movement and account for the relatively low incidence of severe atherosclerosis in the external iliac artery.

In the 100 aortograms studied the femoral and popliteal arteries were found to be patent in 56 (Table III). Femoro-popliteal patency in five patients with aortic occlusion could not be demonstrated by aortography, but can perhaps be assumed because aortic and femoro-popliteal occlusion combined would be more likely to produce gangrene than claudication. If this assumption were correct the distal patency rate would be 61%.

TABLE III.—Incidence of Proved Patency of Femoral and Popliteal Arteries in Relation to Principal Aorto-iliac Lesion in 100 Aortograms

Site of Occlusion	No. of Cases	Femoro-popliteal Patency	
		No.	%
Aorta	10	5	50
Aortic bifurcation stenosis	20	17	85
Common iliac stenosis	21	16	76
Common iliac occlusion	14	8	57
External iliac occlusion	14	4	29
Combined iliac occlusion	9	4	44
Common femoral occlusion	7	1	14
Others (common iliac bifurcation or internal iliac occlusion)	5	1	20
Total	100	56	56

The high patency rate of the distal arteries in aorto-iliac occlusion was first noted by De Bakey *et al.* (1958). Shepherd and Warren (1960) reported a femoro-popliteal patency rate of 59.6% in 52 cases operated on, and Singer (1963) found that the femoral arteries were occluded in only 25% of patients with aorto-iliac lesions. The low incidence of femoro-popliteal occlusion in patients with aorto-iliac occlusion is probably due to the protective effect of the lower distal arterial pressure (Singer, 1963).

In Table III femoro-popliteal patency is analysed with regard to the type of aorto-iliac occlusion present. This shows that the patency rate is high in aortic and common iliac occlusions

and low in external iliac, combined iliac, and common femoral occlusions. Indeed, associated femoro-popliteal occlusion seems to increase as the aorto-iliac occlusion becomes more distally placed in the arterial tree.

Summary

The pattern of occlusion was analysed in the aortograms of 100 patients with intermittent claudication due to aorto-iliac lesions.

Occlusions appeared to originate at three sites with approximately equal frequency: at the aortic bifurcation, in the course of the common iliac artery, and at the common iliac bifurcation.

Occlusion or stenosis of the common iliac artery was the commonest individual lesion, and the origin of lesions in the course of the common iliac artery is discussed in relation to the formation of platelet thrombi and the development of shearing strain at this site.

Femoro-popliteal patency was demonstrated in 56 cases, and the patency rate was found to be highest in the more proximal lesions.

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Guanoclor as an Antihypertensive Drug

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Guanoclor (Vatensol) is a new antihypertensive compound with the structural formula shown in Fig. 1. It is an adrenergic neurone-blocking agent, which also interferes with noradrenaline synthesis by inhibition of the enzyme dopamine beta-hydroxylase. Clinical use of the compound was first reported by Lawrie *et al.* (1964), who achieved satisfactory blood-pressure control in 60% of their cases with guanoclor alone, and in a further 18% with the addition of a thiazide diuretic. They also noted a significant reduction in urinary noradrenaline levels during guanoclor administration. This initial report was sufficiently encouraging to prompt the further studies reported here.

[(2-(2,6-dichlorophenoxy) ethyl) amino] guanidine sulphate

FIG. 1.—Structural formula of guanoclor.

A. Clinical Assessment

Method

Guanoclor has been used singly or in combination with a thiazide diuretic for the treatment of 35 hypertensive patients in regular attendance at the Dunedin Hospital hypertension clinic. Duration of treatment has varied from one month or under for six patients to 14 months or over for three patients, with an average duration of 6.2 months per patient. Clinic attendance was requested every few days at the start of treatment, and later as needed, to maintain stable blood-pressure control. At each clinic visit lying and standing blood-pressure and pulse rate were recorded at two-hourly intervals for a minimum of six hours, together with a standing blood-pressure reading immediately after exercise. Patients were questioned regularly about their health and any possible side-effects noted. In most cases urinalysis and blood cytology and chemistry were carried out before and during guanoclor therapy.

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Twenty-four-hour urine samples from eight patients were assayed for total catecholamines by a modification of the fluorometric method of Crout (1961), three samples being collected from each patient during a control period and three during treatment with guanoclor.

Clinical details of the 35 patients are shown in Table I, the grading of retinal changes being that of Keith, Wagener, and Barker (1939). By this classification eight of the patients had accelerated hypertension with grade III or grade IV changes. The basis of the hypertension was renal in seven, post-toxaemic in one, and essential in the remainder.

