EFFECT OF ADRENALINE ON THE DISTRIBUTION OF BUPIVACAINE IN THE RABBIT FETUS

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

The placental transfer of bupivacaine is known to be influenced by fetal:maternal concentration gradient [1], pH gradient [2], binding protein gradient [3] and umbilical blood flow [4].

Adrenaline given extradurally [5] or i.v. [6] may decrease uterine blood flow in sheep and placental intervillous blood flow in humans [7]. This effect may be associated with increased fetal:maternal ratios of bupivacaine [8], although this is not a consistent finding [9]. Extradural adrenaline has also been associated with umbilical arterial to umbilical venous ratios of bupivacaine greater than 1 [10]. This may indicate reverse transfer of bupivacaine (that is from fetus to mother), but the mechanism of this effect of adrenaline on fetomaternal distribution of bupivacaine is not clear. We have investigated further the effect of adrenaline on the placental transfer and fetal uptake of bupivacaine in pregnant rabbits.

METHOD

Sixteen pregnant New Zealand White rabbits within 4 days of full gestation (30 days) were anaesthetized with i.v. alphaxalone/alphadolone mixture and 25 % urethane solution, administered via a 21-gauge Butterfly needle in a marginal ear vein. Maintenance of body temperature was assisted by a homeothermic under-blanket. The trachea was cannulated and the does breathed air spontaneously, supplemented with oxygen 1 litre min⁻¹. A carotid artery was cannulated (20-gauge Abbocath) for direct measurement of arterial pressure and sampling of maternal blood. Each doe received a continuous i.v. infusion of bupivacaine solution 1.25 mg ml⁻¹ either plain (n = 8) or with adrenaline 1.25 μg ml⁻¹ (n = 8), via a cannulated neck vein (20-gauge Abbocath). The solutions were prepared by a 1 in 4 dilution of the commercially available ampoules, and thus the dose ratio of bupivacaine to adrenaline was similar to that used clinically. The infusion rate started at 12 ml h⁻¹ for 20 min, decreasing to 6 ml h⁻¹ for 60 min and 3 ml h⁻¹ thereafter. This infusion schedule has been shown previously to produce maternal plateau concentrations of bupivacaine [11]. Total infusion volume for the 2 h of the experiment was therefore 12 ml and contained 15 mg of bupivacaine and 15 μg of adrenaline.

Following the start of the infusion, up to eight fetuses were removed at 15-min intervals through individual hysterotomies. As each fetal sac was opened, samples of maternal arterial blood and amniotic fluid were taken and the placenta was retrieved after expulsion of the fetus. Each fetus was decapitated and exsanguinated to provide a sample of mixed fetal blood and the fetal brain.
was removed. The maternal brain was removed at the end of the experiment. Blood samples were
heparinized and centrifuged to obtain plasma. All
tissue samples were homogenized in hydrochloric
acid 0.1 mol litre\(^{-1}\) (fetal brain in 15 ml; placenta
in 20 ml; maternal brain in 40 ml). Concentrations
of bupivacaine were measured in all tissue and
plasma samples by gas–liquid chromatography as
described previously [10]. The volumes of assay
samples were: plasma and amniotic fluid, 0.25 ml;
placenta and fetal brain, 2.5 ml; maternal brain,
0.5 ml. A sample of maternal blood was taken for
measurement of blood-gas tensions during the
course of each experiment.

Data were analysed by Student’s \(t\) test and a
nested analysis of covariance for repeated
measurements. \(P < 0.05\) was considered signifi-
cant.

RESULTS

There were no significant differences in maternal
weight, maternal brain weight, blood-gas tensions
and mean arterial pressure between the two study
groups (table I). In the plain bupivacaine group,
six does each had eight fetuses and two does each
had seven fetuses (total 62 fetuses). In the
bupivacaine with adrenaline group, six does had
eight fetuses each, one doe had six fetuses and one
doe had four fetuses (total 58 fetuses). There were
no significant differences between the groups in

| Table I. Maternal weights, blood-gas tensions and mean
arterial pressure (mean (SD)) |
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<tr>
<td>Bupivacaine plain</td>
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<td>(n = 8)</td>
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<td>Maternal weight (kg)</td>
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<td>Maternal brain weight (g)</td>
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<td>(pH)</td>
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<td>(P_{a_{CO_2}}) (kPa)</td>
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<td>(P_{a_{O_2}}) (kPa)</td>
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<td>Mean arterial pressure (mm Hg)</td>
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<th>Table II. Placenta and fetal weights (mean (SD))</th>
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<td>Bupivacaine plain</td>
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<td>(n = 62)</td>
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<td>Placenta (g)</td>
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<td>Fetus (g)</td>
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<td>Fetal brain (g)</td>
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<th>Table III. Bupivacaine concentrations ((\mu g \cdot ml^{-1})) in placenta (n = 8) and adrenaline (n = 8) groups (mean (SD)). Bupivacaine concentrations in each group were taken into account. No significant difference between groups in time at which they were measured.</th>
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<td>Bupivacaine</td>
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PLACENTAL TRANSFER OF BUPIVACAINE

