DR. SIRCUS: We discussed this case as being something within the common remit of all of us, and deliberately avoided an exercise in the exotic. There are a good many lessons here. What do members of the audience think?

PROFESSOR M. D. MILNE (6): I am rather puzzled to know what causes the impaired glucose tolerance test. It is obviously not atrophy of the islets of Langerhans, which are usually preserved, and are certainly preserved after duct ligation in the experimental animal.

DR. DAWSON: I do not know. You can get islet hyperplasia and hypoglycaemia with duct ligation in animals.

DR. MACLEAN: The obstruction may cause pancreatitis not amounting to necrosis, which would affect the islets. There was some oedema and a minor degree of round cell infiltration.

MR. SMITH: In some cases after surgical resection the glucose tolerance test goes back to normal so that the derangement is reversible.

MEMBER OF AUDIENCE: What about angiography in the early diagnosis of carcinoma in the head of the pancreas?

DR. DAWSON: The Edinburgh series had 100% in three cases and I think that was a lucky first three. It is not by any means an infallible technique.

DR. SIRCUS: With regard to the value of pancreatic scanning, we were among the first units to evaluate it when it was a research study and it gave very striking results. But as soon as the research era ended and it became a service commitment, the value fell away, until scans became almost dangerously misleading. The original position in our unit has been recouped only by recruiting a radiologist who was particularly interested in scanning and using one technician who does that job all the time. The position in respect of arteriography is exactly the same—it needs someone with considerable experience doing large numbers. This is why the Scandinavians have contributed so much.

DR. DAWSON: I would like to make a plea that as radiologists are in short supply they are better employed learning to do good barium meals than doing scanning.

DR. SIRCUS: Yes, except that good endoscopy is making good barium meals less important and in scanning the radiologist's time is occupied only with quality control and interpretation.

DR. DAWSON: Endoscopy is more punitive and takes rather longer.

DR. SIRCUS: I think before we close the discussion we should emphasize the significance of depression occurring for the first time in a man of over 70. Senile melancholia is a common early manifestation of lurking neoplasia. That should have alerted the diagnosticians in today's case.

Acknowledgement

The illustrations are the work of Mr. J. Paul of the Department of Medical Photography, the University of Edinburgh.

Reference

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APPOINTMENTS OF SPEAKERS

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(2) Dr. A. M. Dawson, M.D., F.R.C.P., Consultant Physician, St. Bartholomew's Hospital, London.
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(4) Dr. N. Maclean, M.B., F.R.C.P., Honorary Senior Lecturer, Department of Pathology, University of Edinburgh.
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Occasional Survey

Side Effects of Hypotensive Agents Evaluated by a Self-administered Questionnaire

C. J. BULPITT, C. T. DOLLERY

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Summary

A self-administered symptom questionnaire was completed by 477 patients in a hypertension clinic. The complaints of the patients were analysed according to the type of therapy being given and the dose of drug taken. Methyldopa therapy was associated with sleepiness, weakness of the limbs, sleeping longer at night, and rising more frequently at night to pass urine. Diarrhoea, impotence, failure of ejaculation, blurred vision, depression, and the symptoms of postural hypotension were not related to methyldopa therapy. Bethanidine administration was related to postural hypotension, impotence, and failure of ejaculation but not to weakness of the limbs, blurred vision, depression, or diarrhoea. Patients receiving guanethidine complained of postural hypotension, failure of ejaculation, and had their bowels open more frequently. Similarly, patients receiving propranolol had an increased frequency of defaecation but also tended to complain of weakness of the limbs.

Considering each drug individually, 5% of patients failed to take the prescribed dose of diuretic whereas

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16-22% failed to take the prescribed amount of other therapeutic agents. Overall 27% were not taking exactly the prescribed dose of one or more drugs.

Drug combinations did not increase the prevalence of symptoms and different therapeutic regimens may be used with a view to reducing the prevalence of side-effects.

