COMPARATIVE STUDIES OF GUANFACINE AND METHYLDOPA

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- 1 The antihypertensive effects of the new phenylacetylguanidine compound, guanfacine, a sympathetic inhibitor with a central site of action, were compared with methyldopa in 20 out-patients with essential or renal hypertension (WHO grade I-II).
- 2 During a 6-week period in randomized cross-over conditions, guanfacine 3.5 mg daily caused a mean decrease of 24% in mean arterial blood pressure (MAP). A normalization of blood pressure (BP < 145/95 mm Hg) was achieved in 50% of the patients and a 'good control' (BP < 160/100 mm Hg; > 145/95 mm Hg) in 90%.
- 3 Methyldopa 1.2 g daily led to a mean decrease in MAP of 12%. Normalization of blood pressure occurred in 15% and a 'good control' was achieved with 45% of the patients. Failure due to intolerance or ineffectiveness was observed in 40% of patients.
- 4 During therapy with guanfacine the following side-effects were noted: dryness of the mouth ($n=5$), marked sedation ($n=2$), constipation ($n=2$), orthostasis ($n=1$), collapse ($n=1$) and atrioventricular block grade I on ECG ($n=1$). Methyldopa caused headaches ($n=4$), gastrointestinal disturbances ($n=4$) and dryness of the mouth ($n=1$).
- 5 The experience so far available seems to indicate that guanfacine is an effective antihypertensive drug which is more active than methyldopa in the doses used in this study.

Introduction

In antihypertensive therapy β -adrenoceptor-blocking agents and diuretics are the drugs of first choice. An insufficient blood pressure response to these two groups of antihypertensive agents necessitates the use of vasodilators and of compounds possessing a central site of action.

In drug-resistant hypertension, reduction in blood pressure is often only achieved when four to six of the currently available drugs are used. Although unquestionably effective, they do not yet approach the ideal with respect to efficacy and absence of side-effects. Therefore, the development of new, more effective drugs is required. The new phenylacetylguanidine compound, guanfacine, (Bream, Lauener, Picard, Scholtysik & White, 1975), a clonidine-like sympathetic inhibitor with a central site of action (Bousquet & Guetzenstein, 1973; Kobinger & Pichler, 1974; Low & Waite, 1974; Saameli, Scholtysik & Waite, 1975; Sattler & van Zwieten, 1967; Schmitt, Schmitt, Boissier & Guidicelli, 1967; Schmitt, Schmitt & Fenard, 1973) is a potent antihypertensive compound (Esch, 1976; Röckel, Sabel & Heidland, 1977, 1978; Scholtysik, Lauener & Eichenberger, 1975).

To determine the place of guanfacine in modern antihypertensive therapy, this drug was compared

with methyldopa in a cross-over study in patients with essential and renal hypertension.

Methods

The trial comprised 17 women and 3 men with essential ($n=2$), renoparenchymal (chronic pyelonephritis ($n=5$); chronic glomerulonephritis, ($n=11$); analgesic nephropathy ($n=1$) and renovascular ($n=1$) hypertension. The age, weight and height of the patients divided into group A (guanfacine-methyldopa) and group B (methyldopa-guanfacine) is given in Table 1.

Fifteen patients had been previously treated with diuretics ($n=8$), reserpine ($n=9$), methyldopa ($n=8$), clonidine ($n=3$) and dihydralazine ($n=10$), respectively, as monotherapy or in different combinations. Five patients had never been on antihypertensive therapy. Patients were admitted to the trial if their diastolic blood pressure in the sitting position was between 100 and 120 mmHg during the placebo phase. Applying the WHO classification, eight patients were classified as stage I and twelve as stage II.

Patients with labile hypertension, with complicating congestive heart failure, and with uncontrolled diabetes mellitus, and pregnant women were excluded from the study. Furthermore, patients with psychiatric disorders, especially depression, signs of liver damage and those who did not report for examination as instructed were not included in the study.

The study was designed as a cross-over trial, and patients were randomly allocated to either drug ($2 \times n = 10$). Group A started with guanfacine 1 mg twice or three times daily, and group B with methyldopa 250 mg three times daily. Patients were instructed to take the doses at 0800h, 1400h and 2000 hours. If the blood pressure response was insufficient (diastolic blood pressure > 95 mmHg), the dose of guanfacine was increased up to 6 mg daily and methyldopa up to 2.25 g daily, so as to approach the optimum dosage for the blood pressure reducing effect. Antihypertensive treatment was adjusted while the patients were in hospital; afterwards they measured their blood pressure themselves at home. Previous therapy with other drugs (digitoxin, allopurinol, aluminium hydroxide) was continued during the study.

