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▲ To whom inquiries should be directed.

NOTES

Cardiovascular Effects of Digoxin–Phenelzine Interaction in Rabbits

JEFFREY S. BOHRMAN* and EMMANUEL B. THOMPSON▲

Abstract □ The potential toxicity of combining phenelzine, an MAO inhibitor, and digoxin, a cardiac glycoside, was studied in rabbits. Cardiovascular responses following concurrent administration of these drugs and the administration of these drugs 20 and 60 min. apart, respectively, revealed that phenelzine and digoxin evoked arrhythmias in about 50% of all rabbits tested without markedly altering the arterial blood pressure. Spontaneous heart rate in these animals was found to be lower than control values. The incidence of arrhythmia decreased as the time interval between the administration of both drugs was increased from 20 to 60 min. An increase in the number of days of pretreatment with phenelzine resulted in the use of a higher dose of digoxin to evoke arrhythmia.

Keyphrases □ Digoxin–phenelzine interactions—cardiovascular effects in rabbits, dose–time relationships □ Phenelzine–digoxin interactions—cardiovascular effects in rabbits, dose–time relationships □ Interactions, digoxin–phenelzine—cardiovascular effects in rabbits, dose–time relationships □ Drug interactions digoxin–phenelzine in rabbits

The administration of digoxin in combination with phenelzine is occasionally employed in clinical practice. However, when an antidepressant drug such as phenelzine, a monoamine oxidase (MAO) inhibitor, is administered concurrently with a cardiac glycoside such as digoxin, an interaction may occur. A digitoxigenin–biogenic amine interaction was reported (1) to play a significant role in the development of digitoxigenin toxicity and lethality. Drugs not belonging to the class of MAO inhibitors but that deplete brain monoamines were found to protect mice and rats against digitoxigenin lethality. On the basis of the preceding information, it can be surmised that digoxin toxicity may be enhanced with concurrent phenelzine administration.

This preliminary investigation was undertaken to determine if concurrent digoxin phenelzine administration would result in enhanced toxicity and if such toxicity was dose related and/or time dependent in terms of the two drugs administered together.

EXPERIMENTAL

Cardiovascular Studies of Phenelzine and Digoxin—Adult, female, albino rabbits, weighing 1.96–4.9 kg., were anesthetized with sodium pentobarbital[1], 25 mg./kg. i.v.; supplemental doses of 0.2 ml. sodium pentobarbital were injected as needed. Carotid arterial blood pressure was recorded using a pressure transducer[2], while heart rate was determined from limb lead II electrocardiographic records. All monitored parameters were recorded on an ink-writing oscillograph[3].

Studies of certain cardiovascular responses to either phenelzine (2.5, 5, and 10 mg./kg.) or digoxin (0.125 and 0.250 mg./kg.) administered individually by jugular vein served as the control basis for comparison with concurrent administration of both drugs. At least six rabbits were used in each experiment. Control readings of spontaneous heart rate and arterial blood pressure were recorded at 10-min. intervals prior to the injection of the first drug. Following each drug administration, readings were made at intervals of 0.5, 1.0, 5.0, and 10.0 min. and then every 10 min. thereafter; three nearly similar readings were obtained before a subsequent dose was administered. Replicate observations were made in the same animal (*i.e.*, 0.125 mg./kg. digoxin was given noncumulatively in the same animal three times before attempting the next dose, 0.25 mg./kg., for the next three trials).

Drug Interaction–Time Course—The following three time-spaced studies of phenelzine and digoxin were conducted: (*a*) drugs concurrently injected intravenously; (*b*) drug administration 20 min.

[1] Abbott Laboratories.
[2] Linear Core P-1000A, Narco Biosystems, Inc., Houston, Tex.
[3] Type PMP-4A, Narco Biosystems, Inc., Houston, Tex.

