EFFECT OF ADRENALINE ON PLACENTAL TRANSFER OF BUPIVACAINE IN THE PERFUSED IN SITU RABBIT PLACENTA

R. S. LAISHLEY, R. J. CARSON AND F. REYNOLDS

The effect of adrenaline on placental transfer of bupivacaine remains controversial [1, 2]. Extravascular administration of adrenaline has been associated with increased ratios of umbilical arterial to umbilical venous concentrations of bupivacaine in clinical practice [3]. In sheep, adrenaline may cause uterine and placental vasoconstriction [4], while fetal acidosis may promote placental transfer of bupivacaine [5]. If adrenaline does promote fetal uptake of bupivacaine, it is not clear to what degree this is a placental or a fetal effect.

We have investigated the effect of adrenaline on the transplacental distribution of bupivacaine in the rabbit placenta perfused in situ. This allowed investigation of transplacental pharmacokinetics without modulation by fetal physiology.

MATERIALS AND METHODS

Eighteen pregnant New Zealand white rabbits within 4 days of full gestation were anaesthetized with i.v. alphaxalone/alphadoline mixture and 25% urethane solution. Body temperature was maintained using a homeothermic under-blanket. Following tracheostomy, the animals spontaneously breathed air supplemented with oxygen (1 litre min⁻¹). Arterial pressure was measured directly by cannulation of a carotid artery, which also provided a port for blood sampling. Following tracheostomy, the animals spontaneously breathed air supplemented with oxygen (1 litre min⁻¹). Arterial pressure was measured directly by cannulation of a carotid artery, which also provided a port for blood sampling. Each rabbit received a continuous i.v. infusion of bupivacaine 1.25 mg ml⁻¹, either the plain solution followed by the adrenaline-containing solution (n = 10: group 1) or vice versa (n = 8: group 2). Antipyrine 4 mg ml⁻¹ was added to both solutions as an index of placental exchange [6]. The dose ratio of bupivacaine to adrenaline was the same as that used clinically. The infusion rate started at 12 ml h⁻¹ for 20 min, decreasing to 6 ml h⁻¹ for the next 60 min and to 3 ml h⁻¹ thereafter. This infusion pattern has been shown previously in our laboratory to provide rapid plateau maternal concentrations of bupivacaine [7].

In each mother, a hysterotomy was performed and a single fetal sac opened. The three umbilical vessels were cannulated and the placenta was perfused in situ with buffered Krebs solution containing Dextran. Bupivacaine and antipyrine concentrations were measured in effluent perfusate (fetal) and in maternal plasma sampled simultaneously. Mean maternal arterial pressure and mean placental perfusion pressure were not altered by adrenaline. Fetal:maternal concentration (F:M) ratios of antipyrine decreased significantly (P < 0.05) during the second half of the experiment. In contrast, F:M ratios of bupivacaine were unchanged during the time course of the experiment and unaltered by the addition of adrenaline. It is concluded that neither adrenaline nor minor alterations in maternal placental flow affect placental transfer of bupivacaine.

SUMMARY

Following general anaesthesia, each of 18 pregnant rabbits received an i.v. infusion, at a declining rate, of 0.125% bupivacaine, either plain solution followed by adrenaline (1.25 μg ml⁻¹)-containing solution (n = 10) or vice versa (n = 8). All solutions contained antipyrine as an index of placental exchange. In each rabbit, a single fetal sac was opened, the umbilical vessels were cannulated and the placenta was perfused in situ with buffered Krebs solution containing Dextran. Bupivacaine and antipyrine concentrations were measured in effluent perfusate (fetal) and in maternal plasma sampled simultaneously. Mean maternal arterial pressure and mean placental perfusion pressure were not altered by adrenaline. Fetal:maternal concentration (F:M) ratios of antipyrine decreased significantly (P < 0.05) during the second half of the experiment. In contrast, F:M ratios of bupivacaine were unchanged during the time course of the experiment and unaltered by the addition of adrenaline. It is concluded that neither adrenaline nor minor alterations in maternal placental flow affect placental transfer of bupivacaine.
TABLE I. Mean (SD) maternal weights, initial and final blood-gas values, mean arterial pressures and mean placental perfusion pressures

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 10)</th>
<th>Group 2 (n = 8)</th>
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<tbody>
<tr>
<td></td>
<td>Plain</td>
<td>Adrenaline</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>4.37 (0.43)</td>
<td>4.29 (0.33)</td>
</tr>
<tr>
<td>pH</td>
<td>7.41 (0.07)</td>
<td>7.40 (0.09)</td>
</tr>
<tr>
<td>$P_{O_2}$ (kPa)</td>
<td>19.4 (7.5)</td>
<td>21.3 (5.5)</td>
</tr>
<tr>
<td>$P_{CO_2}$ (kPa)</td>
<td>3.4 (0.4)</td>
<td>2.6 (0.3)</td>
</tr>
<tr>
<td>Mean arterial</td>
<td>84 (11)</td>
<td>81 (11)</td>
</tr>
<tr>
<td>pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean perfusion</td>
<td>5.0 (3.4)</td>
<td>4.7 (3.6)</td>
</tr>
<tr>
<td>pressure (mm Hg)</td>
<td></td>
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Vessels were dissected free from overlying membrane and cannulated. The fetus was removed and the placenta perfused via the umbilical arteries with Krebs bicarbonate buffer containing Dextran as described previously [8], at 1 ml min$^{-1}$. The effluent perfusate was collected from the umbilical vein over 5 min, together with a simultaneous maternal arterial sample. A duplicate pair of samples was obtained and the maternal i.v. infusion changed from bupivacaine plain solution to bupivacaine with adrenaline, or vice versa. After a period of 20 min, to allow stabilization with the new infusion, another two pairs of samples were obtained.