All previous antihypertensive therapy was stopped for a 1–2 week washout period when placebo tablets were given twice daily. The placebo phase was stopped if the blood pressure exceeded 190/110 mmHg. After this period a 6 week phase with methyldopa or guanfacine was started. After a placebo washout period lasting not more than 2 weeks, patients were switched over from guanfacine to methyldopa or *vice versa*. After 6 weeks a further placebo period followed. The drugs being compared were given using a single-blind technique.

The criteria for evaluation were weekly examinations of blood pressure and pulse rate in a sitting position, laboratory tests (blood glucose, electrolytes, BUN, uric acid, creatinine, SGOT, SGPT, alkaline phosphatase, cholesterol, triglycerides, proteinuria, Addis-Count, ECG) at the beginning and the end of each treatment period.

Severe side-effects and/or poorly controlled blood pressure necessitated withdrawal from randomized treatment in some cases. For statistical evaluation the last values of blood pressure and pulse rate before

withdrawing the drug were used. To evaluate the efficacy of both drugs the following criteria were used (Adi, Eze & Anwunah, 1975; Holzgreve, 1973; Oates, Gillespie, Udenfriend & Sjoerdsma, 1960; Weddell, 1973): 'good control' ($< 160/100$, $> 145/95$ mmHg); 'normalization' ($< 145/95$ mmHg); 'bad response' ($> 160/100$ mmHg). The decrease in mean arterial blood pressure ($MAP = BP_{diastolic} + 1/3 (BP_{systolic} - BP_{diastolic})$) was expressed as a percentage.

All values are presented as mean values $\pm$ s.d. Results were subjected to statistical analysis using Student's *t* test.

Results

Table 2 shows the effect of guanfacine and methyldopa on blood pressure before (placebo) and after a 6-week treatment period with guanfacine or methyldopa in cross-over conditions. The analysis is based on the difference between the measurement during the period of active treatment and that during the previous placebo period. Guanfacine produced greater reductions ($P < 0.001$) in systolic and diastolic blood pressures than methyldopa.

Treatment with guanfacine led to a 'normalization' in 50%, and to a 'good control' of blood pressure in 90% of patients. Therapy with methyldopa resulted in a 'normalization' in 15% and a 'good control' in 45% of patients.

In the group receiving methyldopa the treatment had to be discontinued in one patient in group B and in seven patients in group A because of side-effects (headaches, $n=4$; gastrointestinal disorders, $n=4$; dryness of the mouth, $n=1$) and inefficacy, respectively. Monotherapy with methyldopa was refused more often in group A because the patients preferred the previous therapy with guanfacine. One patient had to be withdrawn under treatment with guanfacine because of atrioventricular block grade II, probably not related to the test drug. The side-effects that occurred during treatment with guanfacine (dryness of the mouth, $n=5$; marked sedation, $n=2$; constipation, $n=2$; orthostasis, $n=1$; collapse, $n=1$; atrioventricular block grade II, $n=1$) were classed as mild ($n=5$) and moderate ($n=5$).

Table 1 Age, weight and height of hypertensive patients admitted to the cross-over study

Group	Age (yr)		Weight (kg)		Height (cm)	
	A	B	A	B	A	B
Mean	37.6	42.0	67.0	69.0	167.0	166.0
s.d.	12.9	7.7	5.0	8.0	5.0	5.0
Range	24–56	25–50	59–77	51–80	157–174	155–174

Table 2 Mean values of systolic and diastolic blood pressures ($\pm$ s.d.), and differences in blood pressure and MAP between placebo phase and treatment periods in each group of ten hypertensive patients treated with guanfacine 2-6 mg daily and methyldopa 0.5-2.25 g/daily

	Group A				Group B			
	Placebo I	Guanfacine	Placebo	Methyldopa	Placebo I	Methyldopa	Placebo	Guanfacine
Blood pressure (systolic/diastolic, mmHg) $\pm$ s.d.	201/122 32/11	143/95 16/11	203/124 25/10	180/114 34/13	187/117 19/15	152/104 17/8	193/118 23/10	145/94 11/9
Systolic	-58***		-23		35**		-48***	
Blood pressure (mmHg)	-27***		-10*		-14*		-24***	
Diastolic								
MAP (mmHg)	-37		-14.3		-20		-33	
MAP (%)	-25		-10		-14		-23	

* $P < 0.01$; ** $P < 0.005$; *** $P < 0.001$.

