.36 (1.34–5.47)	4.48 ± 1.26 (3.10–6.02)	4.06 ± 1.42 (2.46–6.40)
t_{max} (min)	30 (10–60)	30 (10–40)	20 (20–120)	25 (10–40)
$t_{1/2}$ (min)	140 ± 58 (68–227)	168 ± 83 (106–320)	149 ± 22 (111–173)	179 ± 37 (118–219)
AUC (μg ml^{-1} min)	1079 ± 113 (900–1225)	888 ± 375 (539–1460)	991 ± 363 (522–1606)	920 ± 295 (625–1333)
CL (ml min^{-1})	374 ± 41 (326–444)	517 ± 194 (274–742)	453 ± 176 (249–767)	546 ± 152 (334–742)
V (l)	76 ± 31 (37–125)	80 ± 33 (33–117)	96 ± 37 (62–164)	118 ± 34 (34–172)

Data are mean ± s.d. (range) except for tmax where data are median (range). * $P < 0.05$ group 1 *vs* all other groups. L = plain lignocaine 2%, L + A = lignocaine 2% + adrenaline 1/200,000, L + C = lignocaine 2% + clonidine 300 μg, L + A + C = lignocaine 2% + adrenaline 1/200,000 + clonidine 300 μg.

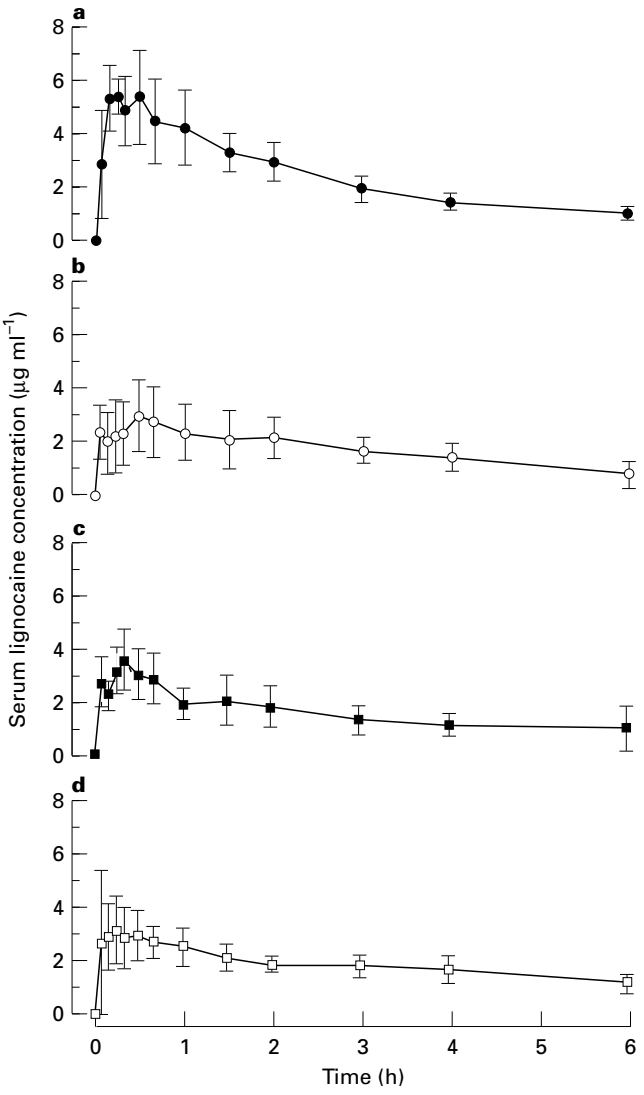

Figure 1 Serum concentration-time profile for plain lignocaine (a), lignocaine + adrenaline (b), lignocaine + clonidine (c), lignocaine + adrenaline + clonidine (d). Data are mean ± s.d.

to lignocaine 2%. The addition of both adrenaline and clonidine (group 4) have led to the same reduction in lignocaine C_{max}, with no additional effect. The decrease in C_{max} when adrenaline was added is in accordance with published results [5], but the results observed when clonidine was added to lignocaine contradict those of Nishikawa & Dohi [13] and of Gaumann *et al.* [15]. However, the former authors used 90 or 180 μg clonidine with lignocaine for epidural block and the latter used 150 μg clonidine with lignocaine for brachial plexus block. We used larger doses of clonidine (300 μg) and this fact may well explain our results. It is admitted that epidurally injected clonidine induces a reduction in local blood flow [10, 11] and that the decrease in local blood flow correlates with the injected dose [10, 16]. It is then possible that the reduction in local blood flow induced by clonidine may be relevant only at the higher doses. Another consideration is that, contrary to the subjects studied by Nishikawa & Dohi [13], none of our surgical patients needed the injection of ephedrine or any other vasoactive drug during the study course. The haemodynamic changes associated with such changes in arterial pressure and vascular resistance may be accompanied by changes in lignocaine disposition. We did not observe any significant difference in V between the four groups. It would be interesting to know if V was similar between the different groups of pregnant women studied by Nishikawa & Dohi [13].

In conclusion, the use of clonidine in combination with lignocaine for epidural anaesthesia or postoperative analgesia is of definite benefit for the patients since pain relief is prolonged without major side effects [1, 2]. Although a higher risk of toxicity due to an increased lignocaine peak concentration has been questioned by some authors [13], our results show that this risk of lignocaine toxicity does not appear to be enhanced by the addition of 300 μg clonidine for epidural anaesthesia.

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