Sympathetic Blocking Action of Iproniazid in the Unanesthetized Dog

By J. N. SPENCER

Iproniazid, on intravenous injection in the unanesthetized dog, inhibited the increase in arterial blood pressure resulting from the intravenous injection of epinephrine, DMPP, and tyramine. Adrenergic blockade appeared to be an important factor in this action of iproniazid, although the possibility of inhibition of the release of norepinephrine from nerve terminals could not be eliminated. These results confirm *in vitro* studies of previous investigators.

THERE is abundant clinical and experimental evidence that drugs which inhibit monamine oxidase (MAO) are capable of altering sympathetic responsiveness. Patients receiving these drugs commonly exhibit orthostatic hypotension (1). On the other hand, the same patients on eating a food high in tyramine, such as cheese, may develop an alarming hypertension (2). The mechanism responsible is not clear. Goldberg and Da Costa (3) as well as Gertner (4) noted that a number of MAO inhibitors block transmission through the superior cervical ganglion of experimental animals. However, Zbinden *et al.* (5) and Brodie (6) are of the opinion that MAO inhibitors do not act at the ganglion, but at the receptor site, preventing the release of norepinephrine from the nerve endings. Either site of action could account for the above effects. Both views, however, are based on *in vitro* studies or studies conducted on animals under barbiturate anesthesia. Barbiturates are known to alter neurohormone release (7) even to the point of reversal of the response to common autonomic stimuli (8). In view of this, it was deemed of value to determine the effect of a MAO inhibitor on the autonomic responsiveness of trained unanesthetized dogs.

EXPERIMENTAL

Healthy, adult, mongrel dogs of either sex, weighing from 12 to 29 Kg., were used in the study. The animals were trained to lie quietly on their backs, with minimal restraint during the recording of arterial blood pressure from a femoral arterial puncture. Records of the blood pressure and the circulatory response to the intravenous injection of epinephrine (0.002 mg./Kg.), DMPP[1] (0.08 mg./Kg.), acetylcholine (0.006 mg./Kg.), and tyramine (0.1 mg./Kg.) were obtained every 48 to 72 hr. until the blood pressure had stabilized and a consistent circulatory response to the above agents had been obtained in at least three successive tests. The average of the values obtained in the three tests served as the experimental control.

The MAO inhibitor, iproniazid,[2] was dissolved in normal saline and injected intravenously in terms of base content in a single dose of 10 or 20 mg./Kg. or in two doses of 20 mg./Kg. each, 24 hr. apart. Records were obtained of the blood pressure and the circulatory response to the injection of epinephrine, DMPP, acetylcholine, and tyramine 24, 48, 72, 96, and 120 hr. after the injection of the iproniazid.

RESULTS

The administration of iproniazid in a single dose of 10 or 20 mg./Kg. was without significant effect on the blood pressure or the circulatory response to the injection of epinephrine, DMPP, acetylcholine, or tyramine. However, following two doses of 20 mg./Kg., each 24 hr. apart, within 24 to 48 hr. there was a marked and statistically significant inhibition of the pressor reaction to the injection of epinephrine, DMPP, and tyramine (Table I). This occurred in the absence of any significant alteration in the recumbent blood pressure or in the depressor action of acetylcholine and was evident for 96 to 120 hr. after the injection of iproniazid. The effect on the action of tyramine was the most marked, the pressor response being reversed to one of the depressor within 24 hr. (Table I and Fig. 1). The alteration in the action of epinephrine and DMPP was not as marked as that of tyramine, although reversal of the pressor action of both agents was observed.

From the above it would appear that iproniazid has an adrenergic blocking action. Adrenergic blockade would account for the inhibition of the action of epinephrine and DMPP as well as the reversal of the pressor action of tyramine. Tyramine not only releases norepinephrine from tissue stores but also acetylcholine (9). In the presence of adrenergic blockade, its cholenergic action predominates. Excitement following the administration of atropine prevented the determination of the involvement of acetylcholine in the depressor action of tyramine in the unanesthetized dog, but in animals anesthetized with chloralose 24 hr. after the injection of iproniazid, atropine completely blocked the tyramine depressor response. Thus, acetylcholine release appeared to be implicated in the reversal of the pressor action of tyramine. However, it cannot be determined from this study if adrenergic blockade was the only factor involved in the alteration of autonomic responsiveness produced by iproniazid. The fact that the pressor action of both DMPP and tyramine were blocked at a time when the inhibition of the action of epinephrine was minimal (120 hr. observation) suggests the possibility of an interference with norepinephrine release from nerve terminals. Such an action, like adrenergic blockade, would uncover the cholinergic action of tyramine (9).