Table I contains three columns of figures for blood-pressure, the first (column 6) being the casual blood-pressure recorded at the first clinic visit for each patient. By the criteria of Lawrie *et al.* (1964) 15 patients had severe or gross hypertension (diastolic B.P. over 125 mm. Hg) when first assessed. Column 7 shows the average of all standing blood-pressure readings obtained at a day test immediately before starting guanoclor, other drug treatment being indicated by an asterisk. The next column lists the average of all standing blood-pressures (except those after exercise) at the last three day tests on guanoclor treatment—usually from 12 to 16 readings.

Effect on Blood-pressure

Most patients failed to show a fall in blood-pressure greater than placebo effects during the first 24 hours of guanoclor treatment. In some cases, however, a single oral dose of 20–40 mg. produced a definite blood-pressure fall which was maximal between four and seven hours after drug administration.

Two patients discontinued the drug before its long-term effect could be assessed. Continued administration to all

remaining patients resulted in the appearance of a hypotensive effect by the second to the fifth day, which increased until two weeks or more from the start of treatment. By this stage most patients showed satisfactory overall control of blood-pressure, with average standing diastolic pressures below 100 mm. Hg. An increased hypotensive effect still occurred at four to six hours after each dose of guanoclor, however, and it was found necessary to give the drug in three doses daily in order to achieve sufficient smoothness of blood-pressure reduction. The fall in blood-pressure produced by guanoclor was largely posture-dependent, being greatest in the standing, intermediate in the sitting, and least in the lying position. Excessive postural swings of blood-pressure proved a disadvantage in the management of three patients in the present series, although one of these (Case 1932) continued to show this tendency when bethanidine was substituted.

No patients were found to be completely resistant to the antihypertensive effect of guanoclor. Unsatisfactory overall control of the blood-pressure during prolonged treatment was due to excess postural hypotension, erratic response to steady dose-levels, or the limitations on dosage imposed by side-effects.

Dosage

As with other hypotensive agents of this type, considerable variation in dose requirements for individual patients has been found. The smallest effective dose used was 20 mg. and the largest 240 mg. daily, though only five patients regularly needed a dose of 100 mg. or more daily. Only minor dose changes were required after the initial period of stabilization, and there has been no evidence of tolerance developing during long-term administration of guanoclor.

TABLE I.—Clinical Details of 35 Hypertensive Patients Treated with Guanoclor

Case No.	Sex	Age	Grade	Type	First Casual B.P.	Average B.P. before Guanoclor	Average B.P. on Guanoclor	Duration on Guanoclor (months)	Final Dose of Guanoclor (mg.)	Thiazide Diuretic	Other Previous Drugs	Remarks
1888	F	65	2	E	210/110	233/130	182/94	15	60	Yes	P	Ankle-swelling before thiazide added
1863	F	54	1	E	210/106*	203/120	164/100	15	80	Yes	B, A	Pain in shoulders during first 3 months
1908	F	52	3	Re	220/135	172/107*	174/119	14	90	Yes	M	Erratic B.P. control with severe postural hypotension at times
1163	F	60	2	E	260/110	180/87	160/79	12	90	No	M, R	No symptoms
1923	M	68	2	E	180/96	178/102	163/90	11	70	Yes	B	Back pain during first month
1295	F	59	1	E	240/140	190/103	154/85	10	55	No	G	Severe shoulder and neck pain for 3 weeks
1887	F	64	2	E	270/100	166/121*	159/79	10	25	Yes	A, R	No symptoms
1928	M	56	2	E	220/115	205/115	175/99	10	90	Yes	Nil	" "
1939	F	51	1	E	210/124	171/121	154/103	10	45	No	Nil	" "
1093	M	68	2	E	236/120	195/105	166/86	8	90	Yes	Pt, R	Moderate postural hypotension only
107	F	53	2	E	200/110	177/98*	167/87	7†	50	Yes	Br, Pt	Atypical chest pain, possibly coronary
1930	M	64	2	E	220/130	182/129	170/111	7†	70	Yes	Nil	Erratic control with guanoclor and bethanidine
1944	F	62	2	E	260/160	239/143	155/99	7	75	Yes	Nil	Mild ankle-swelling. Bad dreams at start
1636	F	55	1	Re	215/125	167/123*	157/100	6	25	Yes	A	No symptoms
1945	F	53	3	E	270/130	204/112	180/106	6	80	Yes	Nil	Pain in neck and back intermittently 4 months
1943	M	51	2	E	190/106	189/108	146/97	6	40	Yes	Nil	Heart failure developed during treatment; cleared with diuretic
1614	M	51	3	E	200/120	142/102*	155/98	6	65	Yes	A	No symptoms
1068	F	62	3	E	280/150	214/143	156/108	6	120	Yes	B, A, R	Mild diarrhoea; not with previous drugs
1716	M	49	1	E	164/110	132/96*	133/86	6	100	No	B	No symptoms
1471	F	47	2	E	216/130	154/105*	146/102	6	40	Yes	A	Ankle-swelling and shoulder pain 2 months
1891	M	54	3	E	218/136	181/135	155/112	6†	70	No	Nil	Erratic control, frequent dose changes needed. No symptoms
1561	F	61	1	E	250/130	187/104	154/94	5	40	Yes	M	Shoulder pain 2 months
1608	F	54	1	E	270/145	139/90*	157/95	5	40	Yes	P	Back and thigh pain 3 months
1226	F	61	3	E	240/130	155/95*	146/94	5	30	Yes	A	No symptoms
1576	F	67	2	E	236/120	168/101*	154/88	5	20	Yes	P	Shoulder pain 1 month
1951	M	66	1	Re	198/100*	188/93	150/76	5	120	No	Nil	Mild ankle-swelling, otherwise well
1536	F	71	2	Re	240/130	165/100*	168/100	4†	35	Yes	P, A	Abdominal pain, preferred pempidine
1978	F	51	4	T	260/160	187/136	149/89	3	100	No	Nil	Control rather erratic. Shoulder pain in first month
1981	M	57	2	Re	190/110	200/113	190/110	3	110	No	Nil	Unsatisfactory control, dose increasing. Well
1902	M	60	2	E	210/138	188/113	131/93	1†	20	Yes	Nil	Elevated E.S.R. and anaemia on guanoclor
1680	F	63	2	Re	165/90*	149/94*	156/97	<1†	35	No	A	Postural hypotension troublesome, preferred alpha methyl dopa
1087	M	65	2	E	140/110	132/85*	—	<1†	30	Yes	P, B, R	Abdominal pain after 1 day. Previous peptic ulcer
1901	M	44	2	E	180/120	162/113	115/106	<1†	80	No	Nil	Mild ankle swelling, nightmares, chest pain
200	F	57	2	E	174/124	168/102	—	<1†	20	Yes	A	Non-anginal chest pain after 1 day—stopped drug
1932	F	56	4	Re	260/160	212/120	135/83	<1†	25	Yes	G	Stroke. Marked postural hypotension guanoclor and bethanidine