Antipyrine and bupivacaine concentrations were measured in umbilical perfusate and maternal plasma by gas–liquid chromatography [3, 9], and concentrations in the infused solutions were checked by the same technique. Perfusate (fetal) to maternal concentration (F:M) ratios of antipyrine and bupivacaine were calculated.

Statistical analyses were performed using analysis of variance and Student's $t$ test. $P < 0.05$ was considered significant. These studies were carried out with Home Office approval under Project Licence numbers ELA 20/3358 and PPL 90/00057.

RESULTS

There were no significant differences between the two groups in weight, arterial blood-gas data and mean arterial pressures (table I), which did not change significantly during the experimental sequence. The use of adrenaline was not associated with a significant change in mean arterial pressure or mean placental perfusion pressure.

The results from one rabbit, which received the
BUPIVACAINE TRANSFER IN PLACENTA

Antipyrine

0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0

Plain 1st Plain 2nd Adren. 1st Adren. 2nd

FIG. 2. Mean (SD) F:M ratios of antipyrine and bupivacaine.

Bupivacaine

0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00

Plain 1st Plain 2nd Adren. 1st Adren. 2nd

Mean antipyrine ratios for all 18 rabbits during plain (□) and adrenaline-containing (■) infusions. There was no significant difference between plain and adrenaline infusions. Mean antipyrine and bupivacaine ratios for each infusion per animal are shown in figure 3. There was no significant difference between plain and adrenaline groups and overall there was a negative correlation between antipyrine and bupivacaine ratios (P < 0.05).

DISCUSSION

Reynolds and Taylor [1] reported increased F:M ratios of bupivacaine associated with extradural adrenaline 5 \( \mu \text{g ml}^{-1} \text{l} \) in human subjects. However, this effect was not observed in two subsequent larger series [2, 10], although recent investigations in intact rabbits [11] and man [3] have suggested again that increased F:M ratios were associated with the presence of adrenaline, but a mechanism for this has not yet been defined. Our study indicates that the transplacental passage of bupivacaine was not influenced by adrenaline when the placenta was perfused in isolation from the fetus.

Earlier work from our laboratory in rabbits demonstrated that, while umbilical flow may affect placental clearances of both antipyrine and bupivacaine [8, 12], maternal placental flow affected only clearance of antipyrine [13]. In the present study umbilical flow was constant, and a decrease in antipyrine ratio, implying impaired placental exchange [14], was therefore likely to reflect a decrease in maternal placental flow [6]. Rosenfeld, Barton and Meschia [4] showed that adrenaline, in doses exceeding 0.1 \( \mu \text{g kg}^{-1} \text{min}^{-1} \), reduced uterine blood flow in sheep; radio-labelled microspheres demonstrated reductions in myometrial, endometrial and placental blood flow. Other
animal studies also have shown that adrenaline may be associated with reductions in uterine blood flow [15, 16]. Jouppila and her colleagues [17] showed that, during extradural anaesthesia for Caesarean section, placental intervillosus blood flow was reduced in association with extradural adrenaline, but this study was not controlled. In a similar study, using chloroprocaine with adrenaline 5 µg ml⁻¹ for analgesia in labour [18] it was concluded that adrenaline had no significant effect on placental blood flow. Thus, although adrenaline may have an effect in pharmacological doses in animals, the doses used clinically may be insufficient to cause this. In the present study, the dose ratio was that used clinically, and the plasma concentration of adrenaline could only have been greater than that resulting from extradural administration. Notwithstanding, it would appear from the antipyrine ratios that adrenaline did not significantly reduce maternal flow, albeit in rabbits, although the passage of time did impair exchange to a small degree.

Transplacental distribution of bupivacaine is governed by binding protein gradient and pH gradient [19], which cannot be controlled in human investigations. In our study, the effect of a variable fetal pH was eliminated by perfusing the placenta with buffered Krebs solution. Binding protein on the fetal side of the placenta may enhance placental transfer of bupivacaine [12], which in itself may mask any effect by adrenaline. Thus our placental perfusate contained only Dextran rather than protein to maintain oncotic pressure.

Bupivacaine is some 100-fold more lipid-soluble than antipyrine [8] and the free fraction can therefore equilibrate readily across the placenta. However, unlike bupivacaine, antipyrine is unbound in maternal plasma, and thus equilibrium ratios of bupivacaine are much lower than antipyrine ratios (fig. 2) and maternal blood provides a significant store of bupivacaine. At high umbilical flows, and at low maternal flows, antipyrine ratios tend to decrease [12, 13, 20], while bupivacaine ratios do not alter significantly, or exhibit a small negative correlation with antipyrine ratios, suggesting that in these circumstances the extraction of bupivacaine from maternal plasma may increase.

It is concluded that, whatever the effect of adrenaline on transplacental distribution of bupivacaine, it has no effect on its placental transfer. These results also tend to confirm those of Vella and Reynolds [13] that bupivacaine transfer is not impaired by poor placental exchange. Moreover, in vivo, equilibrium ratios may be increased in these circumstances, because of fetal acidosis [5].

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REFERENCES


