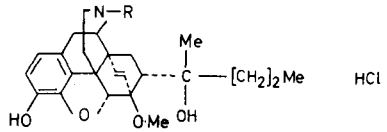
Dissociation of analgesic and respiratory depressant properties in *N*-substituted analogues of etorphine

SIR,—The potent analgesic etorphine (I) shares with all other narcotic analgesics the ability to depress respiratory centres in the brain. This action of the drug, at equinalgesic dose levels, is of greater prominence than that of morphine, both in laboratory species (Blane, Boura & others, 1967) and man (Campbell, McNicol & Lister, personal communication).

Extensive examination of the series of derivatives of tetrahydrothebaine, of which etorphine is a member, has already revealed a number of compounds whose pharmacological characteristics show interesting qualitative and quantitative differences from those of other potent analgesics (Boura & Fitzgerald, 1966; Blane & Boura, 1968). We now find that substitution of the *N*-methyl group in etorphine with allyl, n-propyl, n-pentyl or cyclopropylmethyl groups produces compounds which, whilst retaining morphine-like analgesic properties, are less able to depress respiration. The synthesis of these compounds has already been described (Bentley & Hardy 1967).



I ; R=Me Etorphine
II; R=CH_2—CH=CH_2 R & S 218-M

The hydrochloride of compound (II) [N-allyl-7α-(1-(*R*)-hydroxy-1-methylbutyl)-6, 14 *endo*-ethenotetrahydronororipavine; R & S 218-M] was found to be a potent analgesic after parenteral administration to rats, mice and dogs, using a variety of antinociceptive assays. Thus, given subcutaneously to mice, it was 131 and 100 times more potent than morphine, by the hot plate (Eddy, Touchberry & Lieberman, 1950) or the intraperitoneal phenyl-*p*-benzoquinone (Hendershot & Forsaith, 1959) tests. A similar potency was also found after parenteral administration to rats; the compound caused analgesia at subcutaneous doses which were 52 and 110 times lower than equianalgesic doses of morphine, by the tail pressure (Green & Young, 1951) or inflamed paw (Randall & Selitto, 1957) techniques. A similar action was also caused in dogs, although in this species it appeared less potent. Analgesia could be detected after intramuscular doses approximately 25 times less than those of morphine sulphate (2·5 mg/kg). In each of these test situations the regression lines relating log dose of each drug to intensity of analgesia did not differ significantly from parallelism ($P > 0.05$).

Respiratory depression caused by compound II, as indicated by reduction in frequency of respiratory movements, diminished respiratory minute volume and changes in blood tensions of oxygen and carbon dioxide in mice, rats, rabbits and dogs, was significantly less than that caused by either etorphine or morphine at equianalgesic dose levels. Subcutaneously in mice, the doses of the compound and of morphine required to depress respiratory frequency by 50% were 29·5 mg/kg and 14·6 mg/kg respectively, although compound II was found to be more than 100 times more potent than morphine as an analgesic in this species. In rats a subcutaneous dose of morphine sulphate (10 mg/kg) causing analgesia in the radiant heat test (D'Amour & Smith, 1941) elevated venous pCO_2 levels by 49% compared with controls, whereas an equianalgesic dose of compound II (0·1 mg/kg) increased pCO_2 levels by only 19%. Increasing the dose of either drug five

fold resulted in increased pCO_2 levels of 64 and 25% respectively. At both dose levels these differences between the drugs were statistically significant ($P < 0.01$). Significant differences ($P = 0.01$) were also found between the effects of the two drugs on the frequency of respiratory movements, the higher dose level (50 mg/kg) of morphine causing a decrease in respiratory frequency of 22% and an equianalgesic dose of compound II (0·5 mg/kg) a reduction of 11%.

The compound produced less depression of respiration in the newborn than did morphine after administration in equianalgesic doses to pregnant rats at term. By a method previously described (Blane, 1967) the compound was approximately 6 times more potent than morphine as a depressant of neonatal respiration, after being given subcutaneously to the mothers, while it is about 80 times more potent as an analgesic.