Introduction

When a high blood pressure is reduced by drugs, the likely benefit in reduced morbidity and mortality from the disease has to be balanced against the disadvantages of daily medication which often causes side effects. A separate communication[1] assesses the well-being and symptoms of a large group of hypertensive patients attending the Hammersmith Hospital hypertension clinic and describes a self-administered questionnaire for use in hypertensive subjects. The present paper relates symptoms and side effects to the therapy taken by these patients.

Results

Altogether, 373 patients responded to a single postal questionnaire (82% response rate) and 104 completed the questionnaire in the clinic. Of these, 374 were taking a diuretic, 287 methyldopa, 249 potassium supplements, 117 bethanidine, 31 guanethidine, 28 propranolol, 26 reserpine, and 8 clonidine. The average age, the proportion of males, and the racial distribution of eight treatment groups (omitting six Asians) is given in table I. Excluding the small groups receiving propranolol (seven patients for propranolol and 12 for propranolol + methyldopa) the other groups were reasonably compatible for age, sex, and race.

The average daily dose given in 13 therapeutic groups and the average blood pressures recorded are shown in table II. The groups requiring both methyldopa and bethanidine or methyldopa and propranolol received higher doses of methyldopa than when this drug was given only in combination with a diuretic. Blood pressure control in all positions was least satisfactory in patients receiving both bethanidine and methyldopa, a situation reflecting the difficulty of obtaining good pressure control in this group of patients.

The poor lying blood pressure control in patients receiving guanethidine or bethanidine was due to the difficulty of reducing this lying pressure without a disproportionately large fall in standing blood pressure. The postural fall in systolic blood pressure is also given in the table.

The therapy initiated in the Hammersmith clinic depends on an individual doctor's preference, and intolerable side effects result in a change in therapy to one which the patient is able to tolerate. At the time of the survey the drugs of greatest popularity with the doctors were diuretics, methyldopa, and bethanidine. Less popular were guanethidine and reserpine, and patients with

TABLE I—*Race, Age, and Sex Characteristics of Eight Therapeutic Groups*

Therapy	No. of Patients	Average Age	Percentage		
			Males	Caucasian	Negro
Diuretic alone	51	56	51·0	90·2	9·8
Methyldopa ± diuretic	220	55·8	47·3	90·0	8·2
Bethanidine ± diuretic	60	54·8	40·0	94·9	3·4
Guanethidine ± diuretic	27	57·3	48·2	88·9	11·1
Reserpine + diuretic	24	57·1	37·5	83·3	16·7
Propranolol ± diuretic	7	50·6	(5 M.)	(5 C.)	(1 N.)
Bethanidine + methyldopa ± diuretic	47	53·3	48·9	91·5	8·5
Propranolol + methyldopa + diuretic	12	49·6	50·0	(11 C.)	(1 N.)

TABLE II—*Drug Doses and Blood Pressure Control in Different Therapeutic Regimens*

Drug Combination	No. of Patients	Average Dose (mg/day)	Blood Pressure (mm Hg)				
			Standing Diastolic	Standing Systolic	Lying Diastolic	Lying Systolic	Systolic PosturalDrop
Diuretic alone	51	—	90·0	143·9	89·9	151·8	7·9
Methyldopa alone	55	1,278	92·9	147·7	95·6	164·6	16·9
Methyldopa + diuretic	164	1,478	89·3	140·4	92·1	152·8	12·4
Bethanidine alone	12	43·3	92·1	150·0	100·8	173·7	23·7
Bethanidine + diuretic	48	52·4	94·1	152·1	97·0	169·0	16·9
Guanethidine alone	7	63·6	88·6	141·4	100·7	172·1	30·7
Guanethidine + diuretic	19	65·2	95·2	155·5	97·8	175·5	20
Reserpine + diuretic	24	0·34	83·7	140·1	88·2	151·9	11·8
Propranolol alone	3	150	90·0	128·3	88·3	141·7	13·4
Propranolol + diuretic	4	150	85·0	147·5	85·0	156·2	8·7
Bethanidine (B) + methyldopa (M)	8	42·5 (B) 2,625 (M)	98·4	152·7	99·6	166·5	13·8
Bethanidine (B) + methyldopa (M) + diuretic	39	46·3 (B) 2,288 (M)	97·1	152·1	102·8	171·2	19·1
Propranolol (P) + methyldopa (M) + diuretic	12	280 (P) 1,875 (M)	91·3	136·7	96·3	160·8	24·1

