USE OF LORAZEPAM AS A PREMEDICANT FOR CAESAREAN SECTION
An evaluation of its effects on the mother and the neonate

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Summary
The effects of lorazepam premedication on the mother and baby were compared with those of a placebo in a double-blind study of 10 patients undergoing elective Caesarean section. There was little anxiolytic effect on the mothers, and no harmful effects to the babies occurred in respect of blood-gas tensions, heart rate, temperature or feeding patterns. Lorazepam did produce a transient effect on the neonatal respiratory rate and initially the babies had a reduced score on the Brazelton Assessment System.

Although patients undergoing general surgical procedures have benefited from pre-medication, patients awaiting elective Caesarean section have been less fortunate since the premedicant drugs available had adverse effects on the neonate.

Lorazepam, a potent benzodiazepine, has been shown to have marked anxiolytic and sedative properties (Harry and Richards, 1972). It has a central depressant effect five times as potent as the same dose of diazepam, both in oral and parenteral forms (Comer et al., 1973).

Lorazepam differs from the other benzodiazepines both structurally and in its metabolic pathway. It has a much shorter half-life than diazepam. Less than 1% of the drug is transformed to other metabolites and, as it is excreted predominantly as the glucuronide, it should not be preferentially concentrated in the fetus nor have prolonged effects in the neonate.

In a double-blind trial using lorazepam or a standard premedication of papaveretum and hyoscine, Coleman and Bees (1974) found no difference in the degree of sedation provided. Paymaster (1976) found that lorazepam produced greater loss of recall of events than did papaveretum. Thus, lorazepam would seem to be as good as, if not better than, papaveretum as a premedicant in general surgery. Since papaveretum cannot be used as a premedicant before Caesarean section, because of the respiratory depressant effect on the newborn, lorazepam could prove a useful drug with which to allay anxiety before Caesarean section. Crawford (1979) studied the effects, on the feeding patterns of neonates, of lorazepam administered to the mother before Caesarean section, but no other study has examined the neuro-behavioural effects on the neonate.

Patients and Methods
Ten patients were selected from healthy women, with a normal singleton pregnancy, regularly attending the antenatal clinic at Queen Charlotte's Maternity Hospital. The patients were allocated randomly to one of two groups, in a double-blind manner by Wyeth Laboratories, who kept the coding until the end of the trial. One group received lorazepam and the other a placebo.

Those asked to participate were patients scheduled for elective Caesarean section in whom the fetus was not compromised. The fetus had to have a gestational age greater than 270 days and, to standardize the induction-delivery interval, obese patients were not included and an upper limit of 80 kg was imposed.

All the mothers gave informed consent to the administration of the drug and to the tests performed on themselves and their babies.

Each patient received dichloralphenazone 1.3 g (Weldorm tablets × 2) as night sedation at approximately 10 pm on the night before the Caesarean section. No other drug or additional sedation was permitted. Approximately 90 min before operation each patient received the contents of one randomized phial supplied by Wyeth Laboratories. Half of these contained lorazepam and the remainder lorazepam solvent only. The premedication was given i.m. and the dose calculated at 0.05 mg/kg body weight.
The effects of the premedicant on the patient's anxiety and memory were assessed by the one anaesthetist who anaesthetized all the patients, so that the effects of anaesthesia could be standardized. An objective assessment of anxiety was made by noting the patient's heart rate, arterial pressure and respiratory rate.

Anxiety was tested subjectively by presenting the patient with a card on which was drawn a 100 mm long visual analogue scale (VAS), the left hand of which was marked "I feel relaxed" and the other end of which was marked "I feel petrified". The patient was asked to make a mark at a point along the VAS which she felt represented her degree of anxiety. The distance was measured from the left hand end: the greater the figure, the greater the degree of anxiety.

The effect of the premedicant on the patient's memory was assessed by showing her an object before premedication (a specific coin) and asking her what it was when she came to the anaesthetic room. Then she received the trial medication. Approximately 90 min after premedication, the patient was brought to theatre and the anaesthetist re-assessed her anxiety subjectively and objectively by the same methods and any changes were noted. Memory was tested by asking the patient what object she had been shown before premedication, and she was shown a second object, the nature of which was to be recalled 24 h later.

A standard anaesthetic technique was used (thiopentone, nitrous oxide in oxygen; neuromuscular blockade). All the babies were delivered between 4 and 6 min after the induction of anaesthesia. All the mothers received the same analgesia after operation (papaveretum 10 mg, 6-hourly for 24 h). The anaesthetist saw the mother again 24 h after delivery and assessed the effect of the premedicant on her memory by asking her to recall the object shown her in the anaesthetic room.

The immediate effects on the infants were assessed by the 1-, 5- and 10-min Apgar scores as recorded by the paediatrician present at delivery. The babies' PO₂, PCO₂ and pH were measured on capillary blood taken from a heel prick at 8, 24 and 48 h after birth.