Maternal arterial concentrations of bupivacaine did not change significantly with time. This confirmed the effectiveness of our infusion schedule in producing a plateau concentration (table III). Bupivacaine concentrations in maternal arterial plasma (MA), fetal plasma (FP), fetal brain (FB) and amniotic fluid (AF) did not differ significantly between the plain and adrenaline groups, although concentrations in the adrenaline group were consistently greater. Placental (Plac) concentrations of bupivacaine were significantly greater ($P < 0.025$) in the adrenaline group than in the plain group. There was a significant increase with time in concentrations of bupivacaine in fetal plasma and brain, placenta and amniotic fluid ($P < 0.001$). Mean values of bupivacaine concentrations in both groups combined for all tissues and fluid compartments are summarized in figure 1. Maternal brain concentrations ranged from 1.39 to 2.7 μg ml$^{-1}$ in the plain group and from 1.52 to 3.01 μg ml$^{-1}$ in the adrenaline group. In no individual experiment did fetal brain concentrations exceed maternal brain concentrations.

Bupivacaine concentration ratios were calcu-
lated for FP:MA, Plac:MA, Plac:FP, FB:FP, MB:MA and AF:MA, and there were no significant differences for any of these ratios between plain and adrenaline groups. Ratios increased significantly with time for FP:MA (fig. 2), Plac:MA, AF:MA ($P < 0.001$) and decreased significantly with time for Plac:FP ($P < 0.05$) and FB:FP (fig. 3) ($P < 0.001$).

**DISCUSSION**

Our study in humans showed that the addition of adrenaline to 0.5\% bupivacaine improved the quality of extradural analgesia for Caesarean section [12]. However, adrenaline has been associated previously with increased fetal:maternal ratios of bupivacaine [8], although this effect has not always been observed [9, 13]. If extradural adrenaline is to be recommended in obstetric practice, it is desirable to clarify its effect on placental transfer of bupivacaine and fetal bupivacaine toxicity. Our more recent human work [10] again supported the view that adrenaline does not affect fetal:maternal ratios of bupivacaine, but indicated that adrenaline was associated sometimes with increased UA:UV ratios, implying back transfer of bupivacaine. This effect might be caused by altered fetal physiology or alterations in maternal concentrations of bupivacaine. The method of i.v. infusion of bupivacaine in this study was designed to ensure steady state maternal concentrations of bupivacaine [11], so that any effect of adrenaline on fetal uptake could be clearly distinguished.

In this study, the presence of adrenaline was associated with greater concentrations of bupivacaine in placental tissue, which may have been responsible for the trend towards increased concentrations of bupivacaine in fetal plasma and brain. Although there was an apparently consistent trend in increased FP:MA ratios with adrenaline, this was not significant at the 5\% level. With the usual caveats, extrapolation of these animal data indicates that use of extradural adrenaline in human obstetrics should not significantly increase fetal bupivacaine toxicity.

As reported in part previously [14], this study supports the finding that fetal:maternal plasma concentration ratios increase significantly with time to reach a mean maximum value in the region of 0.3 [11]. In addition, it confirms an earlier finding [11] that, despite higher fetal brain:plasma ratios, the concentration of bupivacaine in fetal brain remains less than that in maternal brain, even after 2 h of administration. It also confirms that fetal brain:plasma ratios decrease significantly with time. Although there is some accumulation with time in the fetal compartment, this is seen less in brain than in plasma. A progressive reduction in fetal but not maternal plasma pH has been observed in subsequent experiments [15], irrespective of the presence of adrenaline, and is probably caused by deterioration of the feto-placental unit following laparotomy and repeated hysterotomy—a situation not totally unfamiliar in clinical practice. The reduction in fetal pH promotes ion trapping of the basic bupivacaine in the more acidic compartment. The superior buffering in fetal brain would allow fetal brain:plasma ratios to decrease with time.

There is no evidence from this study to support the theory that low fetal:maternal ratios of bupivacaine are caused by extensive fetal tissue uptake [16]. Low feto:maternal ratios are predominantly the effect of differences in $\alpha_1$-acid glycoprotein concentrations [17].

**ACKNOWLEDGEMENT**

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**REFERENCES**