# Nikethamide and doxapram effects on pentazocine- and morphine-induced respiratory depression

Hunter & Major (1970) recently described nikethamide reversal of pentazocine- and morphine-induced respiratory depression in rabbits. These authors were concerned with pentazocine depression because it is not antagonized by nalorphine but is reversed by naloxone, a narcotic antagonist not yet available in the United Kingdom.

We now report a comparison of doxapram* and nikethamide in dogs anaesthetized with phenobarbitone sodium, 125 mg/kg. All drugs were administered intravenously. Respiratory parameters were recorded with a pneumotachograph, a volumetric pressure transducer, a unit integrator, and a polygraph. The respiratory stimulants were given 10 min after the analgesics, when respiratory depression was near its maximum. Changes (mean differences) produced by this treatment were considered significant when $P<0.05$ (Students' *t*-test).

Table 1. *Effects*[1] *of nikethamide and doxapram on pentazocine- and morphine-induced respiratory depression in anaesthetized dogs*[2,3].

| Group | After i.v. injection of | minute volume Mean | s.e. | *P* | Respiratory rate Mean | s.e. | *P* | amplitude Mean | s.e. | *P* |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | morphine | 43·8 | 6·0 | >0·05 | 92·5 | 16·8 | >0·5 | 67·7 | 14·0 | >0·2 |
| | nikethamide | 60·8 | 5·0 | | 79·8 | 9·2 | | 88·7 | 15·5 | |
| 2 | pentazocine | 45·2 | 2·3 | >0·5 | 51·3 | 4·3 | >0·5 | 126·2 | 13·8 | 0·5 |
| | nikethamide | 47·7 | 3·8 | | 45·7 | 7·1 | | 140·8 | 15·6 | |
| 3 | morphine | 38·2 | 4·8 | <0·005 | 54·5 | 8·9 | <0·01 | 80·8 | 9·6 | >0·05 |
| | doxapram | 87·3 | 12·4 | | 93·7 | 7·3 | | 111·8 | 13·0 | |
| 4 | pentazocine | 48·8 | 1·0 | <0·001 | 52·5 | 6·2 | <0·001 | 93·2 | 14·8 | >0·2 |
| | doxapram | 138·7 | 15·1 | | 117·8 | 11·3 | | 117·5 | 16·1 | |

[1] expressed as % of control values.
[2] six dogs at each of the four test combinations.
[3] doses: nikethamide, 25 mg/kg; doxapram, 5 mg/kg; pentazocine, 8 mg/kg; morphine, 2 mg/kg (except one dog that received 4 mg/kg).

The results are summarized in Table 1. Respiratory minute volume was decreased by both pentazocine and morphine to about 45% of control values. Subsequent administration of nikethamide did not significantly increase minute volume that had been decreased by either analgesic. In contrast, doxapram significantly improved the respiratory depression that was induced by both analgesics as observed by the increase in minute volume. Respiratory amplitude was not reduced by pentazocine or morphine and it was not enhanced by either nikethamide or doxapram. Nikethamide had no effect on respiratory rate, but doxapram significantly antagonized both pentazocine- and morphine-induced bradypynoea.

Doxapram holds an important advantage over narcotic antagonists also in that it can maintain adequate respiratory function without detectably decreasing the pain-relieving action of narcotic analgesics Newell, Watson & others (1969).

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* Doxapram hydrochloride monohydrate (Dopram, A. H. Robins Co.): to be available in the United Kingdom.

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# Antagonism of (+)-amphetamine-induced hyperthermia in rats by pimozide

Whether hyperthermia induced by amphetamine in rats is due to a central or peripheral site of action is still unanswered. Hessa, Clay & Brodie (1969) stated that amphetamine-induced hyperthermia in rats is due to a peripheral site, whereas Hill & Horita (1970) attributed the hyperthermia in rabbits to a central site. The peripheral action was attributed to increased concentrations of plasma free fatty acid. However, we have demonstrated that increased plasma free fatty acid concentrations are not an integral part of hyperthermia observed after amphetamine administration in rats (Matsumoto & Shaw, 1971). We now present evidence for a central component of amphetamine-induced hyperthermia.

Male Wistar rats (Harlan Industries, Indianapolis, Indiana), approximately 175 g, were housed five per cage of 25 × 25 × 15 cm. After rectal temperatures were measured with a thermister probe (TRI-R), pimozide (10 mg/kg i.p, salt) was administered; 1 h later, (+)-amphetamine (5·52 mg/kg salt) was administered. Rectal temperatures were read at 30, 60, 120, 180 and 240 min after amphetamine,

Amphetamine increased body temperature from 36·8° by ~1° from 30 min to 2 h, and with a maximum at 1 h of 38·4°. At 3 h the temperature had fallen to 37·5° and was normal at 4 h and both saline and pimozide did not alter body temperature. However, pimozide effectively antagonized the hyperthermia due to amphetamine. According to Andén, Butcher & others (1970), pimozide antagonizes the action of dopamine in the cns. Moreover, Janssen, Niemegeers & others (1968) reported that pimozide is an effective antagonist of amphetamine's behavioral effects. Also, Costa & Groppetti (1971) reported that amphetamine increases the turnover of dopamine in the cns. Thus, the antagonism of amphetamine-induced hyperthermia by pimozide would be consistent with a central site of amphetamine's action and may involve a dopaminergic system.

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