TABLE III—*Results According to Six Therapeutic Groups*

Symptom	Diuretic Alone	Methyldopa ±Diuretic	Bethanidine ±Diuretic	Guanethidine ±Diuretic	Reserpine +Diuretic	Methyldopa +Bethanidine ±Diuretic
Postural hypotension (%)	33·3	31·9	43·3	34·6	20·8	42·2
Sleepiness (%)	38·8	56·9	53·4	33·3	50·0	42·6
Hours of sleep	7·2	7·5	6·9	7·0	7·0	7·4
Weak limbs (%)	20·8	27·0	20·7	12·0	12·5	40·0
Slow walking pace (%)	44·7	35·2	31·7	30·8	20·8	40·4
Headache (%)	24·0	15·7	18·6	11·1	16·7	10·6
Blurring of vision (%)	16·7	18·5	22·0	11·1	21·7	23·9
Depression (%)	37·5	30·1	25·0	11·1	29·2	32·6
Bowels open (times/day)	1·2	1·3	1·3	1·5	1·1	1·2
Diarrhoea (%)	36·7	27·3	33·3	28·0	17·4	36·4
Nocturia (times/night)	0·9	1·1	1·2	0·9	1·4	1·2
Dry mouth (%)	33·3	41·3	39·0	33·3	33·3	48·9
Average No. of patients	49	212	59	26	24	46
Impotence (%)	31·8	35·7	66·7	54·5	33·3	47·4
Failure of ejaculation (%)	13·6	18·5	41·2	60·0	14·3	41·1
Frequency of sexual intercourse per year	42·1	26·9	18·2	18·0	6·0	25·5
Average No. of patients	22	84	19	11	6	17

TABLE IV—*Prevalence of Symptoms According to Therapy and Allowing Drug Combinations*

Symptom and Drug	Drug Not Given		Drug Given		Significance
	% Complaining of Symptom	No.	% Complaining of Symptom	No.	
Postural hypotension:					
Bethanidine (excluding guanethidine)	30·2	321	41·2	114	$P < 0.05$
Guanethidine (excluding bethanidine)	30·2	321	40·0	30	N.S.
Sleepiness:					
Methyldopa	44·9	185	55·5	283	$P < 0.05$
Propranolol	50·2	442	67·9	28	N.S.
Methyldopa (excluding propranolol)	43·7	174	54·5	266	$P < 0.05$
Weakness of Limbs:					
Methyldopa	19·9	181	30·8	276	$P < 0.025$
Propranolol	24·9	430	50·0	28	$P < 0.01$
Methyldopa (excluding propranolol)	18·2	170	29·3	259	$P < 0.025$
Propranolol (excluding methyldopa)	18·2	170	45·5	11	N.S.
Failure of Ejaculation:					
Bethanidine (excluding guanethidine)	18·0	128	40·0	40	$P < 0.01$
Guanethidine (excluding bethanidine)	18·0	128	58·3	12	$P < 0.01$

N.S. = Not significant.

side effects on these drugs were likely to have been switched to other therapy. The patients remaining on guanethidine and reserpine were slightly older and, as will be shown, a very uncomplaining group. Propranolol was a relatively new therapy and was therefore being given to somewhat younger patients.

SIDE EFFECTS AND SYMPTOMS ASSOCIATED WITH USE OF VARIOUS THERAPEUTIC AGENTS

The results of six therapeutic groups are presented in table III. each symptom or side effect will be considered individually.