In rabbits the mean intravenous doses of etorphine, compound II and morphine required to cause a fall of 20% in arterial pO_2 levels were 0·0008, 4·2 and 4·0 mg/kg respectively. pCO_2 levels were elevated by 20% after mean doses of the three drugs of 0·0008, 3·2 and 6·6 mg/kg respectively. Hence both parameters showed that compound II caused less respiratory depression in the rabbit, relative to its ability to cause analgesia in the other species used, than did either etorphine or morphine. The doses of etorphine, compound II and morphine required to cause equal depression of respiration as measured by altered gas tensions were approximately 1 : 4,600 : 6,600 which was in marked contrast to the relation found between equianalgesic doses of the three drugs in the rat (1 : 27 : 2,400) and in the dog (1 : 40 : 1,000). A further difference was that the maximum intensity of respiratory depression which occurred after very large doses of compound II was significantly less than that produced by large doses of either etorphine or morphine. After large intravenous doses of compound II (4·5 mg/kg) the maximum respiratory depression was a reduction of 27% in respiratory minute volume, a reduction of 20% in blood pO_2 levels, and an increase of 30% in blood pCO_2 levels. Analogous findings using maximal doses of etorphine (4–10 μg/kg) were 60, 40 and 96% respectively, and for morphine (10–20 mg/kg) 58, 38 and 32% respectively. For each parameter the difference between the effect of compound II and that of either of the other analgesics was statistically significant ($P < 0.01$).

Large doses of compound II (5 mg/kg) given intravenously to anaesthetized dogs caused less respiratory depression than the same dose of morphine. Whereas the latter drug reduced the rate and depth of breathing and evoked periodic respiration, after compound II only reduced respiratory rate was seen.

The actions of compound II on the cardiovascular systems of anaesthetized cats and anaesthetized and unanaesthetized dogs resembled those of morphine and also etorphine by inducing bradycardia and lowered arterial blood pressure. Behavioural changes occurring after its parenteral administration to rodents, cats, baboons and dogs were similar to those which occur after either etorphine or morphine. However, in dogs the compound given intramuscularly failed to cause emesis, and in this respect resembles etorphine rather than morphine (Blane, Boura & Fitzgerald, 1967).

The acute toxicity of compound II seems low. The approximate subcutaneous LD50 values in mice and rats were both > 500 mg/kg, whereas for morphine sulphate they were 506 and 170 mg/kg respectively. The morphine antagonist nalorphine, given parenterally, antagonized analgesia in rats and prostration in dogs caused by compound II.

Substitution of the *N*-methyl group by allyl in several other series of narcotic analgesics, for example the morphines, morphinans and benzomorphans, produces compounds which act as competitive antagonists of narcotic analgesics

(de Stevens, 1965). It is therefore of fundamental interest that an analogous change in the molecular structure of etorphine results in a compound which, although less potent, retains powerful analgesic properties whilst showing altered pharmacological characteristics. The evidence obtained from five laboratory species indicating that in compound II there is dissociation of analgesic and respiratory depressant properties, justifies extension of these studies to man.

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Pharmacological activity of cannabis according to the sex of the plant

SIR,—It is an old tradition, probably originating in India, that the female plants of *Cannabis sativa* contained more activity than male plants (Walton, 1938). In Brazil some planters used to cut the terminal buds to induce more expanded branches, richer foliage and, consequently, more extractable material. According to a popular belief this *castration* of the pistillate plants must be performed only by men (Doria, 1916). By cultivating marihuana near our laboratories (Valle & Hyppolito, 1964) we were able to gather separately the male and female plants, and to prepare a powder of the leaves and flowering tops, and to store the samples by sex under the same conditions. It was possible, then, to reinvestigate whether there existed a difference of activity between the two kinds of powder.

Leaves and flowering tops were separated from other parts of the plant, dried at room temperature (20–24°), powdered and distributed according to the sex of the plant in dark ampoules, 5 g each, closed under nitrogen and kept in the refrigerator (4°). The crude resin to be assayed was obtained: (*a*) after 4–6 hr Soxhlet extraction with light petroleum (b.p. 50–80°), the extracts being treated with activated charcoal, filtered and evaporated under reduced pressure; (*b*) by extracting the powders at room temperature with the same solvent, the charcoal treatment being omitted before filtration. In both instances the residue