* On other antihypertensive treatment. † Stopped guanoclor.

A = Methyldopa. B = Bethanidine. Br = Brevitium tosylate. E = Essential. G = Guanethidine. M = Mecamylamine hydrochloride. P = Pempidine. Pt = Pentolinium tartrate. R = Reserpine. Re = Renal. T = Post-toxaemic.

Effect of Thiazide Diuretics

Twenty-five of the 35 patients were given additionally a thiazide diuretic, either continued from an earlier treatment regimen or started during guanoclor therapy because of unsatisfactory blood-pressure control or fluid retention. Patients on the combination of drugs in general showed less postural hypotension than those on guanoclor alone, though unpredictable swings of blood-pressure still occurred, and were especially marked in Case 1908. The average dose of guanoclor was lower for patients on a diuretic also (53 mg. daily) than for those on guanoclor as sole therapy (78 mg. daily). When a diuretic was added after stabilization on guanoclor the dose of the latter drug was first halved and then again increased until a new effective level was found. There were six patients in this group, requiring an average of 88 mg. of guanoclor before and 66 mg. after addition of the diuretic.

Side-effects

Thirteen of the 35 patients made no complaint of side-effects from guanoclor other than postural giddiness associated with a fall in blood-pressure. Side-effects noticed by the remaining patients are listed in Table II.

TABLE II.—Side-effects Noted by Patients on Guanoclor Therapy

Muscle pains	13 patients	Unpleasant taste ..	2 patients
Ankle-swelling ..	5 "	Palpitations	1 "
Gastro-intestinal upset ..	2 "	Failure of ejaculation ..	1 "
Dreams	2 "		

The complaint of muscular pain was spontaneous and not the result of specific questioning; more than a third of the patients mentioned this symptom at some time during treatment with guanoclor. The pain occurred most commonly in the shoulder region, upper back, and posterior muscles of the neck, but was also experienced at various sites in the trunk and limbs. Described as stabbing and severe, it was unlike the muscular aching characteristic of hypotension from other drugs; moreover, its severity was unrelated to the level of blood-pressure. When it was present in the chest the character of the pain distinguished it from angina, and there was no alteration in the heart sounds, electrocardiogram, or serum enzyme levels. Two patients (Cases 1863 and 1902) complained first of epigastric or right hypochondrial pain of stabbing quality. Liver-function tests remained normal and the symptom was later replaced by more typical pain across the shoulders. The level of serum creatine kinase was estimated after one severe bout of pain but was found to be normal, as were the urinary creatine levels. Experience has shown that these attacks of pain are self-limiting, although they may continue for several weeks. All have eventually disappeared despite continuation of the drug at the same or slightly lower dosage.