Postural Hypotension

Postural hypotension was diagnosed when the patient answered "Yes" to the question "Since your last visit have you suffered from unsteadiness, light-headedness, or faintness?" together with "Yes" to either "Does the unsteadiness or faintness occur only when you are standing?" or "Is the unsteadiness or faintness worse first thing in the morning?".

The prevalence of symptoms of postural hypotension was greatest in the groups receiving either bethanidine or guanethidine. The prevalence of postural hypotension according to whether the patient was receiving or not receiving one of these drugs, irrespective of many drug combinations, is given in table IV. Forty-one per cent. of those receiving bethanidine reported postural hypotension and 40% of those receiving guanethidine. These two proportions were compared with the proportion of patients who had postural hypotension and were not receiving either guanethidine or bethanidine (30%). The difference was significant for bethanidine at the 5% level. The results were confirmed by examining the average systolic postural drop (lying to standing) on bethanidine (18·5 mm Hg), guanethidine (25·1 mm Hg), and patients not receiving these drugs (12·9 mm Hg). The increase in systolic postural drop was significant at the 2·5% level in the bethanidine group and at the 1% level in the guanethidine group.

Sleepiness

Question: "Since your last visit have you often felt sleepy during the day?"

Methyldopa and propranolol were associated with the highest prevalence of sleepiness. The results are presented in table IV according to whether methyldopa and propranolol were given or not and irrespective of the use of drug combinations. Propranolol was mainly given in combination with other drugs. Though 68% of patients receiving propranolol reported sleepiness this excess was not significant at the 5% level. The increase in sleepiness in patients receiving methyldopa over patients not receiving this drug was significant at the 5% level. This was also true when patients receiving propranolol were omitted from the analysis.

The most striking fact was not the number of patients receiving methyldopa who complained of sleepiness but that up to 54% of patients on other therapy complained of this symptom (table III). An association between sleepiness and both a low standing systolic pressure and young age has been noted.[1] The group on methyldopa were on average older than the group not receiving methyldopa and there was no significant difference in standing systolic blood pressure between these two groups.

Number of Hours Slept per Day

Question: "How many hours per 24 do you usually sleep?"

Methyldopa was associated with the maximum average number of hours slept per day (7·4-7·5 hours). When the average number of hours slept for patients receiving methyldopa was compared with the average number of hours slept by patients not receiving the drug (7·1 hours) the difference was significant at the 5% level. No other drug produced a significant change in the number of hours slept, in particular the average number of hours slept by the 28 patients receiving propranolol was not increased at 6·9 hours.

Weakness of Limbs

Question: "Have you since your last visit noticed weakness in the limbs?"

The drugs associated most with weakness of the limbs were methyldopa and propranolol, the prevalence being 27% with methyldopa ± a diuretic, 40% with methyldopa + bethanidine, and 50% for propranolol ± other therapy. Table IV again analyses the prevalence of this symptom according to whether therapy was given, irrespective of drug combinations. The increased prevalence in patients receiving methyldopa was significant at the 2·5% level and the increased prevalence in patients taking propranolol was significant at the 1% level. Re-analysing for methyldopa, excluding propranolol, confirmed the results for methyldopa. Five patients out of 11 receiving propranolol but not methyldopa complained of weakness of the limbs (46%). The relation between weakness of the limbs and these two drugs could not be explained by the height of the blood pressure.

Slow Walking Pace

Question: "Compared to other men and women of your age, do you tend to walk slower?"

A slow walking pace was most prevalent in patients receiving only a diuretic (45%). There was no evidence for an association between any drug and the complaint of slow walking pace.

Waking Headache

Question: "Have you since your last visit suffered from headaches? At what time of the day do the headaches occur?" Answer options: On waking in the morning/during the day but not present on waking/during the evening.