Results comparable to those obtained with iproniazid were observed on occasion in unanesthetized dogs following the intravenous injection of tranylcypromine or β-phenylisopropylhydrazine.

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[1] 1:1 Dimethyl-4-phenylpiperzinium iodide.

[2] Trademarked as Marsilid by Hoffmann-LaRoche, Inc., Nutley, N. J.

TABLE I.—EFFECT OF IPRONIAZID ON BLOOD PRESSURE AND THE ACTION OF EPINEPHRINE, DMPP, ACETYLCHOLINE, AND TYRAMINE (MEAN OF 5 EXPERIMENTS)

Observation Time After Iproniazid	Blood Pressure, mm. Hg			Action of Epinephrine		Action of DMPP		Action of Acetylcholine		Action of Tyramine	
	Systolic Pressure	Diastolic Pressure	Change (Systolic/Diastolic)	mm. Hg Change in Systolic Pressure	% Decrease from Control	mm. Hg Change in Systolic Pressure	% Decrease from Control	mm. Hg Change in Systolic Pressure	% Deviation from Control	mm. Hg Change in Systolic Pressure	% Decrease from Control
0 (control)[a]	119 ± 5[b]	66 ± 3	...	34 ± 6	...	44 ± 7	...	−31 ± 7	..	22 ± 8	...
24 hr.	116	68	−3/2	11	68	27	39	−33	6	−10	145[d]
48 hr.	120	62	1/−4	21	38[c]	21	52[c]	−31	0	−10	145[d]
72 hr.	112	63	−7/−3	13	62[c]	12	73[c]	−26	16	0	100[d]
96 hr.	107	55	−12/−11	13	62[d]	13	70[c]	−38	22	−15	169[c]
120 hr.	116	61	−3/−5	28	18	16	64[c]	−35	13	−4	118[c]

[a] Mean of all control observations. [b] ± Standard error of mean. [c] P, 0.05 (Wilcoxon test of rank sums). [d] P, 0.02 (Wilcoxon test of rank sums).

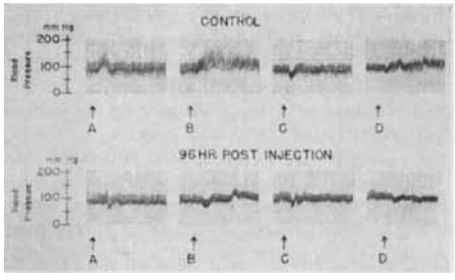

Fig. 1.—Effect of iproniazid on the response of the blood pressure to the injection of autonomic agents. Arrows indicate points of intravenous injection of autonomic agents. Key: A, 0.08 mg./Kg. DMPP; B, 0.002 mg./Kg. epinephrine; C, 0.006 mg./Kg. acetylcholine, D, 0.1 mg./Kg. tyramine. (Dog 4, 23.5 Kg. male.)

The effect, however, tended to be masked by the amphetamine-like action of these drugs (10, 11). Thus, tranylcypromine and β-phenylisopropylhydrazine as well as iproniazid inhibit autonomic responsiveness in the unanesthetized dog. Adrenergic blockade appears to play an important role in this action, although inhibition of norepinephrine release from nerve terminals may be a factor. These observations confirm previous results obtained in *in vitro* studies and in studies conducted on anesthetized animals (5, 6).

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Errata

In the article titled "The Adrenergic Receptor" (1), *Reference 7*, page 366, should read:

(7) Ahlquist, R. P., *Am. J. Pharm. Educ.*, **28**, 708(1964).

(1) Ahlquist, R. P., *J. Pharm. Sci.*, **55**, 359(1966).

In the article titled "Physicochemical and Physiologic Factors Affecting the Absorption of Warfarin in Man" (1), the following sentence should be inserted at the end of paragraph 2, page 436, under *Results and Discussion:*

Subject *1* also received sodium warfarin in solution; less than 10% of the dose was absorbed at 30 min., but absorption was complete 60 min. after drug administration.

(1) O'Reilly, R. A., Nelson, E., and Levy, G., *J. Pharm. Sci.*, **55**, 435(1966).