and "in-process" control to obtain routinely both tablet-to-tablet and lot-to-lot uniformity for a production formulation.

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Notes

Antagonism of Propoxyphene Poisoning in Albino Mice with Nalorphine HCl, Methylene Blue, and Tolonium Chloride

By DAVID E. MANN, JR.

The intraperitoneal administration of propoxyphene HCl to albino mice at a dosage level of 200 mg./Kg. ($LD_{99.5}$) was lethal to 98 per cent of the controls. The prophylactic subcutaneous administration of nalorphine HCl alone, or in combination with either methylene blue or tolonium chloride, significantly increased the number of survivors with the greatest degree of protection being afforded by the nalorphine–dye combinations.

HARPEL AND MANN (1) recently demonstrated the antidotal effectiveness of subcutaneously administered nalorphine HCl and methylene blue, alone and in combination, prior to lethal doses of propoxyphene HCl in mice. The greatest amount of protection against the lethality of the analgesic occurred when nalorphine and methylene blue were administered 5 min. before propoxyphene HCl.

The purpose of this investigation was to confirm the results previously obtained with nalorphine and methylene blue in mice and to determine whether tolonium chloride (toluidine blue), a dye chemically related to methylene blue, also possessed antidotal qualities.

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EXPERIMENTAL

Three hundred and fifty adult male albino mice (Huntingdon Farms, HTF strain), weighing between 20 and 25 Gm., were used in this study. Prior to treatment, the animals were caged in groups of 25 for several days and had access to laboratory chow (Purina) and water *ad libitum*.

The following solutions were prepared with distilled water: propoxyphene HCl, 2.0%, and methyl-

TABLE I.—EFFECT OF SUBCUTANEOUS PRETREATMENT WITH NALORPHINE HCl, METHYLENE BLUE, AND TOLONIUM CHLORIDE ALONE AND IN COMBINATION, UPON THE DURATION AND INCIDENCE OF SURVIVAL FOLLOWING THE INTRAPERITONEAL ADMINISTRATION OF 200 mg./Kg. OF PROPOXYPHENE HCl

Drug[a]	Dose, mg.	Mean Survival Time, sec.	Change in Mean Surv. Time, sec.	Survivors, No.	Survivors,[b] %
Control	...	583	...	1	2
Distilled water	...	580	−3	2	4
Nalorphine HCl	0.1	852	+269	6	12[c]
Methylene Blue	1.0	563	−20	3	6
Tolonium chloride	1.0	480	−103	4	8
Nalorphine HCl and Methylene blue	0.1 1.0	862	+279	19	38[d]
Nalorphine HCl and Tolonium chloride	0.1 1.0	1020	+437	15	30[d]

[a] Drug administered to groups of 50 mice 5 min. prior to propoxyphene HCl. [b] Animals which survived 24 hr. after propoxyphene HCl. [c] χ^2 test, $P < 0.05$. [d] χ^2 test, $P < 0.001$.

ene blue and tolonium chloride, 1.0%, respectively. Ampuls of nalorphine HCl, 5 mg./ml., were obtained from the manufacturer.

The experimental procedure has been previously described (1). In contrast to the former investigation, however, the end point of survival after propoxyphene HCl was extended from 17 min. to 24 hr.

The intraperitoneal LD_{50} of propoxyphene HCl, determined by the method of Litchfield and Wilcoxon (2), was formerly shown to be 118 (106 to 131) mg./Kg. (1). Based upon these data, a dose of 200 mg./Kg. was selected as the lethal amount to be used in future antidotal studies in mice with propoxyphene HCl because theoretically it should produce death in 99.5%.

The treatment schedule consisted of injecting subcutaneously either methylene blue or tolonium chloride (1.0 mg.) into the upper left abdomen, nalorphine HCl (0.1 mg.) or an equivalent volume of distilled water (0.02 ml.) into the upper right abdomen, or nalorphine HCl first (0.1 mg.) followed immediately with either dye (1.0 mg.). Five minutes after prophylactic treatment, propoxyphene HCl (200 mg./Kg.) was injected intraperitoneally and the mice were then placed in individual cages for close observation. Survival time extended from the moment of propoxyphene HCl injection to the cessation of respiration. To determine the precise time of death, the number of animals under observation at one time never exceeded four.

The data obtained from the seven groups of control and treated animals (50 per group) are reported in Table I.

The significance of the per cent survival in the treated group with respect to the control group was estimated by the χ^2 test (3). Probability values greater than 0.05 were considered nonsignificant.

RESULTS

The intraperitoneal administration of 200 mg./Kg. of propoxyphene HCl ($LD_{99.5}$) was fatal to 98% of the controls. The subcutaneous injection of distilled water in a volume equivalent to that employed for nalorphine HCl (0.02 ml.), followed in 5 min. with the intraperitoneal administration of 200 mg./Kg. of propoxyphene HCl, killed 96% of the animals, although the mean survival time (580 sec.) for this group closely approximated that of the controls (583 sec.).

The subcutaneous administration of nalorphine HCl (0.1 mg.) 5 min. prior to propoxyphene HCl resulted in survival of 12% of the mice and extended the mean survival time of the remainder to 852 sec. Interestingly enough, the mean survival time of the controls and nalorphine HCl in the earlier paper is considerably lower than that recorded in this study, yet the increase is approximately the same (256 and 269 sec., respectively). A decrease in the per cent survival after nalorphine HCl from 18.4 to 12 is to be expected because the criterion for survival was changed from 17 min. to 24 hr. These results confirm the earlier observation that definite antagonism of propoxyphene HCl by nalorphine HCl occurs in mice and are in agreement with similar reports in rats (4, 5).

The administration subcutaneously of either methylene blue or tolonium chloride (1.0 mg.) 5 min. prior to propoxyphene HCl did not increase significantly the per cent of survivors (6 and 8, respectively). On the contrary, tolonium chloride increased the convulsant episodes to such an extent that a marked decrease in mean survival time occurred (480 sec.). However, when nalorphine HCl (0.1 mg.) and either methylene blue or tolonium chloride (1.0 mg.) were given together 5 min. prior to propoxyphene HCl, the per cent of survival was significantly increased to 38 and 30, while the mean survival time increased 279 and 437 sec., respectively, beyond that of the controls.

The earlier observation that nalorphine HCl alone or in combination with methylene blue significantly protected mice against lethal doses of propoxyphene HCl has been confirmed under more stringent experimental conditions. In addition, tolonium chloride, a dye chemically related to methylene blue, when administered together with nalorphine HCl, has been shown to enhance the protective activity of the narcotic antagonist in a manner quantitatively similar to its congener.

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