Table I—Effects of Spontaneous Heart Rate and Incidence of Arrhythmias following Interactions of Phenelzine and Digoxin in Rabbits

Treatment	Dosage, mg./kg.	Number of Observations	Mean Spontaneous Heart Rate/min. ± *SE*				Quantal Incidence of Arrhythmias
			Control	5 min.	20 min.	30 min.	
Digoxin	0.125	15	249 ± 5	230 ± 4[a]	236 ± 4	239 ± 4	1/15
	0.250	18	237 ± 4	202 ± 3[a]	201 ± 16[a]	218 ± 13[a]	9/18
Phenelzine	2.5	9	282 ± 2	283 ± 2	283 ± 2	280 ± 2	2/9
	5.0	15	251 ± 6	209 ± 15[a]	247 ± 6	245 ± 5	9/15
	10.0	11	220 ± 9	130 ± 8[a]	193 ± 12	205 ± 11	7/11
Phenelzine and digoxin	2.5 + 0.125[b]	3	268 ± 12	246 ± 3	257 ± 3	270 ± 20	1/3
	5.0 + 0.250[b]	8	234 ± 11	208 ± 20	220 ± 11	227 ± 11	4/8
Phenelzine and digoxin	2.5 + 0.125[c]	4	237 ± 10	200 ± 20[a]	193 ± 33[a]	203 ± 26	2/4
	5.0 + 0.250[c]	4	250 ± 12	215 ± 17[a]	240 ± 10	237 ± 15	2/4
Phenelzine and digoxin	2.5 + 0.125[d]	4	231 ± 8	210 ± 8	225 ± 12	233 ± 10	1/4
	5.0 + 0.250[d]	2	250 ± 7	235 ± 5	205 ± 25	234 ± 16	1/2

[a] Statistically significant from control values ($p < 0.05$). [b] Concurrent administration. [c] Digoxin administered 20 min. after phenelzine. [d] Digoxin administered 60 min. after phenelzine.

apart, with phenelzine being given first followed by digoxin 20 min. later; and (*c*) a similar pattern of drug administration 60 min. apart. The dose levels of digoxin and phenelzine used were 0.125 or 0.25 mg./kg. and 2.5 or 5.0 mg./kg., respectively.

Effects of Phenelzine Pretreatment on Digoxin-Induced Arrhythmias—Six rabbits were pretreated with phenelzine intraperitoneally for varying times, one each for 3, 4, and 5 consecutive days and three for 7 days. Pretreatment days with phenelzine were varied to determine long- and short-term effects of this drug when interacting with digoxin. Two dose levels of phenelzine were tested: 2.5 and 5 mg./kg. The first three rabbits received 0.125 mg./kg. i.v. of digoxin on a cumulative basis every 20 min. until arrhythmias developed. Similarly, the other three animals received digoxin, 0.25 mg./kg. A control study of six other rabbits pretreated with normal saline in the same dose regimen described for phenelzine was also conducted. These rabbits were similarly challenged with digoxin.

RESULTS

Spontaneous Effects of Digoxin—Of the two doses of digoxin tested in anesthetized rabbits, only 0.25 mg./kg. produced a sustained decrease in spontaneous heart rate (Table I). The heart rate of animals receiving 0.125 mg./kg. was slowed significantly only at 5 min. after administration and returned to a near preinjection value by 30 min.

A prompt elevation of arterial blood pressure was noted following administration of 0.25 mg./kg. digoxin but was not significant 30 min. later (Table II). Only one out of the 15 observations recorded at the dose level of 0.125 mg./kg. showed a transient arrhythmia following digoxin administration while the dose of 0.25 mg./kg. produced a 50% incidence of arrhythmia (Table I). In almost all of these observations, the arrhythmia was of the ventricular type; onset was noted about 1 min. after injection and the duration was approximately 10 min.

Spontaneous Effects of Phenelzine—All doses of phenelzine, except 2.5 mg./kg., produced varying degrees of reduction of spontaneous heart rate in 5–10 min. (Table I). With each injection of phenelzine, a transient hypotensive effect was noted, generally followed by hypertensive response. The hypertensive response to 2.5 mg./kg. was minimal in some rabbits and nonexistent in others (Table II). There was an increase in pulse pressure with this hypertensive response, which was sustained for approximately 5 to 10 min. by doses of 5 and 10 mg./kg., respectively. The incidence and severity of the ventricular arrhythmias that occurred after injection of phenelzine varied directly with increasing dose (Table I). Most of these arrhythmias were short lived, lasting only about 5 min.