Waking headache was diagnosed when the patient answered "Yes" to the first question and "On waking in the morning" to the second question. The symptom was most prevalent in the group receiving only a diuretic (24%) and was less prevalent in the group receiving both bethanidine and methyldopa (11%). The complaint of headache was least in patients receiving both propranolol and methyldopa. None of these 12 patients complained of headache.

These relationships suggest either that the reduction in headache was an effect of therapy or that patients not requiring potent hypotensive agents were a group of mild hypertensives entering the clinic because of their complaints. In the group on diuretics only, the excessive prevalence of headache was true only for women and not for men.

Blurring of Vision

Question: "Have you since your last visit had blurring of vision?"

This symptom was not affected by therapy.

Depression

Question: "Have you since your last visit been depressed?" The symptom was graded as 1 or 2, grade 2 if the patient answered "Yes" to the question "Did you consult a doctor about your depression?"

There was no evidence that this symptom was affected by therapy.

Frequency of Defecation

Question: "How often do you usually open your bowels? Indicate times per day or times per week."

Patients taking guanethidine had their bowels open on average 1·5 times a day. Allowing drug combinations, the frequency of defecation was significantly greater in the groups receiving guanethidine (1·58 times daily in 31 patients) and propranolol (1·82 times daily in 26 patients) than the corresponding groups not receiving these drugs (1·28 times in 438 patients and 1·27 times in 443 patients, $P < 0.05$ and $P < 0.01$ respectively).

Giving a diuretic reduced the average frequency of defecation by a small but significant amount ($P < 0.025$). Patients receiving a diuretic had their bowels open an average of 1·26 times daily as opposed to an average of 1·45 times daily for patients not receiving a diuretic. The diuretic effect tended to mask the true increased frequency found with guanethidine and propranolol.

Diarrhoea

Question: "Are your motions often loose or liquid?"

This symptom was not related to the therapy given and probably patients developing this complaint had had their therapy changed to a second drug.

Nocturia

Question: "How many times, on average, do you rise at night to pass urine?"

The average times that a patient rose to pass urine at night varied from 0·9 for the diuretic and guanethidine group to 1·4 for the reserpine group. None of these deviations was significant at the 5% level. The dose of methyldopa was related to the frequency of nocturia and will be discussed under the section on therapeutic doses and symptoms.

Dry Mouth

Question: "Do you suffer from a dry mouth?"

There was no significant difference between the proportion of patients receiving a diuretic who complained of a dry mouth (37%) and patients who did not receive a diuretic (41%, drug combinations allowed). Similarly, when considering the other therapeutic groups there was no significant association between dry mouth and therapy. The greatest prevalence of dry mouth was in patients receiving both methyldopa and bethanidine (49%), compared with 41% for methyldopa ± diuretic, 39% for bethanidine ± diuretic, and 33% for a diuretic alone (table III).

Impotence

Question: "During sexual intercourse are you troubled by failure to sustain an erection?"

The drugs associated with impotence were bethanidine (67% of 18 patients) and guanethidine (54% of 11). Sixty-one per cent. of patients taking bethanidine (drug combinations allowed) complained of impotence against 36% for patients taking neither bethanidine nor guanethidine. The excess in bethanidine-treated patients was significant at the 1% level. Only 36% of patients taking methyldopa ± diuretic complained of impotence.

Failure of Ejaculation

Question: "During sexual intercourse are you troubled by failure to pass semen?"

Six out of 10 men taking guanethidine complained of failure of ejaculation and 41% of 17 men taking bethanidine. Allowing drug combinations, only 18% of patients receiving neither bethanidine nor guanethidine complained of failure of ejaculation. The corresponding results for bethanidine (40%) and guanethidine (58%) are shown in table IV, both increases being significant at the 1% level.

Frequency of Sexual Intercourse

Question: "How often do you have sexual intercourse?"

Comparison of the annual frequency of sexual intercourse in therapeutic groups did not show significant differences. As would be expected, however, the groups complaining of impotence or failure of ejaculation tended to have a low frequency of sexual intercourse (table III).

