Comparison of guanadrel and guanethidine

Both guanadrel and guanethidine caused a statistically significant reduction of blood pressure when compared to placebo, but there was no significant difference between the 2 drugs, regarding antihypertensive potency. With guanadrel it was possible to achieve significantly more control of the blood pressure throughout the day. There also were fewer complaints of early morning dizziness during the guanadrel period, and there was less diarrhea. The effects of both drugs on cardiac output and total peripheral vascular resistance were identical in the resting recumbent position and during tilting.

Lennart Hansson, M.D., Arturo Pascual, M.D., and Stevo Julius, M.D.
Ann Arbor and Detroit, Mich.
Department of Internal Medicine, Hypertension Section, University of Michigan Medical Center, Ann Arbor, and Department of Internal Medicine, Metabolic and Hypertension Section, Henry Ford Hospital, Detroit

For many years guanethidine (Ismelin) has been a widely used drug for the control of severe hypertension. Its hypotensive effect stems from moderate reduction of cardiac output[8-11] in combination with decreased peripheral vascular resistance.[4, 13] Both effects are the result of catecholamine depletion in the adrenergic nerve endings in the myocardium and the blood vessel walls. Some of the side effects of guanethidine are disturbing, e.g., its tendency to cause early morning hypotension[5, 6] and diarrhea. In addition, the slow onset of action and the sustained effect following withdrawal[6, 9] often make fine adjustments of blood pressure control difficult in patients. For these reasons, there has long been a need for a drug with the potency of guanethidine but without some of its undesirable effects.

Received for publication Aug. 3, 1972.
Accepted for publication Sept. 8, 1972.

Guanadrel, which was introduced recently, is an adrenergic blocking agent with hypotensive action. It is similar to guanethidine in many ways and acts by causing a peripheral catecholamine depletion.[7] However, its effect is considerably shorter than that of guanethidine, being in the order of 6 to 8 hours.[2] Thus, it would seem possible to achieve a more balanced control of blood pressure throughout the day. As initial results with guanadrel seemed to suggest complete absence of diarrhea and less morning hypotension than with guanethidine,[1] the present study was undertaken. Our main interest has been to study the hemodynamic effects of oral treatment with guanadrel and to compare the blood pressure control and side effects of guanadrel and guanethidine.

Materials and methods

Twenty-one patients with moderately severe hypertension took part in the study:

Table I. *Means and standard errors of blood pressure on guanadrel, guanethidine, and placebo*

	Morning				*Afternoon*			
	Recumbent		*Standing*		*Recumbent*		*Standing*	
	S	*D*	*S*	*D*	*S*	*D*	*S*	*D*
Guanadrel	152.8 ± 5.0	105.2 ± 6.1	139.3 ± 4.8	101.1 ± 3.0	156.8 ± 4.3	100.7 ± 3.0	141.9 ± 3.6	97.7 ± 2.9
Placebo	172.7 ± 8.0	116.0 ± 3.9	171.8 ± 8.6	121.7 ± 4.0	175.0 ± 7.8	114.7 ± 4.4	171.7 ± 8.7	118.7 ± 4.1
Difference	20.1	10.8	32.5	20.6	18.2	14.0	29.8	21.0
p value	0.05	0.0005	0.005	0.0005	0.05	0.01	0.0005	0.0005
Guanethidine	152.8 ± 5.4	99.6 ± 1.9	137.6 ± 7.1	94.7 ± 4.8	159.7 ± 4.1	105.6 ± 3.1	146.8 ± 4.4	100.5 ± 3.6
Placebo	165.8 ± 4.2	113.3 ± 2.9	164.6 ± 4.9	119.5 ± 3.4	168.4 ± 4.3	111.9 ± 3.6	164.5 ± 5.2	116.4 ± 3.5
Difference	13.0	13.7	27.0	24.8	8.7	6.3	17.7	15.9
p value	0.02	0.0002	0.002	0.0005	ns	ns	0.005	0.01
(Guanadrel-guanethidine) Difference	0	5.6	1.7	6.4	−2.9	−4.9	−4.9	2.8
p value	ns	ns	ns	ns	ns	0.02		

19 males and 2 females whose average age was 41 years (range 17 to 68). Only patients in whom diuretic treatment alone had failed to control the blood pressure were selected. All were without overt heart failure (less than Grade II, New York Heart Association classification), severe kidney failure (creatinine clearance over 40 ml. per minute), or Grades III and IV hypertensive retinopathy (Keith-Wagener-Barker). Twenty patients had essential hypertension, as determined after complete laboratory work-up including: serum electrolytes, urinary ketosteroids, catecholamines, and aldosterone, as well as normal hypertensive urograms. One patient had chronic pyelonephritis with secondary hypertension.

