Effect of Chronic Nortriptyline Pretreatment on the Acute Toxicity of Various Medicinal Agents in Rats

By D. B. MEYERS, D. O. KANYUCK, and R. C. ANDERSON

A method using rats that can be of value in predicting the effects of chronic treatment with psychotherapeutics on the acute toxicity of other medicinal agents is described. Results obtained by this method showed that nortriptyline, like amitriptyline, enhanced the toxicity of most cerebral depressants in an additive manner. Both of the antidepressive compounds were shown to markedly potentiate the toxicity of physostigmine and to a lesser degree pilocarpine. Ephedrine toxicity was significantly antagonized by thymoleptic pretreatment. The test failed to verify reports that the tricyclic antidepressives dangerously potentiate the toxicity of alcohol or monoamine oxidase inhibitors. Results indicated that a variety of medicinal agents can be used in the nortriptyline treated patient without any problem of significant drug interaction.

NUMEROUS but sometimes contradictory reports of clinical problems resulting from the interaction of antidepressive agents with various other drugs have appeared in recent months. The potentiation of toxicity of thymoleptics by ethyl alcohol has been reported by some workers but not confirmed by others (1, 2). Various articles have cited the hazards of concurrent use of the tricyclic antidepressives and monoamine oxidase inhibitors while others have minimized the danger and cited evidence of the value of such combinations (3–8). More isolated cases in which a thymoleptic agent has been suspected of potentiating the toxicity of barbiturates, chlordiazepoxide, amphetamine, digitoxin, meperidine, or isopropylarterenol have been reported.

In view of the controversial nature of many of these observations this study was designed to evaluate the effect of chronic pretreatment of rats with nortriptyline HCl upon the acute toxicity of a variety of medicinal agents. It was felt that information gained from a systematic animal study might be of value in predicting the safety or hazards of administering other drugs to patients receiving thymoleptic treatment.

Lethality rather than more subtle pharmacological effects was chosen as the criterion for measuring interaction as it clearly predicts the actual hazard of drug therapy. It also provided a well-defined end point free of operator bias.

EXPERIMENTAL

Materials.—The rats used in this study were Harlan strain males weighing about 250 Gm. Animals of this size were 100–120 days of age and were considered sexually mature.

The nortriptyline HCl and amitriptyline HCl used to pretreat the rats were medicinal grade compounds obtained from the manufacturers. Both were incorporated as the dry powder into the standard rat diet by means of a Hobart mixer.

All of the neuro-pharmacologic agents used to challenge the pretreated rats were standard medicinal preparations. Most of them were soluble enough so that they could be injected intraperitoneally in aqueous solutions of suitable concentration. Acetylsalicylic acid, meprobamate, and isocarboxazid were given by the same route suspended in a 3% acacia vehicle.

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Method.—Rats were divided into groups so that one group received a standard control diet and a second group the same diet containing 0.04% nortriptyline HCl. For comparison purposes a third group was placed on a diet containing 0.04% amitriptyline HCl. The 0.04% drug concentration was great enough to produce overt signs of thymoleptic activity without undue debilitation of the animals. The rats were caged separately with food and water available *ad libitum*. After remaining on their respective diets for 11–15 days, five animals from each group were used for each interaction test. The compounds used to challenge the thymoleptic pretreated animal for a test of interaction included a variety of neuro-pharmacological agents with established clinical uses. In each interaction test predetermined doses of the challenging agent were given intraperitoneally every 30 min. to the control and thymoleptic pretreated rats until death ensued. A cumulative lethal dose (CLD) for the challenging agent was computed for the individual animals by multiplying the amount of drug per dose (mg./Kg.) by the number of doses required to produce death. An index of interaction (I.I.) was then established by dividing the geometric mean of the CLD values for the control animals by the geometric mean of the CLD's in each of the thymoleptic pretreated groups. Thus, an I.I. significantly larger than 1.00 indicated a synergistic interaction, while an index significantly less than 1.00 was considered evidence of antagonism.

RESULTS AND DISCUSSION

Table I shows the effects of pretreatment of rats with nortriptyline HCl and amitriptyline HCl on the acute toxicity of several compounds that have primary cerebral depressant activity.

Thymoleptic pretreatment augmented the lethal action of most of the cerebral depressants in rats. This observation was in accord with previous findings that many depressants increase nortriptyline toxicity in mice, and lends support to the statement that the newer antidepressives increase barbiturate toxicity in man (5). The increase in depressant toxicity may be explained in part by the fact that the tricyclic antidepressives possess a measurable CNS depressant component of activity (9). Contrary to some reports, this study failed to reveal any significant effect on ethyl alcohol toxicity by either amitriptyline or nortriptyline.

Table II illustrates the influence of nortriptyline and amitriptyline on the toxicity of various types of CNS stimulants.