RELATION BETWEEN DRUG DOSE AND SYMPTOMS

The average daily dose of methyldopa, bethanidine, guanethidine, and reserpine for patients complaining of different symptoms, irrespective of diuretic therapy, is given in table V. The dose taken according to the patient was recorded and not the dose prescribed.

Methyldopa.—The group complaining of sleepiness were receiving a significantly greater dose of methyldopa (1,515 mg daily) than the group receiving methyldopa but not complaining of sleepiness (1,237 mg daily, $P < 0.02$). Other comparisons did not reach statistical significance but it is interesting that average daily dose levels in excess of 1,500 mg were associated with postural hypotension lasting for less than one hour (grade 1), a slow walking pace, depression not accompanied by a visit to

TABLE V—*Average Daily Dose According to Symptoms. (Figures in Parentheses are No. of Patients in Group)*

	Average Daily Dose of Drug Given (mg) with or without Diuretic			
	Methyldopa	Bethanidine	Guanethidine	Reserpine
All patients	1,403 (220)	51 (60)	65 (27)	0·34 (24)
Postural hypotension:				
<1 hour/day	1,528 (44)	70 (21)	48 (7)	0·25 (2)
1-2 hours/day	1,458 (12)	33 (4)	53 (2)	0·28 (2)
>2 hours/day	1,168 (12)	70 (1)	—	0·30 (1)
Sleepiness	1,515 (123)*	52 (31)	53 (9)	0·30 (12)
Weakness of limbs	1,487 (57)	43 (12)	42 (3)	0·25 (3)
Slow walking pace	1,542 (77)	39 (19)	48 (8)	0·36 (5)
Headache:				
<1 per week	864 (11)	25 (4)	53 (2)	0·63 (2)
1-6 per week	1,143 (14)	58 (5)	60 (1)	0·28 (2)
>6 per week	1,531 (8)	38 (2)	—	—
Blurring of vision	1,322 (38)	52 (13)	51 (3)	0·37 (5)
Depression:				
Grade 1	1,590 (55)	78 (12)	129 (3)	0·31 (6)
Grade 2	1,350 (10)	33 (3)	—	0·20 (1)
Diarrhoea	1,417 (57)	58 (19)	89 (6)	0·28 (4)
Dry mouth	1,474 (85)	60 (23)	74 (9)	0·33 (8)
Impotence	1,603 (29)	44 (13)	47 (6)	0·40 (2)
Failure of ejaculation	1,650 (15)	59 (8)	89 (6)	0·50 (1)

* Significant at the 5% level (see text).

TABLE VI—*No. of Patients Failing to Take Prescribed Dose*

	Diuretic	Methyldopa	Bethanidine	Guanethidine	Reserpine	Propranolol	Potassium Supplements
Receiving drug	378	289	116	32	29	28	252
Percentage who have altered prescribed dose	4·8	18·3	16·3	21·9	20·7	21·0	21·0

the doctor (grade 1), impotence, and failure of ejaculation. Sleepiness was therefore shown to be dose related but the other symptoms will require further investigation. The frequency of passing urine at night was related to the daily dose of methyldopa. It has been shown[1] that this frequency is related to age and lying blood pressure, but when the dose of methyldopa was corrected for both of these variables (by multiple regression techniques) there was a significant methyldopa dose effect on the frequency of nocturia ($t = 2{\cdot}5$ on 467 D.F.). The frequency of nocturia increased with the dose of methyldopa. Thirty-three patients complaining of a headache received on average less methyldopa than 177 patients not having a headache and taking methyldopa (mean 1,144 mg against 1,451 mg, $P < 0{\cdot}05$).

Bethanidine.—There was no significant increase in daily dose in association with any symptom. In common with methyldopa, however, high dose levels were recorded in association with postural hypotension of short duration (grade 1, 70 mg daily) and depression not accompanied by a visit to the doctor (grade 1, 78 mg daily). It has previously been shown[1] that postural hypotension lasting for less than one hour a day was associated with the largest postural pressure drop.

