Cardiovascular Profile of the Antihypertensive Agent, Guanadrel (36195)

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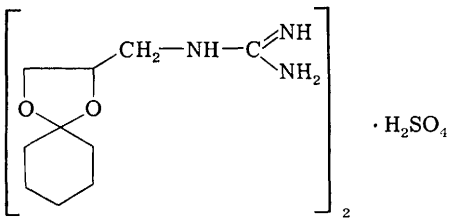
Guanethidine lowers the blood pressure of hypertensive patients because of its ability to induce sympathetic atony (1), but its clinical usefulness is limited by side affects (2). Recent clinical studies (3–5) have shown that a new drug, guanadrel, is an effective antihypertensive agent and causes fewer adverse effects than guanethidine.

This report describes some of the pharmacological studies which led to the clinical testing of guanadrel. Guanadrel Sulfate is (1, 4-dioxaspiro [4, 5] decan-2-ylmethyl) guanidine sulfate, and has the following structure:



Methods. The basic procedure was the same in all the following work. Dogs were used unless otherwise specified. Anesthesia was induced with thiopental sodium, 20 mg/kg iv, and maintained with α-chloralose, 60 mg/kg iv. Blood pressure was recorded on a Gilson polygraph from a femoral artery catheter connected to a Statham pressure transducer. Drugs were administered via a catheter in the femoral vein. Open chest dogs were maintained by means of a Harvard positive-pressure respiratory pump.

The carotid arteries were isolated, then occluded for 30 sec with serafine clamps to produce the typical hemodynamic response. For measure of peripheral vascular resistance changes, blood was shunted from a femoral arterial catheter to a Sigmamotor pump and returned distally to the femoral artery at a constant flow and at a pressure approximating systemic arterial pressure. A pressure transducer was inserted by a T-tube in the line distal to the pump for recording changes in femoral perfusion pressure.

The ventral limb of the ansa subclavia nerve to the caudal cervical ganglion was exposed through a left-side thoracotomy. The nerve was sectioned peripherally and the central end was stimulated electrically (5 V, 20/sec, 30 sec). The resulting increase in myocardial contractility and heart rate before and after guanadrel was measured by a Brodie-Walton strain gauge arch sutured onto the left ventricle.

In a like manner the greater splanchnic nerve was isolated as it left the thoracic sympathetic chain. It was transected and the peripheral end stimulated electrically (5 V, 20/sec, 30 sec) both before and after guanadrel.

Cats were anesthetized with Dial–urethane, 0.6 ml/kg ip (allobarbital, 100; urethane, 400; and monoethylurea, 400 mg/ml). The superior cervical ganglion and its pre- and postganglionic fibers were isolated, then stimulated (20 pulses/sec, 20 msec duration, 5 V). Nictitating membrane contractions were recorded using a Statham force-displacement transducer.

Cardiac output was determined using the dye-dilution technique. In the anesthetized dog, a catheter was inserted into the abdominal aorta via the femoral artery. Blood was drawn through a densitometer at a constant rate by a Harvard infusion-withdrawal pump and returned to the dog via a femoral vein. Indocyanine green, 1.25 mg, was injected iv in the area of the right atrium. Cardiac output was calculated using the formula of Hamilton *et al.* (6). Three sets of

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TABLE I. Effect of Guanadrel Sulfate (5 mg/kg iv) on Increased Peripheral Resistance Following Carotid Occlusion in Four Anesthetized Dogs.

	$M \pm$ SE		
	Control	Posttreatment, 30 min	p
Increase in mean arterial pressure (mm Hg)	41.9 ± 2.8	5.0 ± 2.7	< .01
Increase in mean femoral perfusion pressure (mm Hg)	34.4 ± 3.7	3.8 ± 1.6	< .01

control values were obtained, guanadrel was injected, and cardiac output and stroke volume were determined 5, 10, 15, and 20 min after dosing.

Beagle dogs received 0, 25, or 75 mg/kg of guanadrel sulfate daily for 6 weeks. The animals were anesthetized, prepared for hemodynamic recording and the response to carotid occlusion was obtained. The animals were then sacrificed and the heart, intestine, nictitating membrane, and a section of the brain (approx 1 cm^3 encompassing the hypothalamus) were analyzed for norepinephrine (NE) content. Although this section of tissue contains more than just the hypothalamus, it is referred to below as "hypothalamus." In addition, one adrenal from each dog was analyzed for total catecholamine content. Catecholamine content was determined using the method of Creveling *et al.* (7).

