Protective Action of N-Allylnormorphine Against Demerol.* (19250)

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Hart and McCawley(1) and Unna(2) showed that N-allylnormorphine would protect mice against the respiratory depressant action of morphine. This observation was later extended by Huggins, Glass, and Bryan (3) who demonstrated in dogs that N-allylnormorphine protected against lethal amounts of codeine (methylmorphine), Dilaudid (dehydromorphinone), Metapon (methyldihydromorphine), and Methadon (6-dimethylamino-4, 4-diphenyl-3-heptanone hydrochloride). However, no protective action was evident against Demerol (ethyl 1-methyl-4-phenylisonipecotate hydrochloride). In their experiments the dogs had previously received sodium barbital, and it seemed possible that a protective action of N-allylnormorphine against Demerol might have been present but obscured by the barbital, although this was not true for the lethal doses of the other drugs tested. This point was considered worth further investigation because of the extensive use of Demerol and the potentiality of N-allylnormorphine as an antagonist to lethal amounts of many of the other narcotics. It was tested by determining the effect of N-allylnormorphine on mice that had received an LD 50 of Demerol.

Method. All injections were made subcutaneously, using the hydrochloride salts of Demerol and N-allylnormorphine. Gaddum's method(4) was used for determining the LD 50 of Demerol, which for this strain† of mice was found to be 188.3 mg/kg, but for convenience of administration 190 mg/kg was used. The experimental animals were then given the LD 50 of Demerol followed within one minute by varying amounts of N-allylnormorphine. Subsequently trials were made in which the doses of the two drugs were kept constant but the time between their administration lengthened.

Results. N-allylnormorphine in either 10 or 20 mg/kg doses, if given within one minute after the Demerol, reduced the mortality to 7 and 8%, respectively (Table I). Amounts less than 10 mg/kg were not so effective although 0.25 mg/kg reduced the mortality to 23%. If the time of injection of N-allylnormorphine was delayed for 5 minutes after the administration of Demerol, it provided no protection (Table II).

Mice receiving N-allylnormorphine after Demerol were observed to have convulsions in only 14% of the trials as opposed to 66% in animals receiving Demerol alone. Examination of Table III will show that of the animals that had convulsions about 50% died, regardless of which treatment they received. The average length of time between the injection of Demerol and the time of the first convulsion was 29 minutes in N-allylnormorphine treated animals as opposed to 13 minutes for animals

TABLE I. Data on Mice Receiving an LD_{50} Dose of Demerol Followed Within One Min by Different Amounts of N-allylnormorphine.

No. of mice	N-allyl-normorphine, mg/kg	No. of mice surviving	No. dying	% dying
63	20	58	5	8
28	10	26	2	7
28	5	23	5	18
28	1	18	10	35
38	.5	30	8	21
30	.25	23	7	23

TABLE II. Data on Mice Given an LD_{50} Dose of Demerol Followed at Varying Intervals of Time by 20 mg/kg of N-allylnormorphine.

Time between admin. of Demerol and inj. of N-allyl-normorphine, min	No. living	No. dying	% dying
1 or less	58	5	8
5	9	10	53
10	13	6	32
15	8	10	55

* We wish to express our appreciation to Merck and Co., Inc., for the N-allylnormorphine.

† Test animals were Harlan's Swiss albino mice, males, avg wt 19.1 g.

TABLE III. Relationship Between Treatment Given, *i.e.* Demerol Alone in Varying Amounts or Demerol and N-allylnormorphine, and % of Mice Having Convulsions. Time of onset of first convulsion.

Demerol, mg/kg	% having convulsions	% mice showing convulsions who died during exp. period	Avg time between inj. of Demerol and 1st convulsion, min	Time between inj. and 1st convulsion, min
175	66	65	18	2-65
200	75	50	13	2-66
190, followed within 1 min by 20 N-allylnormorphine	14	60	29	5-93

treated with 200 mg/kg of Demerol and 18 minutes for those receiving 175 mg/kg of Demerol. There was a wide range of time intervals before the onset of the first convulsion, but in some mice convulsions developed within 2 minutes after the injection of Demerol.

Discussion. Contrary to the findings of Huggins, Glass, and Bryan(3) using dogs, N-allylnormorphine does have a protective action against Demerol when tested on mice. There would seem to be at least two possible explanations for their failure to find this effect. First, barbitalization of their dogs may have obscured the action of N-allylnormorphine, although this did not occur with the other narcotics they tested. The second possibility is that the very rapid action of Demerol in mice, and perhaps in dogs, necessitates the immediate use of N-allylnormorphine if any reduction in mortality is to be effected. For example, if N-allylnormorphine is given 5 minutes after the injection of Demerol, the number of mice dying approaches 50%, while Unna(2) found protection against an LD 50 of morphine for as long as 15 minutes after its injection. The rapidity with which Demerol may act is also indicated by the onset of convulsion within 2 minutes after its subcutaneous injection in some of the mice.

Summary. (1) N-allylnormorphine in amounts of 10 mg/kg or more, if given within one minute after an LD 50 of Demerol, provides significant protection in mice. (2) If N-allylnormorphine is given 5 minutes after the LD 50 of Demerol, it provides little protection even if 20 mg/kg is given.

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3. Huggins, R. A., Glass, W. G., and Bryan, A. R., PROC. SOC. EXP. BIOL. AND MED., 1950, v75, 540.

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Nutrition of Animal Cells in Tissue Culture. VI. Low Toxicity of Barium.*† (19251)

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During studies on the development of a synthetic medium for animal cells in tissue culture(1-4), it was observed that small

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