Guanethidine.—No symptom group included more than nine patients and the high dose levels found in association with diarrhoea, failure of ejaculation, and depression require further investigation.

Reserpine.—The symptom groups were small and failed to suggest any dose-related symptoms.

NUMBER OF PATIENTS FAILING TO TAKE PRESCRIBED DOSE

The prescribed dose was obtained from a copy of the last prescription and was compared with the dose of drug that the patient reported he was taking. The results are shown in table VI. When considering the drugs separately only 5% of patients given a diuretic failed to take the prescribed dose, presumably partly due to the use of a simple therapeutic regimen—for example, one tablet daily—whereas the proportion not taking the prescribed dose of methyldopa, bethanidine, guanethidine, reserpine, propranolol, and potassium supplement varied from 16 to 22%. Alterations in therapy may be due to intolerable side effects but the dose may be changed for many reasons and the results in table VI cannot be interpreted as an index of the prevalence of side effects. Overall 27% of patients failed to take the prescribed dose of one or more drugs.

WHICH THERAPEUTIC REGIMEN WAS MOST FREE OF SIDE EFFECTS?

As discussed above, there was probably considerable selection into the guanethidine, reserpine, and propranolol groups. Methyldopa, bethanidine, and diuretics are all currently popular in the Hammersmith clinic. The group on diuretics alone was probably selected on the basis of a relatively easily controlled hypertension. The methyldopa and bethanidine groups were assumed to be comparable and the methyldopa plus bethanidine group to be selected owing to the difficulty in controlling the blood pressure with either drug alone.

The average total complaint rate for the four therapeutic groups and both sexes is given in table VII. The total complaint rate was the sum of unit scores for each of the following symptoms: postural hypotension, sleepiness, weakness of the limbs, headache, blurred vision, depression, diarrhoea, dry mouth, slow walking pace, impotence, failure of ejaculation, nocturia of more than once a night, bowels open more than three times a day, and sleeping more than 10 hours in 24; a theoretical maximum of 14 for men and 12 for women. In men methyldopa appeared to produce less side effects than bethanidine (3·3 on average instead of 4), whereas in women there was no such differential. Bethanidine when given in combination with methyldopa did not produce an excessive number of symptoms in either sex.

TABLE VII—*Average Total Complaint Rate According to Therapy and Sex*

	Males		Females	
	Rate	No.	Rate	No.
Diuretic alone	2·6	26	3·7	25
Methyldopa ± diuretic	3·3	104	3·3	116
Bethanidine ± diuretic	4·0	24	3·2	36
Methyldopa + bethanidine ± diuretic	3·0	23	3·4	24

SIDE EFFECTS WHILE USING DRUG COMBINATIONS

If in a survey there is a group of patients receiving a certain daily dose of drug A, a group receiving this dose of A plus another hypotensive agent, B, a group receiving only a similar dose of drug B, and a group not receiving either drug, a side effect produced by both drugs may be said to be additive or non-additive. In the additive situation the patient receiving both drugs has an increased probability of getting the side effect, the increased chance being due to combining the probabilities with either drug alone. In the non-additive situation the patient on combined therapy either has less than the expected increase in probability—that is, a negative interaction is said to be present—or the combined group has a much higher prevalence of the side effect than would be expected from the additive situation (a positive interaction).

The combination of a diuretic with methyldopa therapy was not associated with an increase in complaints and similarly the combination of methyldopa and bethanidine was related to fewer complaints in men and no significant increase in women (table VII). This was not due to the combined therapy groups taking a smaller dose. The group receiving both methyldopa and bethanidine tended to receive more methyldopa than the methyldopa ± diuretic groups and a similar dose of bethanidine to the bethanidine ± diuretic group (table II). Individual side effects were therefore examined to determine the presence of any significant negative interactions.