The results were analyzed using the nonpaired Student's t test (8). A p value equal to or less than 0.05 was considered significant.

Results. Guanadrel sulfate, 5 mg/kg iv, inhibited the reflexogenic increase in mean arterial pressure and femoral perfusion pressure induced by bilateral carotid occlusion (Table I). This inhibitory effect appears to be partly due to postganglionic nerve ending blockade, since the compound inhibited the contractile response of the nictitating membrane to both pre- and postganglionic stimulation (Table II). The effect on the response of the nictitating membrane was determined 30 min after administration of guanadrel to three anesthetized cats. The response to bilateral carotid occlusion was also inhibited after oral administration of the compound for a 6-week period (Table III). This result indicates

TABLE II. Effect of Guanadrel Sulfate (5 mg/kg iv) on the Contractile Response of the Nictitating Membrane.

Inhibition (%, $\overline{M} \pm$ SE)	
Preganglionic stimulation	Postganglionic stimulation
90 ± 5	91 ± 5

TABLE IV. Effect of Guanadrel Sulfate on the Response to Stimulation of the Anterior Ansa Subclavia.

	Increase (%) in myocardial contractile force ($\overline{M} \pm$ SE)
Control	52 ± 2
Response after guanadrel sulfate	2 ± 2

TABLE III. Effect of 6 Weeks Oral Administration of Guanadrel Sulfate on the Carotid Occlusion Response in Dogs.

		$M \pm$ SE; increase in:		
	n	Mean arterial pressure (mm Hg)	Pulse pressure (mm Hg)	Heart Rate (beats/min)
Control	4	+ 41.6 ± 3.4	+ 20.8 ± 1.9	+ 17.0 ± 2.2
Guanadrel sulfate				
25 mg/kg/day	4	+ 22.9 ± 1.8 ($p < .01$)	+ 7.9 ± 3.2 ($p < .01$)	+ 8.0 ± 3.1 ($p < .05$)
75 mg/kg/day	4	+ 19.5 ± 2.3 ($p < .01$)	+ 1.0 ± 1.0 ($p < .01$)	+ 3.6 ± 1.3 ($p < .01$)

TABLE V. Effect of Guanadrel Sulfate on the Mean Arterial Pressure Response to Greater Splanchnic Nerve Stimulation.

Increase in mean arterial pressure (mm Hg; $M \pm SE$)		
Control	Post treatment	p
106 ± 12	65 ± 6	$< .05$

that the compound is effective when administered by the oral route.

Guanadrel can also inhibit the myocardial response to sympathetic nervous system stimulation as indicated by the results summarized in Table IV. The increase in contractile force induced by stimulation of the anterior ansa subclavia was inhibited in three anesthetized dogs by guanadrel sulfate, 5 mg/kg iv.

The compound was evaluated for its effect on the arterial pressure response to stimulation of the greater splanchnic nerve in the anesthetized dog. Since the systemic pressure reponse to this manipulation is primarily due to adrenal medullary stimulation the degree of blockade by guanadrel at the adrenal gland could be readily demonstrated. As the results in Table V indicate, guanadrel sulfate (10 mg/kg iv) produced a significant inhibition of this response in four anesthetized dogs. The effect was evaluated approximately 1 hr after drug administration.

Guanadrel itself caused a pronounced increase in mean arterial pressure after acute intravenous injection. A dose of 5 mg/kg iv of guanadrel sulfate caused an average increase in mean arterial pressure in four anesthetized dogs of 94 ± 16 mm Hg. At this dose, the elevation in pressure lasts approximately 30 min. This increase in arterial pressure is due to an increase in both peripheral vascular resistance and an increase in cardiac output. At the peak of the pressor response, mean femoral perfusion pressure increased by 101 ± 21 mm Hg. In four other experiments conducted in anesthetized dogs, this dose of guanadrel increased cardiac output from 1.8 ± 0.2 to 2.3 ± 0.2 liters/min. Since heart rate decreased, apparently due to reflex mechanisms, stroke volume increased from 13 ± 2 to 21 ± 3 ml.

