## Absence of respiratory depression in the new-born rat after maternal administration of etorphine by the sublingual route

SIR,—Blane, Boura & others (1967) described the general pharmacology of etorphine, a morphine-like analgesic. This drug was found to be remarkably potent by the subcutaneous or intramuscular routes. Nevertheless, respiratory depression in animals was as great, and possibly greater than that seen with equi-analgesic doses of morphine. Campbell, Lister & McNicol (1964) made similar observations in man with the closely related acetorphine (M183 Reckitt). Etorphine was found to be relatively inactive when administered to a variety of species by stomach tube.

More recently the respiratory depressant effect of subcutaneous etorphine was shown again, this time in pregnant rats at term (Blane, 1967) although, surprisingly, the young delivered by Caesarian section from mothers that had received twice the ED80 for analgesia showed significantly less depression of oxygen consumption than did those from mothers receiving an equivalent dose of morphine or methadone. On the other hand, maternal doses of etorphine substantially above the analgesic ED80 resulted in some neonatal mortality—an effect which was seen to a lesser extent with methadone but which did not occur with morphine.

Since etorphine is active by the sublingual route in the rat the respiratory depressant effect in the pregnant animal has now been investigated.

Etorphine hydrochloride was administered in saline solution to 21-day pregnant rats in a dose-volume of 0·001 ml per 10 g rat. The volume placed in the buccal cavity of the largest pregnant animal was thus about 0·03 ml. No spitting occurred and good dose-response lines were obtained for analgesia. Parallel experiments with morphine were impracticable since effective net doses of this drug could not be contained in sufficiently small volumes of saline to

TABLE 1. EFFECTS OF SUBLINGUALLY ADMINISTERED ETORPHINE ON PREGNANT RATS AND THEIR CAESARIAN-DELIVERED OFFSPRING COMPARED WITH SUBCUTANEOUS ETORPHINE AND MORPHINE. Non-pregnant rats were used in the evaluation of analgesic activity. All the values for % reduction of maternal respiratory frequency at analgesic ED80 × 2 differ from each other at significance levels between 1·0 and 0·1%. Subcutaneous etorphine is significantly less depressant on neonatal oxygen consumption at the maternal analgesic dose of ED80 × 2 than morphine ($P = <0·001$) and sublingual etorphine has no significant effect at this dose-level.

| | Maternal effects | | Neonatal effects | | |
|---|---|---|---|---|---|
| | Analgesic ED80 (mg/kg) 95% confidence limits in parentheses | % reduction of respiratory frequency at analgesic ED80 × 2 | Dose reducing $O_2$ consumption by 20% (mg/kg) 95% confidence limits in parentheses | % reduction of oxygen consumption at maternal analgesic ED80 × 2 | Minimum dose at which deaths occurred (mg/kg) |
| Etorphine sublingual | $38·7 \times 10^{-3}$ ($25·3 \times 10^{-3}$–$59·2 \times 10^{-3}$) | 28·5 | $\geqslant 160 \times 10^{-3}$ | <7·7* | $\geqslant 160 \times 10^{-3}$ |
| Etorphine s.c. | $2·52 \times 10^{-3}$ ($1·85 \times 10^{-3}$–$3·42 \times 10^{-3}$) | 52·0 | $8·65 \times 10^{-3}$ ($6·0 \times 10^{-3}$–$16·0 \times 10^{-3}$) | 16·7 | $12·0 \times 10^{-3}$ |
| Morphine s.c. | 3·36 (2·57 – 4·40) | 11·5 | 1·65 (0·80 – 3·80) | 27·8 | >200 |

* Not significantly different from controls.

avoid spillage from the buccal cavity. Trial experiments showed that analgesia was maximal within 15 min of sublingual etorphine administration and began to wear off after 45 min.

Maternal respiratory rates were measured before treatment and again 30 min later, before the mothers were killed by dislocation of the neck. The young were delivered immediately by Caesarian section and incubated individually in the chambers of a respirometer (Blane, 1967).

It was evident that sublingual etorphine (Table 1) caused less depression in maternal respiratory rate than did equi-analgesic doses by the subcutaneous route ($P = <0{\cdot}01$), although it was still greater than morphine. Of greater interest was the absence of effect of even large maternal doses of sublingual etorphine on the new-born. There was no significant depression of oxygen consumption at twice the ED80 for maternal analgesia. When the young were allowed to remain *in utero* for periods longer than 30 min after maternal administration of the drug (up to 2 hr) the oxygen consumption on delivery still fell within the control range. There was also no neonatal mortality at the highest maternal doses of etorphine used so far (160 $\mu$g/kg).

It is not yet possible to put forward a completely adequate explanation for the apparent absence of neonatal respiratory depression seen in the young rat delivered from mothers receiving analgesic doses of etorphine sublingually. For the present it is suggested that this route avoids the rapid uptake from the site of administration which results in the occurrence of a sharply defined peak in the maternal blood-concentration curve almost immediately after parenteral etorphine (Blane & Dobbs, 1967). It is possible that the levels of etorphine in neonatal brain which cause respiratory depression and sometimes deaths after parenteral administration are consequent to the development of this short-lived peak blood level on the maternal side of the placental barrier and are avoided when the blood-concentration curve is smoothed by slower absorption after sublingual administration to the mothers.

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