The babies' respiratory rate, heart rate and rectal temperature were taken 8-hourly for the first 48 h and thereafter daily for the 1st week of life.

The neonate's feeding pattern was recorded by the nurses on the ward by giving the baby a score of 0 if it refused to feed. The score was 1 for a poor feed: if it required a great deal of urging to suck, or if bottle-fed, it took less than 30 ml. A score of 2 was given for an average feed: it required some urging to suck, or took 30–90 ml, or was slow to feed. The baby scored 3 for an excellent feed if it required little or no urging to suck, took 90 ml, or fed very quickly.

The final observations were those made by the paediatrician on the babies' neuro–behaviour. These observations, at 2, 8, 24 and 48 h, then after 7 days, were based on the Brazelton Behavioural Assessment Scale (Brazelton, 1953). The scale is an overall measure of an infant's behavioural and neurological condition at the time of examination. Each index of neuro–behaviour is given a score, and these are "clustered" or combined to give the baby an overall score, ranging from 1 (worrisome) to 4 (average) and to 7 (superior) performance.

Statistical methods
For each measurement, the mean and standard error of the mean (SEM) were calculated. Statistical significance was calculated by Student's t-test.

RESULTS
Memory recall and maternal anxiety
Lorazepam had no effect on the recall of the items shown, since all the patients in both groups were able to remember the objects both 90 min after premedication and the following day.

The percentage changes (after premedication) in maternal vital signs and position of mark on the Visual Analogue Scale are shown in table I. No statistically significant differences were found between the two groups.

Neonatal vital signs
Table II shows the effect of lorazepam on the babies' respiratory and heart rates and rectal temperatures. The babies born to subjects who received lorazepam had a significantly ($P<0.001$) faster respiratory rate for the first 3 days; by 7 days (when the effects of the drug would have been eliminated) the difference was less marked ($P=0.02$). The lorazepam produced tachycardia during the 1st day of life, but this was not statistically significant; by day 2 there was no difference between the two groups of babies. Rectal temperature was not affected by lorazepam at any time.

Neonatal feeding patterns
No significant difference in the feeding patterns (table III) was seen between the two groups.
Table I. Effect of lorazepam on maternal vital signs and anxiety.

Parameter                      Lorazepam (Mean ± SEM)          Placebo (Mean ± SEM)
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Heart rate (beats min⁻¹)         -1.6 ± 2.7 *                     +9.4 ± 2.9
Systolic AP (mm Hg)              +3.4 ± 0.9 n.s.                   +1.8 ± 5.1
Diastolic AP (mm Hg)             +11.1 ± 1.5 **                    +5.1 ± 4.5
Respiratory rate (b.p.m.)        -0.3 ± 5.3 n.s.                   +7.8 ± 4.7
Anxiety level (on 100 mm VAS)    -11.2 ± 14.9 n.s.                  +12.2 ± 11.4

Table II. Effects of lorazepam on neonatal vital signs. *P < 0.02; **P < 0.001

Parameter                      Lorazepam (Mean ± SEM)          Placebo (Mean ± SEM)
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Respiratory rate (b.p.m.)        Day 1 54 ± 2 **                     33 ± 3
                                   Day 2 52 ± 3 **                     34 ± 1
                                   Day 3 49 ± 3 **                     30 ± 2
                                   Day 7 48 ± 5 *                      35 ± 1
Heart rate (beats min⁻¹)         Day 1 148 ± 5 n.s.                   138 ± 5
                                   Day 2 143 ± 2                       142 ± 2
                                   Day 3 142 ± 5 n.s.                   142 ± 1
                                   Day 7 142 ± 7                       141 ± 5
Rectal temperature (°C)          Day 1 36.4 ± 0.1 n.s.              36.8 ± 0.1
                                   Day 2 37.0 ± 0.1 n.s.              37.0 ± 0.1
                                   Day 3 36.9 ± 0.2 n.s.              36.9 ± 0.2
                                   Day 7 36.9 ± 0.1 n.s.              37.0 ± 0.1

Table III. Effect of lorazepam on neonatal feeding patterns

Parameter                      Lorazepam (Mean score ± SEM)          Placebo (Mean score ± SEM)
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Day 1                           1.9 ± 0.4 n.s.                     1.7 ± 0.2
Day 2                           2.4 ± 0.2 n.s.                     2.1 ± 0.1
Day 3                           2.4 ± 0.2 n.s.                     2.2 ± 0.2
Day 4                           2.8 ± 0.1 n.s.                     2.5 ± 0.2

Apgar score and Brazelton categories

Lorazepam had no significant effect on the babies’ Apgar scores at 1, 5 or 10 min (table IV). The babies born to mothers given lorazepam were, however, in a lower Brazelton category (0.01 >P> 0.001) 2 h after birth; and the difference remained significant until 8 h. From the age of 1 day, there was no statistically significant difference.