By taking the four groups, diuretic alone, methyldopa ± diuretic, bethanidine ± diuretic, and methyldopa + bethanidine ± diuretic, and ignoring the effect of diuretic therapy, the results can be regarded as a factorial set of proportions. A solution of the problem by taking contrasts and using a logistic transformation and empirical weights has been described in detail by Armitage.[2]

The results for the methyldopa/bethanidine interaction are presented in table VIII as approximate normal deviates. There was a significant negative interaction for both sleepiness and impotence, confirming that the combination of methyldopa and bethanidine did not increase the prevalence of these two symptoms. There was no significant positive interaction with any symptom.

TABLE VIII—*Methyldopa/Bethanidine Interactions Expressed as Normal Deviates (see text)*

Postural hypotension	+0·2	Depression	+1·3
Sleepiness	−4·6	Diarrhoea	−1·1
Weakness of limbs	+1·0	Dry mouth	−0·3
Slow walking pace	+1·5	Impotence	−2·2
Headache	−0·2	Failure of ejaculation	−0·4
Blurring of vision	−0·1		

Discussion

Methyldopa therapy was associated with two side effects—sleepiness and weakness of the limbs. Patients receiving this drug slept more hours and had a greater frequency of nocturia. Sleepiness and the frequency of nocturia were both dose-related. Methyldopa administration was not associated with an increased complaint of diarrhoea, impotence, failure of ejaculation, blurred vision, depression, or postural hypotension.

The administration of bethanidine was associated with three side effects—postural hypotension, impotence, and failure of ejaculation. Bethanidine therapy was not associated with a significant increase in weakness of the limbs, blurred vision, depression, or diarrhoea.

Only 31 patients received guanethidine but this drug was shown to be associated with three side effects—postural hypotension, failure of ejaculation, and an increased frequency of defaecation. In 28 patients taking propranolol there was evidence of an association with weakness of the limbs, and patients receiving this drug had an increased frequency of defecation. Twenty-six patients were receiving reserpine and no associated side effects could be identified.

The association between methyldopa and sleepiness has been well documented,[3–5] and in this study the patients on methyldopa slept longer hours. We are not aware of a previous report of weakness of the limbs due to methyldopa or propranolol, nor of the association between the dose of methyldopa and the frequency of nocturia.

Postural hypotension has been found troublesome in many patients on guanethidine[6 7] and bethanidine,[8 9] and much less troublesome with methyldopa.[7 9 10] These results are confirmed in the present survey. Failure of ejaculation due to guanethidine[6 7 9] and bethanidine[8 9] has been well described, together with impotence while taking bethanidine[8 9]; again these findings have been confirmed in this survey.

Guanethidine and propranolol were associated with an increased frequency of defecation. Guanethidine has consistently been reported to produce diarrhoea[6 9] and a patient has been reported with looseness of the bowels associated with propranolol.[11]

The use of drug combinations did not increase the production of side effects. The widespread clinical practice of treating mild hypertension with a diuretic ± reserpine would appear to be justified by the paucity of side effects, though it must be stressed that patients with severe depression would have been excluded from the survey group receiving reserpine. This treatment has been advocated[12] together with the use of methyldopa plus a diuretic for more severe hypertension, and the addition of bethanidine if required. This treatment schedule would also appear reasonable, especially as in this survey the use of drug combinations did not increase the number of side effects. An alternative solution is to tailor the therapy to the individual patient according to his or her complaints. For example, a woman complaining of tiredness should be offered guanethidine or bethanidine, whereas one not complaining of this symptom may be more pleased with methyldopa. A young man may be greatly troubled by impotence and should be offered methyldopa, whereas an older man complaining of sleepiness may prefer bethanidine or guanethidine. Patients troubled by diarrhoea should of course avoid guanethidine.

More research is required into the symptoms and side effects experienced by hypertensive patients and the use of self-administered questionnaires should allow a degree of standardization which has been lacking in many previous studies.

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