Five patients developed ankle-swelling, and two others went into mild left ventricular failure during treatment with the drug. In all these cases the signs disappeared within a few days of the addition of a thiazide diuretic.

Both patients who complained of gastro-intestinal symptoms had experienced similar trouble at some time in the past. The majority of patients (including one with a healed duodenal ulcer) had no similar trouble. One patient noticed mild diarrhoea during guanoclor therapy. No skin rashes occurred.

Blood tests revealed abnormalities in nine cases. One patient showed a rise of the erythrocyte sedimentation rate from 16 to 99, 89, and 80 mm. per hour after three weeks' treatment with guanoclor. No other cause could be found for this abnormality, which reverted to normal when bethanidine was substituted. Two patients had minor rises in serum transaminase (S.G.O.T.) levels, and seven showed initial rises of blood urea. The greatest increase in urea level observed was

47 mg./100 ml. (from 24 to 71 mg.), and the average increase was 20 mg./100 ml. (from 35 to 55 mg.). With continued treatment the level of blood urea tended to return somewhat towards normal levels.

Urinary Catecholamine Levels

Measurements of total catecholamine levels were carried out on three 24-hour urine samples from each of eight patients during a control period, and again after three weeks of guanoclor treatment. The results, expressed as micrograms of noradrenaline per 24 hours, are shown in Table III.

TABLE III.—Total Catecholamines (Expressed as Noradrenaline) in the Urine of Eight Patients During a Control Period and While on Guanoclor Treatment. Each Value Represents a Separate 24-hour Sample

Case No.	At Time of Sample Collections		Urinary Noradrenaline (μ g./24 hours)						
	Guanoclor Dose (mg. daily)	B.P. Control	Control Period		Average	On Guanoclor		Average	
1891	200	Good	46.0	44.0	—	45.0	11.3	6.6	13.3
1163	90	"	25.8	19.8	30.7	25.4	14.1	15.3	14.4
1901	80	Fair	42.9	52.0	40.0	45.0	13.8	15.5	30.1
1093	70	"	52.5	52.5	70.8	58.6	22.8	19.8	15.5
1930	60	Good	21.9	21.5	31.5	25.0	14.1	22.0	18.7
1295	50	Fair	93.0	39.4	24.9	52.4	20.7	15.8	21.4
1908	40	Good	10.3	18.0	12.2	13.5	20.2	15.0	10.0
1902	20	"	30.1	31.0	—	30.6	13.3	20.0	15.9

It can be seen that a fall in noradrenaline levels occurred during treatment with guanoclor for all patients except Case 1908, whose control levels were already low. The average fall for the whole group was to below 50% of control values.

B. Animal Studies

The pharmacology of guanoclor was studied in the rat, and the results found were in general agreement with those of Lawrie *et al.* (1964), who used the dog and cat. The compound is an adrenergic neurone-blocking drug, interfering with the normal release of noradrenaline in response to sympathetic-nerve stimulation and tyramine injection. The pressor response to intravenously administered noradrenaline is unaffected or enhanced following guanoclor (Fig. 2). Potentiation of the pressor effect of dopamine occurs after guanoclor administration, due to the inhibitory effect of the drug on the enzyme dopamine beta-hydroxylase (Fig. 2). Continued administration

FIG. 2.—Kymograph recording of the femoral artery pressure in a chloralose-anaesthetized intact rat. Time marker in minutes. NA = 0.2 μ g. noradrenaline. DA = 0.1 mg. dopamine. IO29 = 1 mg. guanoclor. Phen. = 0.5 mg. phenolamine. All substances given intravenously at times of arrows.

TABLE IV.—Effect of Guanoclor on Tissue Catecholamine Concentration in the Rat (12.5 mg. Intraperitoneally Per Rat Daily for 12 Days)

Group	Catecholamine Concentration ($\pm$ S.D.)				
	Heart	Brain	Adrenal Medulla (mg./g.)		
	Total Amines (μ g./g.)		Adrenaline	Noradrenaline	Total Amines
Control (5) ..	0.68 $\pm$ 0.04	0.46 $\pm$ 0.06	2.42 $\pm$ 0.93	0.34 $\pm$ 0.18	2.76 $\pm$ 1.01
Treated (9) ..	0.29 $\pm$ 0.07	0.47 $\pm$ 0.04	0.55 $\pm$ 0.24	0.19 $\pm$ 0.07	0.74 $\pm$ 0.31
Sign. of diff. ..	P < 0.001	P = N.S.	P < 0.001	0.05 > P > 0.02	P < 0.001

S.D. = Standard deviation. Figures in parentheses indicate number of animals in each group.

of guanoclor causes a significant depletion of catecholamines in cardiac muscle and adrenal medulla without affecting brain levels (Table IV).

