LETTER TO THE EDITOR

POTENTIATION OF THE CATALEPTIC EFFECT OF MORPHINE AND CLONIDINE BY AMODIAQUINE IN MICE

Sir,

(Received on October 2, 1984)

Muley *et al.* (3) and Jadhav *et al.* (2) have recently shown histamine to be responsible for the cataleptic effect of morphine and clonidine in mice. Since amodiaquine is reported to inhibit histamine-N-methyl transferase, an enzyme concerned with major catabolism of brain histamine by methylation (4), we have investigated the effect of pre-treatment with amodiaquine on morphine-and clonidine-induced catalepsy in mice.

Male albino mice, 20 to 30 g, were used in groups of 10 for each treatment. They had free access to tap water and a diet locally composed as per Haffkine Institute's specifications. Each animal was used once only. All observations were made at room temperature (27°-30°C), between 10.00 and 16,00 hr in a noiseless, diffusely illuminated room.

For assessment of catalepsy, mice were placed individually in Perspex cages (27 x 20 x 15 cm) 30 min before drug treatment to allow for adaptation. Catalepsy was evaluated by placing both front paws of the animal over a 4 cm high wooden block and measuring the time that the animal maintained this posture. Scoring, modified from that of Ahtee and Buncombe (1), was as follows : maintaining the cataleptic posture for 0 to 10 sec, 0; for 10 to 30 sec, 1; for 30 to 60 sec, 2; for 1 to 2 min, 3; for 2 to 3 min, 4; and for 3 min and more, 5. Animals were tested for catalepsy at 15 min intervals for 90 min only, beginning 15 min after morphine and clonidine treatment.

Amodiaquine HCl (Parke-Davis) was dissolved in distilled water while morphine sulphate (Burroughs Wellcome) and clonidine HCl (Unichem) injection solutions were diluted with distilled water. All drugs were injected ip in a volume of 0.1 *ml*/10 *g* body weight. Doses quoted refer to the salt. Amodiaquine (or distilled water, in control groups) was injected 1.5 hr before morphine or clonicine.

Statistical significance of differences between groups was tested by a two-tailed Mann-Whitney U-test for non-parametric data.

Morphine (10 and 20 *mg/kg*) and clonidine (0.25 and 0.5 *mg/kg*) induced a dose-dependent degree of catalepsy (Table I), without loss of righting reflex or apparent change

in muscle tone or motor coordination. The cataleptic effect of morphine was maximum at 15 min and, depending upon the dose, lasted for 45-60 min after the injection, while with clonidine, the cataleptic effect was present at 15 min and reached maximum 30 min after the injection (Table I).

TABLE I : Effect of pretreatment with amodiaquine (AMD), given 1.5 hr before, on the intensity of catalepsy induced by morphine (MOR) and clonidine (CLN) in mice.

Pretreatment and drug	*Mean catalepsy score (±S.E.M.) from 10 mice*					
(dose, mg/kg)	*15 min*	*30 min*	*45 min*	*60 min*	*75 min*	*90 min*
Vehicle (water) +MOR 10	1.2±0.13	1.0±0.00	0.5±0.16	0.0±0.00	0.0±0.00	0.0±0.00
AMD 60+MOR 10	2.1±0.10*	1.9±0.10*	1.4±0.16*	0.8±0.13*	0.3±0.15	0.0±0.00
Vehicle (water) +MOR 20	2.0±0.00	1.8±0.13	1.3±0.15	0.7±0.15	0.0±0.00	0.0±0.00
AMD 60+MOR 20	3.1±0.10*	2.9±0.10*	2.2±0.13*	1.6±0.16*	1.0±0.00*	0.5±0.16
Vehicle (water) +CLN 0.25	1.0±0.00	1.2±0.13	1.1±0.10	0.7±0.15	0.1±0.10	0.0±0.00
AMD 60+CLN 0.25	1.8±0.13*	2.1±0.10*	2.0±0.00*	1.5±0.16*	0.9±0.10*	0.4±0.16
Vehicle (water)+CLN 0.5	2.1±0.10	2.3±0.15	2.2±0.13	1.9±0.10	1.3±0.15	0.8±0.13
AMD 60+CLN 0.5	3.0±0.00*	3.3±0.15*	3.1±0.10*	2.8±0.13*	2.2±0.13*	1.6±0.16*

*P<0.05 (or less) in comparison with respective control group.

Amodiaquine (30 and 60 *mg/kg*) did not produce any apparent change in the muscle tone or any detectable changes in the gross behaviour of the animals nor did it induce catalepsy when the mice were tested upto 3 hr after injection. Pretreatment with amodiaquine (30 *mg/kg*) did not significantly influence the cataleptic effect of morphine (10 and 20 *mg/kg*) and clonidine (0.25 and 0.5 *mg/kg*). However, pretreatment with 60 *mg/kg* amodiaquine did significantly ($P<0.05$ or less) potentiate the cataleptic effect of 10 and 20 *mg/kg* morphine at 15-60 min and 15-75 min testing time intervals respectively, and of 0.25 and 0.5 *mg/kg* clonidine at 15-75 min and 15-90 min testing time intervals respectively (Table I).

We have earlier reported that L-histidine, a precursor of histamine, potentiates while chlorcyclizine, a H_1-receptor blocker, antagonises the cataleptic effects of morphine and clonidine in mice (2,3) indicating the role of histamine in morphine- and clonidine-induced catalepsy in mice. Our observation that amodiaquine, an inhibitor of the enzyme histamine-N-methyl transferase concerned with major catabolism of brain histamine (4), increases the intensity and prolongs the duration of morphine- and clonidine-induced

catalepsy is consistent with our previous reports and reaffirms the involvement of histamine in the cataleptic effect of morphine and clonidine in mice

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