Eight patients were chosen for evaluation of the hemodynamic effect of both drugs. These patients were studied in the early phase when initial experience was needed in an open label design. The aim of the treatment was to achieve best practical blood pressure control with increasing doses of both compounds. Best practical control was defined as normal blood pressure or lowest possible reading without causing intractable side effects after a minimum of 6 or maximum of 12 weeks of treatment. At the end of each period, intra-arterial blood pressures were measured and cardiac outputs were determined by dye dilution technique. The method has been described in detail previously.[12]

Thirteen patients were chosen for a single-blind crossover study to compare the effect of both drugs on home blood pressure recorded by patients who were unaware of the treatment regimen. Side effects were evaluated by a "blind" observer who used a standardized questionnaire. Patients were receiving chlorothiazide, 50 mg. 2 times daily, and the "active" drug for 2 periods each 6 weeks in length. Between those 2 periods there was a 2 week period of placebo when the only active treatment was chlorothiazide. Two of the authors (L. Hansson and A. Pascual) were in touch with patients and adjusting the "active drug" to achieve the best practical blood pressure control. Randomization was assured by predetermined closed envelopes so that patients started with either guanadrel or guanethidine. Six patients were started with guanadrel, while 7 received guanethidine during the first period of active treatment. The average daily dosage of guanadrel was 70 mg. (25 to 150) and of guanethidine, 57 mg. (25 to 125). Guanethidine was administered once daily while guanadrel was used in 3 divided doses.

Table II. *Differences between guanadrel and guanethidine regarding morning to afternoon alterations of blood pressure*

	A.M. to P.M. differences			
	Systolic recumbent blood pressure	*Diastolic recumbent blood pressure*	*Systolic standing blood pressure*	*Diastolic standing blood pressure*
Guanadrel	3.1	−4.7	1.6	−0.2
Guanethidine	6.1	6.2	9.3	9.5
Difference	3.0 ± 2.5	10.9 ± 4.4	7.7 ± 4.5	9.7 ± 3.6
p value	ns	< 0.05	ns	< 0.05

Table III. *Side effects mentioned by patients*

Side effects	*Guanadrel*	*Placebo*	*Guanethidine*
Dizziness on arising	2	3	7
Dizziness during the day	3	4	5
Headaches	5	7	7
Dreams	5	6	6
Insomnia	4	1	4
Tiredness	7	7	9
Shortness of breath	3	3	5
Nasal blocking	3	3	5
Cold extremities	1	1	4
Dry mouth	6	7	5
Unpleasant taste	3	5	4
Sore tongue	—	—	1
Pain in angle of jaw	2	2	1
Diarrhea	3	2	6
Constipation	1	1	1
Nocturia	6	4	6
Failure of ejaculation	10	8	10
Poor erection	4	3	4
Conjunctivitis	1	—	2
Blurred vision	1	—	1

The student t test for paired observations has been used in all statistical comparisons. When comparing the effect on the blood pressure, the average home blood pressure recordings during the last 7 days of guanadrel, guanethidine, and placebo treatment, respectively, have been used.

Results

Randomized study.

Blood pressure control. As can be seen in Table I, both guanadrel and guanethidine caused a significant reduction of blood pressure. There was no significant difference in antihypertensive potency of the active drugs. In the afternoon, both recumbent and standing diastolic blood pressures increased significantly more during treatment with guanethidine (Table II). This, however, was not the case with systolic blood pressure.

Side effects. Both drugs caused a number of side effects (Table III). Complaints of failure of ejaculation were made by 10 patients after both drugs. Only 2 patients complained of early morning dizziness during guanadrel treatment as compared to 7 after guanethidine. Diarrhea occurred in 3 patients during the guanadrel period and in 6 while taking guanethidine. The total number of complaints during guanadrel treatment was 70, 93 during guanethidine, and 67 during "placebo" therapy.

Hemodynamic effects. There was no significant difference between the effects of guanethidine and guanadrel on heart rate, intra-arterial blood pressure, cardiac index, and total peripheral vascular resistance either in the recumbent or tilted position (Table IV). Both drugs caused a marked reduction of cardiac output during tilt, with a substantial drop of systolic blood pressure and a moderate increase of total peripheral resistance.