Discussion

This trial has confirmed that guanoclor is an active drug capable of lowering the blood-pressure in all hypertensive subjects tested. Both immediate and cumulative actions are demonstrable, and, as with other adrenergic neurone-blocking drugs, the greatest effect on blood-pressure occurs in the standing posture. The smoothness of its hypotensive effect has been found to vary considerably: while some patients have given no concern, others have shown wide swings of blood-pressure, and three were changed to other antihypertensives because of erratic control at steady dose levels. The hypotensive action of guanoclor is enhanced by the addition of a thiazide diuretic, so that a lower dose of the former drug is then needed.

Most patients who had been on antihypertensive therapy with other drugs preferred guanoclor to their previous regimen; however, this includes a number who had been changed because of side-effects while on other drugs. Four patients expressed a definite preference for their earlier therapy.

Wide variation has been found between individual patients in dose requirements, an effect being seen in three patients at a dose of 20 mg. daily and others requiring over 100 mg. daily. A comparison of doses in patients who were changed from other drugs has shown a rough correlation between the effective dose of guanoclor and that of other antihypertensives (Table V). In many cases patients were on more complicated regimens previously, and such a comparison was not possible.

TABLE V.—Comparison of Dosage of Drugs

Previous Drug	Case No.	Daily Dose (mg.) of	
		Previous Drug	Guanoclor
Methyldopa	1863	1,625	80
	1614	1,250	65
	1471	1,375	40
	1680	1,125	35
	1887	750	25
Bethanidine	1716	65	100
	1901	30	80
	1930	50	70
	1891	40	70
	1923	15	70
Guanethidine	1902	15	20
	1295	30	55
	1932	20	25
Pempidine	1888	9	60
	1608	8	40
	1536	8	35
	1576	4½	20

Minor side-effects attributable to guanoclor have been relatively frequent, and the most troublesome has been skeletal muscle pains, often of considerable severity. The cause of this symptom is obscure. It is readily distinguished from the tiredness and aching of muscle groups associated with excessive hypotension from other drugs, and appears to be unrelated to blood-pressure level. The symptom is fortunately self-limiting, and it now seems that it can be minimized by a more gradual increase in dosage. Fluid retention similar to that with other adrenergic neurone-blocking drugs has been found

in one-fifth of patients treated with guanoclor: this can be promptly reversed by the use of a thiazide diuretic.

One of the effects of guanoclor is an inhibition of dopamine beta-hydroxylase, the enzyme responsible for the conversion of dopamine to noradrenaline. The other pharmacological actions of the compound make it difficult to assess the importance of enzyme inhibition in regard to lowering of the blood-pressure. Lawrie *et al.* (1964) have found some correlation between the 24-hour excretion of noradrenaline and the level of diastolic blood-pressure, but this has not been confirmed in the present study. Further work will be needed before such a relationship can be established or disproved, and meanwhile the drug is assured a place among compounds of investigational importance.

Summary

A clinical study of the antihypertensive compound guanoclor is described.

The drug has been administered to 35 hypertensive subjects in doses of from 20 to 240 mg. orally each day. Two patients discontinued the drug before its effect on blood-pressure could be assessed; in all the others an antihypertensive action was demonstrated.

Guanoclor has been given for periods of up to 15 months without the development of tolerance to its antihypertensive effect. Even during prolonged administration an immediate action was evident: this was greatest with the patient in the standing posture, and had a duration of less than 12 hours. Fluctuation of the blood-pressure could be reduced by administration of the drug in divided doses three times daily; however, an erratic effect was responsible for unsatisfactory overall blood-pressure control in five cases.

The action of guanoclor was enhanced by the concurrent use of a thiazide diuretic, which also counteracted the tendency towards fluid retention.

Minor side-effects were described by 22 patients, rises of blood urea occurred in seven, two showed small rises in serum S.G.O.T. levels, and one had a persistently raised erythrocyte sedimentation rate while on treatment with guanoclor.

The 24-hour urinary noradrenaline levels were found to be approximately halved by guanoclor administration, and a significant reduction occurred in the noradrenaline content of rat heart muscle and adrenal gland (but not brain) after parenteral guanoclor.

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