The pressor response induced by guanadrel is apparently due to release of tissue norepinephrine. When tyramine (0.2 mg/kg iv) was administered 90 min after guanadrel sulfate (10 mg/kg iv), it induced an average increase in arterial pressure in four dogs of only 15 mm Hg compared to 80 ±6 mm Hg in nonpretreated dogs ($p < .05$). Since tyramine is an indirect acting sympathomimetic amine (9), this result suggests that guanadrel produced its pressor response by releasing and depleting the available stores of norepinephrine.

Guanadrel not only released norepinephrine acutely but also caused significant depletion of norepinephrine stores (Table VI). The organs listed in Table VI were removed from beagle dogs, which were treated with guanadrel for a period of 6 weeks. Along with depletion of peripheral organs, guanadrel appeared to cause significant depletion of "hypothalamic" norepinephrine. This finding suggests that the compound crosses the blood–brain barrier. No depletion of norepinephrine appeared to occur in intestinal tissue. Although the depletion of adrenal catecholamines was not significant, it does appear to be real in that it is pronounced and is dose related.

Discussion. Guanadrel possesses a cardiovascular profile which resembles, in many respects, that reported for guanethidine (1, 10). Like guanethidine, guanadrel appears to produce an acute block of the sympathetic nerve ending, and, on chronic administration, does produce a pronounced depletion of norepinephrine from storage sites.

However, guanadrel does appear to differ from guanethidine in several respects. First, guanadrel appears to cause a partial acute block of splanchnic nerve stimulation to the adrenal medulla and does appear to cause depletion of adrenal medullary catecholamines. This effect apparently does not occur with guanethidine (1, 10). Secondly, guanadrel did not cause depletion of intestinal catecholamines. Intestinal catecholamine depletion and diarrhea have been reported for guanethidine (11). Guanadrel has been reported not to induce diarrhea when administered clinically (3–5); nor was diarrhea observed in any of the dogs in these experiments. One might postulate that the side effect of diarrhea is associated with intestinal

TABLE VI. Effect of Guanadrel Sulfate, Administered Chronically, on the Norepinephrine Content of Various Organs.

Tissue	Guanadrel sulfate (mg/kg/day)	n	Norepinephrine ($\mu g/g$ $\bar{M} \pm$ SE)	p
Heart	Controls	4	1.23 ± 0.30	
	25	4	0.21 ± 0.02	$< .05$
	75	4	0.17 ± 0.01	$< .05$
"Hypothalamus"	Controls	4	0.52 ± 0.06	
	25	4	0.31 ± 0.01	$< .05$
	75	4	0.23 ± 0.02	$< .05$
Nictitating membrane	Controls	3	0.67 ± 0.08	
	25	4	0.36 ± 0.09	$< .05$
	75	4	0.28 ± 0.02	$< .01$
Adrenals	Controls	4	1403 ± 124	$> .05$
	25	4	848 ± 84	$> .05$
	75	4	687 ± 161	
Intestine	Controls	4	0.39 ± 0.004	
	25	4	0.35 ± 0.015	$> .05$
	75	4	0.34 ± 0.007	$> .05$

catecholamine depletion.

Guanadrel also caused a significant decrease in "hypothalamic" norepinephrine content. Besides indicating that the compound does cross the blood–brain barrier, this "hypothalamic" catecholamine depletion may be involved in the antihypertensive effect induced by the compound.

The cardiovascular profile of guanadrel closely resembles that of guanethidine. Pharmacological attenuation of the sympathetic nervous system, either by blockade at the nerve ending or centrally at the hypothalamus, would probably inhibit pressor impulses induced by baroreceptor activation or by other mechanisms. This is apparently the effect achieved when the compound is administered clinically to hypertensive patients (4).

Summary. Guanadrel was evaluated for its cardiovascular profile and was found to possess properties which are desirable in the treatment of hypertension. The compound causes blockade of the sympathetic nerve ending and depletion of peripheral and "hypothalamic" catecholamines. Guanadrel does not deplete intestinal norepinephrine, which may be the reason for the fact that it does not produce diarrhea when administred experimentally or clinically.

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