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Departments of Neurosurgery and Pharmacology,
University of Göteborg,
Sweden.
September 6, 1968

HUGO ANDERSSON
BJÖRN-ERIK ROOS

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The effect of promethazine on the antinociceptive actions of some narcotic analgesics

SIR,—Moore & Dundee (1961) showed that the clinical effectiveness of pethidine as an analgesic was reduced when given in association with promethazine. Siker, Wolfson, & others (1966) confirmed this finding in man by tests with an ear lobe algesiometer. Moore & Dundee also reported that promethazine had a hyperalgesic effect.

Dundee (1960) and Clutton-Brock (1960) had previously found that thiopentone and pentobarbitone would reduce the effectiveness of pethidine and were hyperalgesic. Neal (1965) was able to demonstrate, in mice, a reduction of the antinociceptive activity of morphine and pethidine with thiopentone and other barbiturates. He showed also that the barbiturates were hyperalgesic in mice.

We have tried to show an antagonism of the antinociceptive action of pethidine and other analgesics in mice using an electroshock method devised by Reinhard & DeBeer and described by Burn, Finney & Goodwin (1950).

SASTO strain female mice weighing between 15 and 20 g were first tested to ensure that they would vocalize in response to electroshocks applied at 1 sec intervals to their tails. Animals which did not respond to five or fewer shocks were rejected.

Groups of ten mice were given subcutaneous injections of either saline or a solution of promethazine hydrochloride (10 mg/kg) 15 min before the subcutaneous injection of the analgesic. Thirty min later the animals were again tested for a vocalizing response to the electroshocks. Failure to respond to five more shocks than were previously required to induce a response was our

TABLE 1. THE EFFECT OF PROMETHAZINE ON THE ANTINOCICEPTIVE ACTION OF ANALGESICS

Drug	Mean ED50 mg/kg s.c.	s.d.	No. of experiments	s.e.	Probability
Diamorphine HCl	1·9	0·3	7	0·1	< 0·001
,, ,, after promethazine	2·9	0·5	7	0·2	
Morphine sulphate	7·7	1·8	8	0·6	< 0·001
,, ,, after promethazine	12·1	2·5	8	0·9	
Codeine phosphate	73	12	7	4·5	< 0·001
,, ,, after promethazine	121	19	7	7·2	
Pethidine HCl	29	6	9	2	< 0·05
,, ,, after promethazine	32	7	9	3·5	

selected end point for antinociception for that animal. From the dose response curve, the dose of analgesic causing abolition of response in 50% of the animals (ED50) was measured. Each determination of ED50 was repeated at least seven times.

Promethazine itself had no measurable effect on the nociceptive response at doses ranging from 2·5 to 40 mg/kg; it caused neither analgesia nor hyperalgesia. The mean number of shocks required to produce a vocalizing response in 80 mice treated with saline was 2·78 $\pm$ 0·4. The mean number required to produce a response in 80 mice treated with promethazine hydrochloride 10 mg/kg was 2·82 $\pm$ 0·5.

The results in Table 1 show that although promethazine antagonizes the antinociceptive actions of codeine, morphine and diamorphine in mice in this test, it does not show a significant effect on pethidine.

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Department of Chemistry and Biology,
Barking Regional College of Technology,
Longbridge Road,
Dagenham, Essex,
England.

G. B. LESLIE
BARBARA NUNN

September 3, 1968

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