EFFECT OF TETRABENAZINE ON MORPHINE ANALGESIA IN RATS

By

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It has been reported that some agents which increase the concentration of catecholamines in brain potentiate morphine analgesia (3). It has also been reported that reserpine which depletes catecholamines from the brain and peripheral tissue antagonizes morphine analgesia (5). Since the role of catecholamines in morphine analgesia is a subject of great interest, it was thought worthwhile to see if tetrabenazine., which depletes catecholamines from the brain only, has any effect on analgesia caused by morphine.

MATERIALS AND METHODS

There are various methods for the assessment of analgesic activity in animals. These have been reviewed by Gujral *et al* (1). In the present study, we have used the radiant heat method. An analgesiometer of the pattern described by Gujral and Khanna was used (2). The tail of the rat was subjected to the heat stimulus and the normal "reaction time" noted for each rat. The current was so adjusted that the reaction time was approximately 5 seconds. The rats used in the study were screened initially and those not showing the response within 5 seconds were discarded. In group of 10 rats each, morphine in different doses was injected subcutaneously. To each animal of one group same dose was injected. The reaction time was noted after 20 minutes, keeping the current at the same strength which gave a reaction time of approximately 5 seconds. A reaction time of more than 10 seconds was taken to be indicative of complete analgesia. ED_{50} of morphine was found out by log dose-probit response method of Finney (Fig. 1).

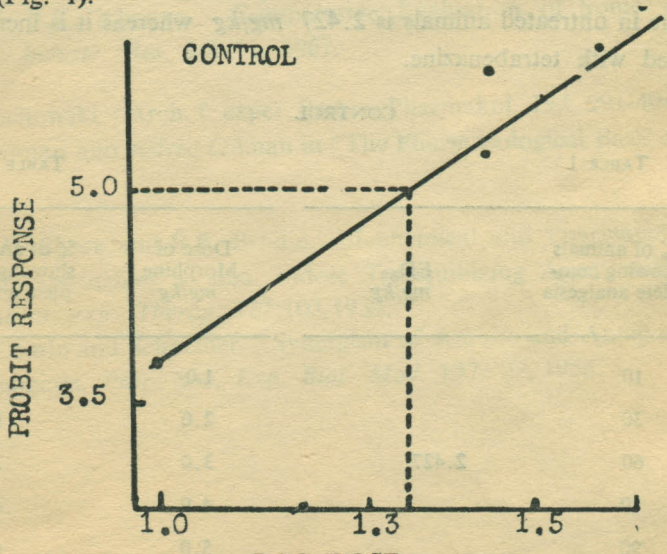

FIG. 1

The effect of tetrabenazine was studied by injecting different doses of the compound to groups of 10 rats each. Four hours after the injection, the ED^{50} of morphine was found out again as described previously (Fig. 2).

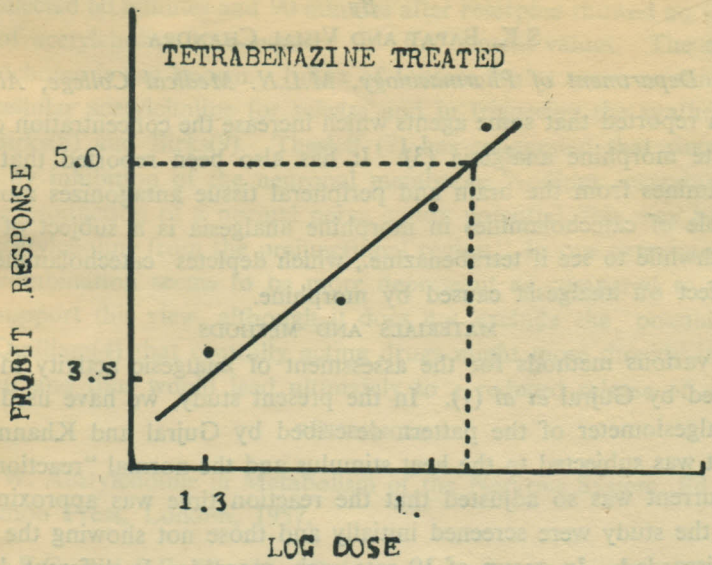

FIG. 2

Fig. 1 and 2 *Showing the Regression Lines and ED^{50} values of Morphine before and after tetrabenazine.*

RESULTS

It is observed that tetrabenazine significantly antagonizes the action of morphine. The ED_{50} of morphine in untreated animals is 2.427 *mg/kg* whereas it is increased to 4.572 *mg/kg* in animals treated with tetrabenazine.

CONTROL

TABLE 1

Dose of Morphine *mg/kg*	% of animals showing complete analgesia	ED_{50} *mg/kg*
1.0	10	
2.0	30	
3.0	60	2.427
4.0	80	
5.0	90	

TABLE 2

Dose of Morphine *mg/kg*	% of animals showing complete analgesia	ED_{50} *mg/kg*
1.0	0	
2.0	10	
3.0	20	4.571
4.0	40	
5.0	60	

DISCUSSION

Tetrabenazine is a peculiar compound in the sense that it depletes catecholamines and 5-HT from brain and has no marked effect on their peripheral stores. It is more potent a depletor of catecholamines than that of 5-HT. The maximum effect is seen in 4 hours (4). Hence in this study tetrabenazine was injected 4 hours prior to the injection of morphine. The increase in ED_{50} of morphine in tetrabenazine treated animals is significant. Previously the same findings have been reported for reserpine. But the change due to tetrabenazine is more significant because it is a more selective depletor of catecholamines (4). There appears to be a possibility that catecholamine (N.A.) concentration in brain plays a role in analgesia by morphine. The findings that adrenaline and noradrenaline in high doses and amphetamine and ephedrine posses analgesic properties (5), points out to the same fact. It would be worthwhile to see the effect of tetrabenazine on duration of morphine analgesia and the effects of drugs which increase the concentration of catecholamines in C.N.S. such as MAO inhibitors. Further work is in progress.

SUMMARY

The effect of tetrabenazine, a central catecholamine depletor, is seen on analgesia by morphine in rats. It has been observed that tetrabenazine when given 4 hours prior to morphine significantly increase the ED_{50} of morphine.

REFERENCES

1. Gujral, M.L., K.P. Bhargava, P.N. Saxena, R.P. Kohli and R.K.P. Maheshwari. Experimental Evaluation in Human Beings of Analgesic Agents. *J. Ind. Med. Prof.* **1**:232, 1954.

2. Gujral, M.L. and B.K. Khanna. Comparative Evaluation of Some of the Narcotic Analgesics *J. Sci. Industr. Res.* **168**:11, 1967.

3. Kiessig and Orzechowski : Arch. f. exper. Path. u.Pharmakol. 197, 291-404, 1941—Quoted by Louis. S. Goodman and Alfred Gilman in "The Pharmacological Basis of Therapeutics." 1965 Ed.

4. Quin, G. P., P.A. Shore and B.B Brodie. Biochemical and Pharmacological Studies of RO 1-- 9569, (Tetrabenazine) a non Indole Tranquillizing Agent with Reserpine-like Effects. J. *Pharmacol. exp. Therap.* **127**:103,1959.

5. Sigg, F.B., G. Caprio and Schneider. Synergism of Amines and Antagonism of Reserpine to Morphine Analgesia. *Proc. Soc. Exp. Biol Med.* **197**: 97, 1958.