Neonatal blood-gas tensions

The neonatal pH, P O₂ and P CO₂ (table V) were not significantly different between the two groups at any time.

Table IV. Effect of lorazepam on Apgar scores and Brazelton categories. *P = 0.01; **0.01 >P> 0.001

Parameter                      Lorazepam (Mean ± SEM)          Placebo (Mean ± SEM)
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Apgar score                     1 min 7.6 ± 1.2 n.s.                6.8 ± 1.4
                                   5 min 9.0 ± 0.3 n.s.              9.4 ± 0.6
                                   10 min 8.6 ± 1.4 n.s.             10.0 ± 0.0
Brazelton category              2 h 2.8 ± 0.2 **                    5.0 ± 0.5
                                   8 h 3.2 ± 0.4 *                    5.6 ± 0.6
                                   1 day 4.2 ± 0.2 n.s.              5.4 ± 0.6
                                   2 days 4.4 ± 0.2 n.s.             4.8 ± 0.7
                                   7 days 5.8 ± 0.4 n.s.             5.2 ± 0.7

Table V. Effect of lorazepam on neonatal blood-gas tension

Parameter                      Lorazepam (Mean ± SEM)          Placebo (Mean ± SEM)
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P CO₂ (kPa)                      8 h 6.59 ± 0.22 n.s.              6.00 ± 0.23
                                   24 h 5.58 ± 0.31 n.s.             5.42 ± 0.25
                                   48 h 5.68 ± 0.33 n.s.             4.81 ± 0.12
P O₂ (kPa)                       8 h 5.96 ± 0.21 n.s.              5.65 ± 0.25
                                   24 h 5.92 ± 0.27 n.s.             5.97 ± 0.34
                                   48 h 6.62 ± 0.24 n.s.             6.27 ± 0.46
pH (unit)                       8 h 7.30 ± 0.01 n.s.              7.30 ± 0.01
                                   24 h 7.31 ± 0.01 n.s.             7.31 ± 0.01
                                   48 h 7.31 ± 0.01 n.s.             7.31 ± 0.01

Discussion

Previous investigations with lorazepam (Harry and Richards, 1972; Heisterkamp and Cohen, 1975; Paymaster, 1976) have shown it to be an effective...
Lorazepam have shown it to be a safe drug when given in labour (Cree, Meyer and Hailey, 1973), although this effect had worn off by 7 days. This substantiated the findings of McBride and Dundee (1977). They also showed evidence of respiratory depression, although this was not statistically significant. The present study has shown that lorazepam increased the neonate’s respiratory rate, but had no effect on its heart rate. This has been consistent in other studies. In a study of primigravidae given lorazepam 2 mg by mouth (a smaller dose than in the present study) in labour, McAuley and colleagues (1982) found that the infants of those mothers who were premedicated with lorazepam 1 mg before general surgical operations had a tendency to be smaller and more sedated than those who were not premedicated. However, this difference was not statistically significant. The present study has shown that lorazepam increased the neonate’s respiratory rate, but had no effect on its heart rate. This substantiated the findings of Mertens (1974) in his study of the babies born to women given lorazepam during labour. Nor was it a cause of neonatal hyperthermia, which supports the findings of McBride and Dundee (1977). They also found that lorazepam had no effect on the babies’ feeding patterns and Apgar scores, and this also seemed to be so in the present study, although Crawford (1979) had noted a high frequency of “reluctance to feed” when the mother had been premedicated with lorazepam 1 mg before Caesarean section. However, the present study did show that lorazepam decreased the Brazelton scores, although this effect had worn off by 7 days. This compares favourably with diazepam which, when given in labour (Cree, Meyer and Hailey, 1973), produced infants with low Apgar scores, hypothermia and poor feeding patterns. However, these particular workers had used very large doses of diazepam (30 mg or more).

The lack of significant effects on neonatal pH, PO₂ and PCO₂ was similar to the findings of an earlier study on diazepam (Yeh et al., 1974), using comparable doses.

Previous studies on the neonatal effects of lorazepam have shown it to be a safe drug when given to the mother during labour, but no other trial has studied the neuro–behavioural effects on the neonate when given as a premedicant before Caesarean section. Lorazepam resulted in poorer scores on the more comprehensive Brazelton testing scheme, and so its use would be better restricted to specialized hospitals, as recommended by Whitelaw, Cummings and McFadyen (1981).

It was unfortunate that only 10 subjects were studied, but within the time-span of the project it was not possible to recruit further patients. However, in the small group studied, the effects on respiration and neuro–behaviour were statistically significant.

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REFERENCES