Discussion

In a randomized single-blind cross-over study, both guanadrel and guanethidine decreased blood pressure to the same extent, probably by similar hemodynamic mechanisms since no significant differences of cardiac output or total peripheral re-

Table IV. *Comparative hemodynamic effects of guanethidine and guanadrel*

	Recumbent					*Tilt*				
	HR	*BAs*	*BAd*	*TPR*	*Qi*	*HR*	*BAs*	*BAd*	*TPR*	*Qi*
Guanethidine	56.7 ± 6.5	166.1 ± 24.5	90.2 ± 15.2	22.74 ± 8.38	2.84 ± 0.62	63.8 ± 8.3	139.6 ± 25.1	86.8 ± 20.8	26.98 ± 8.10	2.10 ± 0.04
Guanadrel	59.6 ± 6.3	153.6 ± 19.8	84.2 ± 5.9	21.51 ± 0.05	2.74 ± 0.61	65.7 ± 14.2	134.1 ± 13.6	82.1 ± 10.8	27.53 ± 9.67	2.02 ± 0.43
Significance	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns

Hemodynamic response to guanethidine and guanadrel resting recumbent and after 5 minutes of 45° head-up tilt. HR = heart rate (beats/min.); BAs = brachial artery systolic blood pressure (mm. Hg.); BAd = brachial artery diastolic blood pressure; TPR = total peripheral resistance $\left(\frac{\text{Mean blood pressure}}{\text{Cardiac output}}\right)$; Qi = cardiac index (liters/min./body surface area).

sistance were detected. However, the usually observed rise in blood pressure throughout the day during guanethidine therapy was not seen after guanadrel. Consequently, morning to afternoon changes of recumbent and standing diastolic blood pressure were larger with guanethidine ($p < 0.05$). This difference may be attributed to the shorter duration of the guanadrel effect, which necessitates administration 3 times daily, but in turn gives a more stable control of the blood pressure. On the other hand, it has been shown that the early morning hypotension of guanethidine treatment persists even if the drug is administered 3 times daily.[6]

The complaints of dizziness upon rising were also more frequent during the guanethidine period and thus further support the impression that guanadrel offers a more even control of blood pressure.

Another important side effect of guanethidine treatment is diarrhea; again, guanadrel caused fewer complaints. This may be attributed to the fact that guanadrel depletion of intestinal catecholamine stores is less than quanethidine depletion.[10]

Other side effects such as failure of ejaculation seem to be equally frequent. The surprisingly high frequency of this complaint during the intervening placebo period is of interest, but may be attributable to the short duration of placebo.

In summary, the following conclusions can be drawn: (1) The hypotensive effective and other hemodynamic effects of guanadrel are comparable to those of guanethidine. (2) Guanadrel provides a more stable control of the blood pressure characterized by a more even reduction of diastolic blood pressure throughout the day. (3) Diarrhea is less frequent during treatment with guanadrel.

We acknowledge the efficient help of Ms. Nancy Bassett, R.N., and the Upjohn Center for Clinical Pharmacology at the University of Michigan Medical Center. We also thank Dr. John R. Caldwell, Henry Ford Hospital, Detroit, for his contributions.

References

1. Bloomfield, D. K., and Cangiano, J. L.: Guanadrel and guanethidine in hypertension, CLIN. PHARMACOL. THER. **11**:200-204, 1969.
2. Bloomfield, D. K., and Cangiano, J. L.: Clinical experience with a new antihypertensive agent, guanadrel sulfate, Curr. Ther. Res. **11**: 727-735, 1969.
3. Boura, A. L., and Green, A. F.: Adrenergic neurone blocking agents, Ann. Rev. Pharmacol. **5**:183-212, 1965.
4. Cohn, J. N., Liptak, T. E., and Freis, E. D.: Hemodynamic effects of guanethidine in man, Circ. Res. **12**:298-307, 1963.
5. Cranston, W. I., and Brown, W.: Diurnal variation in plasma volume in normal and hypertensive subjects, Clin. Sci. **25**:107-114, 1963.
6. Dollery, C. T., Emslie-Smith, D., and Milne, M. D.: Clinical and pharmacological studies with guanethidine in the treatment of hypertension, Lancet **2**:381-387, 1960.
7. Freyburger, W. A.: Peterson, L. J., Kaiser, D. G., et al.: Clinicians brochure on U28,288D (CL-1388R), Kalamazoo, Mich., 1968, Upjohn Co.

8. Novack, P.: The effect of guanethidine on renal, cerebral and cardiac hemodynamics, *in* Brest, A. N., and Moyer, J. H., editors: Hypertension: Recent advances, Philadelphia, 1961, Lea & Febiger.
9. Page, I. H., and Dustan, H. P.: A new potent antihypertensive drug. Preliminary study of [2-(octahydro-1-azocinyl)-ethyl] guanidine sulfate, (guanethidine), J. A. M. A. **170**:1265, 1959.
10. Pruss, T. P., and Hidalgo, J.: Cardiovascular profile of the antihypertensive agent, Guanadrel (36195), Proc. Soc. Exp. Biol. Med. **139**:600, 1972.
11. Richardson, D. W., and Wyso, E. M.: Human pharmacology of guanethidine, Ann. N. Y. Acad. Sci. **88**:944-955, 1960.
12. Sannerstedt, R., Julius, S., and Conway, J.: Hemodynamic responses to tilt and beta-adrenergic blockade in young patients with borderline hypertension, Circulation **42**:1057-1064, 1970.