Although treatment had to be frequently discontinued in group A and cross-over conditions could not be strictly observed, the statistical evaluation was carried out for the second treatment period (group A: placebo—methyldopa; group B: placebo—guanfacine) with those patients remaining.

To compare each case in respect of response and side-effects the contingency table shown in Table 3 was carried out. Guanfacine shows a clear superiority over methyldopa in this analysis.

Heart rate showed insignificant changes during both periods of active treatment.

The laboratory tests, carried out on the conclusion of the first placebo period and after the end of each period of active treatment, did not indicate any treatment-specific pathological alterations.

Discussion

For many years methyldopa has been one of the most important antihypertensive drugs (Mohammed, Fasola, Privitera, Lipicky, Martz & Gaffney, 1969; Oates *et al.*, 1960; Onesti, Brest, Novack & Moyer, 1962; Winer, Chokshi, Yoon & Freedman, 1969). Guanfacine has shown good antihypertensive effects in earlier studies Esch, 1976; Röckel *et al.*, 1977, 1978; Scholtysik *et al.*, 1975). The present investigation was designed to evaluate the place of guanfacine in modern antihypertensive therapy.

In the majority of the patients treated with guanfacine, there were substantial reductions in systolic and diastolic blood pressures, compared with the lesser decrease in blood pressure during therapy with methyldopa: 90% of patients taking guanfacine and 45% receiving methyldopa showed a blood pressure reduction below 160/100 mmHg after the 6-week treatment period. MAP decreased 24% during monotherapy with guanfacine and 12% with methyldopa. Comparable results have been reported by Esch (1976). The data obtained with methyldopa correspond to those of other authors (Mroczek, Fotin & Davidov, 1974; Safar, Corvol & Weiss, 1974).

Table 3 Contingency table for response and side-effects of guanfacine and methyldopa during a 6-week cross-over treatment period

	x^+/y^+	x^+/y^-	x^-/y^+	x^-/y^-	Total
Guanfacine	6	11	0	3	20
Methyldopa	2	4	3	11	20

x^+ , Good responses of systolic and diastolic blood pressures.

x^- , Bad responses of systolic and diastolic blood pressures.

y^+ , Side-effects; y^- : no side-effects.

When designing the present study it was difficult to define comparable dosage levels of the agents which differ in their site of action. Commonly used and accepted doses were therefore taken to obtain an optimal response in each patient. With methyldopa the adjustment seemed to be more tedious and the blood pressure was on the whole more labile. Methyldopa caused side-effects which forced withdrawal of the treatment in three cases. In five patients in group B, in whom methyldopa was given in the second period of active treatment, it was necessary to withdraw the drug prematurely, because the effect on blood pressure was inadequate despite high daily doses amounting to 2.5 g. These drop-outs were later treated successfully with guanfacine (Röckel *et al.*, 1977; 1978). Because of the high number of drop-outs during the methyldopa phase, the statistical evaluation of the second active therapy period must be judged with reserve.

Our data do not provide evidence concerning rebound hypertension occurring on the withdrawal of

guanfacine because the placebo periods were interrupted when the blood pressure increase exceeded 190/110 mmHg.

The laboratory tests did not indicate any drug-specific pathological disorder. Increases in transaminases and alkaline phosphatase, suggesting a lesion of liver cells or cholestasis, did not occur.

Side-effects occurring during treatment with guanfacine were dryness of the mouth, constipation and sedation, especially at high doses and at the beginning of therapy; these side-effects often decreased after 1 week of treatment.

The limited number of patients restricts the possibility of drawing generalized conclusions from the present results, but our data do suggest that at the doses tested guanfacine has greater potency and better patient acceptability than methyldopa. Guanfacine should therefore be considered for use alone or in combination therapy (Röckel *et al.*, 1977; 1978) in the treatment of hypertension.