Interactions of Phenelzine and Digoxin—The immediate response to concurrent intravenous administration of phenelzine and digoxin appeared to be bradycardia. This decrease in spontaneous heart rate was statistically significant 5 min. after drug treatment when both phenelzine and digoxin were administered 20 min. apart (Table I). This decrease in heart rate was evident up to 30 min. after drug treatment. The drug combination generally caused a fall in arterial blood pressure, and such a hypotensive response was significant when higher doses of phenelzine and digoxin were administered 20 min. apart (Table II). Phenelzine–digoxin administration evoked arrhythmias of very short duration in 45% of the animals tested.

In these time-dependent studies, the frequency of occurrence of arrhythmias appeared to be inversely related to the prolongation of the time interval between injection of phenelzine and digoxin.

Table II—Effects on Arterial Blood Pressure following Interactions of Phenelzine and Digoxin in Rabbits

Treatment	Dosage, mg./kg.	Number of Observations	Mean Arterial Blood Pressure ± *SE*							
			Systolic				Diastolic			
			Control	5 min.	20 min.	30 min.	Control	5 min.	20 min.	30 min.
Digoxin	0.125	15	131 ± 2	132 ± 2	130 ± 2	129 ± 2	108 ± 3	107 ± 2	107 ± 3	107 ± 2
	0.250	18	134 ± 2	149 ± 6[a]	145 ± 13	138 ± 3	112 ± 3	121 ± 4	120 ± 3	114 ± 4
Phenelzine	2.5	9	125 ± 1	122 ± 6	124 ± 1	123 ± 1	97 ± 1	94 ± 2	98 ± 2	97 ± 2
	5.0	15	150 ± 6	156 ± 11	141 ± 6	141 ± 5	119 ± 5	120 ± 6	114 ± 4	110 ± 4
	10.0	11	119 ± 2	159 ± 3[a]	124 ± 3	116 ± 2	95 ± 9	125 ± 3[a]	100 ± 4	93 ± 3
Phenelzine and digoxin	2.5 + 0.125[b]	3	110 ± 10	113 ± 9	107 ± 10	118 ± 3	89 ± 4	85 ± 9	83 ± 11	95 ± 5
	5.0 + 0.250[b]	8	112 ± 4	116 ± 4	100 ± 9	98 ± 9	90 ± 4	86 ± 5	77 ± 10	75 ± 10
Phenelzine and digoxin	2.5 + 0.125[c]	4	112 ± 7	110 ± 13	118 ± 17	117 ± 16	82 ± 7	86 ± 12	96 ± 14	91 ± 11
	5.0 + 0.250[c]	4	113 ± 5	108 ± 4	94 ± 6[a]	89 ± 10[a]	87 ± 6	78 ± 6	69 ± 7	69 ± 8
Phenelzine and digoxin	2.5 + 0.125[d]	4	100 ± 5	98 ± 6	100 ± 7	99 ± 7	80 ± 4	77 ± 4	78 ± 4	79 ± 6
	5.0 + 0.250[d]	2	99 ± 2	100 ± 0	100 ± 0	100 ± 0	75 ± 0	68 ± 3	75 ± 0	75 ± 0

[a] Statistically significant from control values ($p < 0.05$). [b] Concurrent administration. [c] Digoxin administered 20 min. after phenelzine. [d] Digoxin administered 60 min. after phenelzine.