TABLE I.—EFFECT OF THYMOLEPTIC PRETREATMENT ON THE ACUTE TOXICITY OF CEREBRAL DEPRESSANTS IN RATS

	Interaction Indices	
	Nortriptyline	Amitriptyline
Sodium pentobarbital	1.38[a]	1.40[a]
Sodium phenobarbital	1.08	1.11
Sodium secobarbital	1.54[b]	...
Methapyrilene HCl	1.67[b]	1.21
Meprobamate	1.07	1.33[a]
Chlordiazepoxide HCl	1.30[b]	...
Ethyl alcohol	.95	1.10

[a] $p = 0.1$. [b] $p = 0.05$.

TABLE II.—EFFECT OF THYMOLEPTIC PRETREATMENT OF RATS ON TOXICITY OF CNS STIMULANTS

	Interaction Indices	
	Nortriptyline	Amitriptyline
Pentylenetetrazol	0.94	1.01
Desoxyephedrine HCl	0.81	1.12
Isocarboxazid	0.92	0.90
Tranylcypromine sulfate	1.21	...
Procaine HCl	0.94	0.98
Methylphenidate HCl	1.01	...

TABLE III.—EFFECT OF THYMOLEPTIC PRETREATMENT OF RATS ON THE ACUTE TOXICITY OF AUTONOMIC AGENTS

	Interaction Indices	
	Nortriptyline	Amitriptyline
Ephedrine HCl	0.49[b]	0.64[a]
Isoproterenol HCl	0.83	0.96
Atropine sulfate	0.84	0.81[a]
Scopolamine HBr	1.00	0.87
Physostigmine sulfate	>2.72[b]	>3.60[b]
Pilocarpine HCl	1.68[b]	1.16[a]

[a] $p = 0.1$. [b] $p = 0.01$.

TABLE IV.—INFLUENCE OF THYMOLEPTIC PRETREATMENT OF RATS ON THE ACUTE TOXICITY OF VARIOUS OTHER AGENTS

	Interaction Indices	
	Nortriptyline	Amitriptyline
Meperidine HCl	0.92	1.06
Dextropropoxyphene HCl	0.82	0.68[a]
Acetylsalicylic acid	1.05	1.01
Chlorpromazine HCl	0.96	1.07
Scopolamine HBr	1.00	0.87
Nortriptyline HCl	1.15	...
Quinidine sulfate	0.92	0.95

[a] $p = 0.1$.

Although the intensity of the stimulant-induced convulsions was somewhat moderated in the pretreated animals, there was no significant interaction between the thymoleptics and any of the stimulants tested. Neither type of monoamine oxidase inhibitor, isocarboxazid or tranylcypromine, proved to be significantly more toxic in the pretreated animals.

The influence of pretreatment with the thymoleptics on the toxicity of various types of agents that actively affect the autonomic nervous system is shown in Table III.

Marked influences of the antidepressive pretreatment on the toxicity of some of the drugs which act upon the autonomic system were apparent. In general the toxicity of the adrenergic stimulants and cholinergic blockers was reduced. The most significant reductions occurred with ephedrine and atropine, both of which possess a measurable component of central stimulation. The most dramatic potentiation of toxicity was seen with physostigmine which killed the thymoleptic pretreated rats with intraperitoneal cumulative doses as low as 0.9 mg./Kg. Evidence that this potentiation of toxicity might be applicable to human medicine was found in a medical report which described an abnormal response to neostigmine in a patient who was concurrently receiving therapeutic doses of nortriptyline HCl (10). Pilocarpine toxicity was also increased in the pretreated animals but not in the same magnitude as was physostigmine.

The effect of the cyclazid antidepressives on the acute toxicity of other drugs with neuro-pharmacological properties is shown in Table IV.

The only compound in this group to show an interaction was dextropropoxyphene HCl. The significant reduction in toxicity can be accounted for by the fact that dextropropoxyphene when administered intraperitoneally or intravenously exhibits a stimulating action in rodents which contributes greatly to its lethality. It is probable that this component of action was antagonized by the thymoleptics. The result obtained with nortriptyline HCl indicated that neither tolerance nor sensitivity to the compound itself developed during the pretreatment period.

CONCLUSION

The data collected by the method described show that nortriptyline, like amitriptyline pretreatment, enhances the toxicity of most cerebral depressants in rats. Quantitatively, the results indicate that the increase is probably in the order of an additive effect.

The test confirmed that the concurrent use of physostigmine and the cyclazid antidepressives may produce dangerous results. The data indicate that the physostigmine–thymoleptic interaction should be described as marked potentiation. The increase in pilocarpine toxicity may also be regarded as potentiation but of a much milder degree.

The test failed to supply confirming evidence to clinical reports of the potentiation of the toxicity of alcohol by the antidepressive compounds. Nor did it substantiate the validity of the controversial warning that the concurrent use of thymoleptics and monoamine oxidase inhibitors should be strictly avoided.

The experimental results indicated that a wide variety of medicinal agents could be used following thymoleptic pretreatment without danger of drug interaction.

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