References

- ADI, F.C., EZE, C.J. & ANWUNAH, A. (1975). Comparison of debrisoquine and guanethidine in treatment of hypertension. *Br. med. J.*, **1**, 482-485.
- BOUSQUET, P. & GUETZENSTEIN, P.G. (1973). Localization of the central cardiovascular action of clonidine. *Br. J. Pharmac. Chemother.*, **49**, 573-579.
- BREAM, J.B., LAUENER, H., PICARD, C.W., SCHOLTYSIK, G. & WHITE, T.G. (1975). Substituted phenylacetylguanidines: A new class of antihypertensive agents. *Arzneimittel-Forschung*, **25**, 1477-1482.
- ESCH, I. (1976). Erste Erfahrungen mit BS 100-141, einer neuen blutdrucksenkenden Substanz. *Int. J. clin. Pharmac.*, **14**, 109-112.
- HOLZGREVE, H. (1973). Die Frühbehandlung der leichten Hypertonie. *Internist.*, **14**, 313-316.
- KOBINGER, W. & PICHLER, I. (1974). Evidence for direct alpha-adrenoceptor-stimulation of effector neurons in cardiovascular centers by clonidine. *Eur. J. Pharmac.*, **27**, 151-154.
- LOEW, D.M. & WAITE, R. (1974). A quantitative assessment of the effects of clonidine on pre-ganglionic sympathetic nerve activity in the cat. *Br. J. Pharmac. Chemother.*, **50**, 456-457.
- MOHAMMED, S., FASOLA, A.F., PRIVITERA, P.J., LIPICKY, R.J., MARTZ, B.L. & GAFFNEY, T.E. (1969). Effect of methyldopa on plasma renin activity in man. *Circulat. Res.*, **25**, 543-548.
- MROCZEK, W.J., DAVIDOV, M. & FINNERTY, F.A., JR. (1972). Prolonged treatment with clonidine: comparative antihypertensive effects alone and with a diuretic agent. *Am. J. Cardiol.*, **30**, 536-541.
- MROCZEK, W.J., FOTIU, S., DAVIDOV, M.E. & FINNERTY, F.A., JR. (1974). Prazosin in hypertension: A double-blind evaluation with methyldopa and placebo. *Curr. ther. Res.*, **16**, 769-777.
- OATES, J.A., GILLESPIE, L., UNDEFRIED, S. & SJOERDSMA, A. (1960). Decarboxylase inhibition and blood pressure reduction by alpha-methyl 3,4-dihydroxy-DL-phenylalanine. *Science*, **131**, 1890-1891.
- ONESTI, G., BREST, A.N., NOVACK, P. & MOYER, J.H. (1962). Pharmacodynamic effects and clinical use of alpha methyldopa in the treatment of essential hypertension. *Am. J. Cardiol.*, **9**, 863-867.
- RÖCKEL, A., SABEL, B. & HEIDLAND, A. (1977). N-amidino 2-(2,6-dichlorophenyl) acetamid-hydrochlorid (BS 100-141) in der Langzeittherapie der schweren Hypertonie. *Verh. dt. Ges. inn. Med.*, **83**, 314-318.
- RÖCKEL, A., SABEL, B. & HEIDLAND, A. (1978). Therapie der essentiellen und renalen Hypertonie mit BS 100-141 (Guanfacinum). *Herz. Kreislauf*, **3**, 136-142.
- SAAMELI, K., SCHOLTYSIK, G. & WAITE, R. (1975). Pharmacology of BS 100-141, a centrally acting antihypertensive drug. *Clin. exp. Pharmac. Physiol.*, **2**, 207-212.
- SAFAR, M., CORVOL, P. & WEISS, Y. (1974). Action hypertensive de trois drogues inhibant le système nerveux sympathique. *Nouv. Presse méd.*, **3**, 871-875.
- SATTler, R.W. & VAN ZWIETEN, P.A. (1967). Acute hypotensive action of 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride (ST 155) after infusion into the cat's vertebral artery. *Eur. J. Pharmac.*, **2**, 9-13.
- SCHMITT, H., SCHMITT, H., BOISSIER, J.R. & GUIDICELLI, J.F. (1967). Centrally mediated decrease in sympathetic tone induced by 2-(2,6-dichlorophenylamino)-2-imidazoline (ST 155, Catapresan). *Eur. J. Pharmac.*, **2**, 147-148.

- SCHMITT, H., SCHMITT, H. & FENARD, S. (1973). Action of adrenergic blocking drugs on the sympathetic centres and their interactions with the central sympatho-inhibitory effect of clonidine. *Arzneimittel-Forschung.*, **23**, 40–45.
- SCHOLTYSIK, G., LAUENER, H. & EICHENBERGER, E. (1975). Pharmacological actions of the antihypertensive agent *N*-amidino-2-(2,6-dichlorophenyl)-acetamide hydrochloride (BS 100–141). *Arzneimittel-Forschung.*, **25**, 1483–1491.
- WEDDELL, J.M. (1973). Control of moderately raised blood pressure. *Br. med. J.*, **3**, 434–436.
- WINER, N., CHOKSHI, D.S., YOON, M.S. & FREEDMAN, A.D. (1969). Adrenergic receptor mediation of renin secretion. *J. clin. Endocrin. Metab.*, **29**, 1168–1175.