Table III—Effects of Phenelzine Pretreatment on Digoxin-Induced Arrhythmias in Rabbits

Animal Number	Days of Pretreatment	Daily Dosage of Phenelzine, mg./kg.	Digoxin Dosage to Induce Arrhythmia, mg./kg.	p^a
1	3	2.5	0.250	~0.350
2	4	2.5 (3 days), 5.0 (1 day)	0.625	~0.150
3	5	2.5 (2 days), 5.0 (3 days)	1.125	≪0.010
4	7	2.5 (2 days), 5.0 (5 days)	1.000	≪0.010
5	7	2.5 (1 day), 5.0 (6 days)	1.000	≪0.010
6	7	5.0	0.750	~0.025
7–12	7	—[b]	0.38 ± 0.15[c]	-

[a] Level of significance relative to the saline controls. [b] Saline controls. [c] Mean value ± *SE*.

When digoxin was administered 20 and 60 min. after phenelzine, the incidence of arrhythmias was observed in 50 and 33%, respectively, of the animals.

Phenelzine Pretreatment on Digoxin Toxicity—Six rabbits pretreated with varying doses of phenelzine and for varying times responded to injected digoxin with a bigeminal type of ventricular arrhythmia. Because of the variability in the autonomic response of these rabbits to phenelzine pretreatment, it was sometimes necessary to administer a large loading dose for a longer period followed by a smaller sustaining dose for a shorter period, and vice versa. By increasing the number of pretreatment days to 5 and 7, respectively, the amount of the cardiac glycoside required to evoke arrhythmias was similarly altered (Table III). Each injection of digoxin produced an immediate decrease in the heart rate and a slight hypotensive effect.

DISCUSSION

These studies point out certain potential cardiovascular dangers inherent with concurrent phenelzine–digoxin administration. The results in rabbits showed that a dose–time relationship existed for both spontaneous heart rate and arterial blood pressure. While spontaneous heart rate decreased significantly after 0.125 and 0.25 mg./kg. i.v. digoxin, the systolic arterial pressure was significantly increased at the 0.25-mg./kg. dose level. This increase in arterial blood pressure might have been caused by increased peripheral vascular resistance due to the well-known vasoconstrictor action of digitalis on the resistance vessels of the systemic circulation (2–5). Rabbits injected with phenelzine alone, 5 and 10 mg./kg., showed instantaneous bradycardia, which may partly be a reflex response to elevated blood pressure and partly be due to a possible vagal action (6).

The fact that phenelzine and digoxin when administered alone caused a significant decrease from control values in spontaneous heart rate, but failed to do so significantly when given together, may suggest a partial explanation for their potential toxicity in combination. A potential for increased automaticity in the heart muscle may have been created, with consequent precipitation of arrhythmias. Table I shows that the low incidence of arrhythmias occurred at the digoxin dose of 0.125 mg./kg. but was greatly increased when this dose was given in combination with 2.5 mg./kg. phenelzine. The transient hypotension, occurring immediately after phenelzine injection, may have been caused by a temporary decrease in peripheral sympathetic tone with a consequent decrease of peripheral vascular resistance (7). The subsequent rise in arterial blood pressure suggests sympathetic activity, perhaps due to increased catecholamine levels. In terms of dose–time relationships, spontaneous heart rate was significantly decreased for the dosages of 5 and 10 mg./kg. phenelzine whereas all doses did not significantly depress heart rate 20 min. after injection ($p = 0.6$). Arrhythmia frequency produced by phenelzine increased with increasing dose (Table I). However, when varying the intervals between injections of phenelzine and digoxin, it was observed that administration of these drugs 20 min. apart was as toxic as concurrent injection as seen by the incidence of arrhythmias. This incidence was decreased when both drugs were given 60 min. apart (Table I).

Pretreatment of rabbits with phenelzine for some days appears to modify the dose of digoxin needed to produce arrhythmias. An increase in the number of pretreatment days correspondingly caused a significant increase in the arrhythmogenic dose of digoxin (Table III). The dose levels of digoxin and the length of phenelzine pretreatment period seem to be important factors in modifying the toxicity of concurrent administration. These findings may be relevant to those occasional clinical situations in which depressed patients with advanced cardiac failure are given doses of digitalis concurrently with a mood elevator such as phenelzine.

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* Present address: Department of Physiology Pharmacology, School of Pharmacy, University of the Pacific, Stockton, CA 95207

▲ To whom inquiries should be directed.