Title: ANALGESIC AND ANESTHETIC EFFECTS OF AMITRIPTYLINE AND PHENOTHIAZINES

Authors: A. M. de Rosayro, M.D., T. Rutter, M.D., M. Taylor Busch, M.S., A. R. Tait, B.Sc., and J. M. Bieszki, B.S.

Affiliation: Department of Anesthesiology, The University of Michigan Medical Center, Ann Arbor, MI 48109

Introduction. The tricyclic antidepressants and phenothiazines, singly or in combination, are used extensively in the management of chronic pain. It has been suggested that both these groups of drugs may possess intrinsic analgesic properties in addition to their primary pharmacologic actions. This study was designed to test this hypothesis using amitriptyline and two phenothiazines, fluphenazine and methotrimeprazine, in an experimental animal model simulating acute and chronic pain.

Methods. 12 groups of 10 female Sprague-Dawley rats weighing between 180 and 220 gm were used in this study. There were 3 groups of control animals: 1) not handled at all; 2) given an injection of 0.2 ml sterile saline i.m. twice daily for two weeks; or 3) given distilled water via oral feeding tube once daily for three weeks. The experimental groups received drugs and doses as indicated in Tables 1 and 2, i.m. doses twice daily for two weeks and oral doses once daily for three weeks. At the end of this period the following tests were performed: 1) Tail flick test - the animal was placed in a restraining box with its tail free and a 150 watt light source was centered on its tail. The time taken for a positive flick response was noted; 2) Formalin test - an injection of 0.05 ml sterile 5% formalin was made just under the skin on the dorsum of a forepaw. The animals were then observed continuously for a period of 60 min and the behavioral responses noted as described by Dubuisson and Dennis[1] on a scale of 1-4. Numerical ratings were calculated for 3 min periods from 0-60 min; 3) Halothane MAC - determined by the method described by White, et al.[2] Statistical analysis for all data was accomplished using unpaired Student's t-test.

Results. In a preliminary study using amitriptyline i.m. tail flick times were significantly prolonged in the treated group as compared to both control groups (Table 1). There was no significant difference between the amitriptyline group and rats given a single dose of 1 mg/kg morphine i.m. Similar results were obtained in the experimental groups that were dosed orally (Table 2). There was significant prolongation of tail flick times with all 3 drugs. In the formalin test (Fig.) there was a reduction of pain intensity scores during the second half-hour in all the experimental groups when compared to control and this achieved statistical significance at the times shown. MAC was significantly prolonged only in the amitriptyline group (Table 2).

Discussion. Our results lend support to the contention that tricyclic antidepressants and some phenothiazines do have intrinsic analgesic properties following long term administration. The apparently contradictory elevation of MAC by amitriptyline may be due to differential effects on the serotonergic and noradrenergic systems.

References.

1. Dubuisson D, Dennis SG: The formalin test: a quantitative study of the analgesic effects of morphine, meperidine, and brain stem stimulation in rats and cats. Pain 4:161-174, 1977

2. White PF, Johnston RR, Eger EI II: Determination of anesthetic requirement in rats. Anesthesiology 40:52-57, 1974

Table 1. I.M. Administration (means ± SEM)

	Dosage	Tail Flick Test (sec)
Control 1		2.96 ± .12
Control 2 (saline)		2.11 ± .18*
Amitriptyline	10 mg/kg	5.14 ± .56* †
Morphine	1 mg/kg	5.96 ± 1.23*†

* P< 0.05 vs Control 1 †P < 0.05 vs Control 2

Table 2. Oral Administration (means ± SEM)

	Dosage	Tail Flick Test (sec)	MAC
Control (water)		2.30 ± .10	1.00 ± .04
Amitriptyline	60 mg/kg	3.21 ± .18*	1.10 ± .06*
Fluphenazine	2 mg/kg	3.25 ± .32*	1.04 ± .05
Methotrimeprazine	10 mg/kg	3.58 ± .3*	1.08 ± .04

* P< 0.05 vs Control