

**Modification of the analgesic action of pethidine and morphine by three opiate antagonists, a respiratory stimulant (doxapram) and an analeptic (nikethamide); a study using an experimental pain stimulus in man**

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The ability to antagonize opiate-induced respiratory depression without affecting analgesia would be of considerable clinical value. This paper reports studies carried out with clinically used doses of three opiate antagonists—nalorphine, levallorphan and naloxone, a new effective respiratory stimulant—doxapram, and an established analeptic—nikethamide, with respect to their influence on the analgesic action of pethidine and morphine. It is a continuation of work reported by Hamilton *et al.* (1967).

Sensitivity to pain was measured by the manual application of a measurable pressure to the anterior surface of the tibia, noting two end points: (a) first appreciation of any pain and (b) unbearable pain. The applications, limitations and expected range of observer error of this method of algometry have been studied in detail by Dundee and Moore (1960). Preinjection control readings were carried out in duplicate or triplicate and patients were excluded from the study if these lay outside the accepted range of individual variation. Algometry readings were carried out at 1–2 min intervals for up to 10 min after the test drug was given.

Drugs were given intravenously and observations were carried out in a quiet room on subjects of both sexes. Doses were calculated on a weight basis and are expressed as the equivalent for a 60 kg subject. In the first part of the study a demonstrable degree of analgesia was induced by 100 or 200 mg pethidine and the test drug injected 5 min later. (Doses employed were nalorphine 10 mg, levallorphan 1–2 mg, naloxone 0.4 mg, doxapram 60 mg, nikethamide 250 mg). The second part was carried out using a 'double blind technique', 10 mg morphine being given alone or premixed with nikethamide, doxapram or naloxone. A placebo (saline) group was included in this part of the study. Each drug combination was given to 8–10 subjects. The incidence of significant changes in the average of the two end-point readings is presented and the statistical significance of the findings determined by Fisher's exact probability test.

All three opiate antagonists markedly reduced, or in some instances abolished, pethidine-induced analgesia. The overall effect was related to the relative dose of agonist and antagonist and was most marked and prolonged when 2 mg levallorphan was given after 100 mg pethidine. Pethidine-induced analgesia was abolished temporarily by nikethamide but not affected by doxapram.

Analgesia was demonstrated in a significantly smaller number of subjects after morphine-naloxone than after morphine alone. Antagonism of morphine analgesia by nikethamide was very transient while doxapram had no detectable effect on the analgesic action of the opiate.

Doxapram has been given in combination with postoperative analgesics and preliminary results suggest that it does not interfere with pain relief in a clinical situation.

#### REFERENCES

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#### Ascorbic acid and cholesterol mobilization by fenfluramine

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On a scorbutic diet, guinea-pigs initially gain weight before weight loss occurs; females can make metabolic readjustments so that they maintain higher tissue ascorbic acid