Br. J. clin. Pharmac. (1978), **5**, 29S–34S

ANTICHOLINERGIC AND BLOOD PRESSURE EFFECTS OF MIANSERIN, AMITRIPTYLINE AND PLACEBO

H. KOPERA

Department of Experimental and Clinical Pharmacology, University of Graz, Austria

1 Eighteen healthy male volunteers were treated at random in double-blind conditions with mianserin, amitriptyline, or placebo for 8 days. Measurements were made of various parameters indicative of anticholinergic and blood pressure effects.

2 Mianserin showed no significant anticholinergic effects on any of the measures used. Compared with placebo, mianserin significantly reduced pupil diameter and tended to increase salivary production and increase the distance of the near point.

3 Amitriptyline showed evidence of anticholinergic effects in that salivary production fell to a level significantly lower than that of the mianserin- or placebo-treated subjects. The distance of the near point tended to increase during amitriptyline treatment. Compared with placebo, amitriptyline also significantly reduced pupil diameter on some occasions.

4 Amitriptyline produced postural hypotension to a statistically significant degree, whereas this effect was not observed during mianserin treatment.

5 In conclusion, mianserin in doses of up to 60 mg daily given to healthy males seemed to lack the anticholinergic effects and postural hypotension associated with amitriptyline treatment.

Introduction

MOST antidepressants in current use have anticholinergic and blood pressure (BP) effects which lead to various untoward clinical symptoms. The demonstration of the anticholinergic effects is impeded by the fact that the clinical features of depression can also include anticholinergic symptoms. The autonomic effects of tricyclic antidepressants include postponement of onset and stuttering of urination, at least in patients with diseases affecting the urinary flow. Such disturbances of micturition are not found among the symptoms of depression. Thus, measurement of the anticholinergic effects of antidepressants in healthy subjects, and the recording of initiation of urination and urinary flow, might facilitate the differentiation between autonomic effects of depression and of antidepressants.

In contrast to the tricyclic antidepressants, the novel tetracyclic compound, mianserin (Org GB94), has been shown to have little or no anticholinergic action in effective antidepressant doses in therapeutic practice (Coppen *et al.*, 1976; Jaskari *et al.*, 1977; Vogel *et al.*, 1976) and in clinical pharmacology studies in depressed patients (Ghose *et al.*, 1976). Nothing is yet known about the effect of mianserin on micturition.

The aim of the present study was to compare the BP and anticholinergic effects, including possible effects on micturition, of mianserin with those of amitriptyline and placebo in healthy volunteers.

Methods

Volunteers

The study was carried out using 18 healthy male volunteers, aged 18–30 yr. Increased intraocular pressure was a reason for exclusion. The subjects had to be drug-free for at least 7 d before the trial, and no medication other than the trial treatment was allowed during the investigation period. Each volunteer was supplied with ten tablets of Glaphenine to use in case analgesic treatment was required.

Volunteers were asked to refrain from driving a car or operating any complicated machinery during the treatment period, to abstain from abrupt changes in the normal way of living, and to avoid excessive use of alcohol.

All volunteers gave written informed consent to take part in the study.

Treatment

The preparations used were mianserin in tablets of 10 mg, amitriptyline in tablets of 25 mg, and placebo tablets. The preparations were identical in appearance, with the exception of the amitriptyline tablets which differed by having the producer's emblem – MSD45 – on one side. All tablets were packed in identical bottles labelled with the numbers 1–18. Each preparation was contained in six bottles distributed randomly within the 18 bottles. Each volunteer received one bottle of

medication. In this way, three treatment groups, with six subjects in each, were formed, and the treatment of each volunteer was determined aselectively. The daily dose was gradually increased from one tablet on day 1 to the full level of three times two tablets daily by day 6. Every subject took the same number of tablets daily. The volunteers were instructed to swallow the tablets with a sip of water without chewing.

Treatment was given during 7 consecutive days. On day 8 all volunteers had the morning dose, some had lunch-time medication but no volunteer had the evening dose.

Parameters studied

Clinical investigations Each volunteer underwent a thorough physical examination before the first dose and on trial day 8. Before the start of the study, haemoglobin, complete red and white blood count, blood sedimentation rate, SGOT, SGPT, serum creatinine and alkaline phosphatase were measured, and urinalysis was carried out in each volunteer. Only subjects with normal pre-study values were accepted for the trial.

Urinary flow The volunteers were asked to empty their urinary bladder 2 h before each measurement, and immediately after voiding to drink 500 ml of mineral water which was supplied to them. Subsequently, they were asked not to urinate until requested to do so in the laboratory. Volunteers scheduled for investigation at 0800 and 0830 were allowed to report for the session without having voided in the morning. Measurements of micturition were made with the prototype of a urodropspectrometer produced by Organon Teknika, Oss, The Netherlands. This drop spectrometer uses the interruption of a light-beam to provide electronic recording of the passage of urine drops; it allows accurate measurements of individual drop diameters, their temporal spacings and velocity. In the present study, only onset of urination and the number of interruptions of the urine flow were of interest. Volunteer and recorder were placed in separate rooms to minimize psychological influences. The volunteers were asked to start voiding after a light signal was given and to empty the bladder if possible without break. One or two such trials were made as an exercise with each subject before the drug testing started.

Intraocular pressure After local anaesthesia with two drops of Benoxinate 0.4%, intraocular tension was measured with the improved Schioetz tonometer (plunger load 5.5 g) with the patient in recumbent position.

Accommodation The distance of the near point of each eye was determined with the help of Scheiner's experiment (Taylor, 1950). Median values of at least three readings per eye were recorded at each session.

Pupil diameter The transverse diameter of each pupil was measured with a binocular microscope which had a graded ocular. The head of the volunteer was at the same distance from the microscope at each session and the light conditions were kept constant.

Saliva production This was measured first in millilitres using the method of Kingsley & Turner (1974), with the modification that the volunteers were instructed to move the acid drop from one buccal pouch into the other slowly but continuously (the acid drop was in each buccal pouch 9–11 times/minute. Secondly, saliva production was measured in grams using the method of Dollery *et al.* (1976), with dental cotton wool cylinders.

Blood pressure This was recorded indirectly using the Riva–Rocci apparatus. Measurement in a recumbent position was made after the volunteer had rested for 5 min, and immediately thereafter BP was recorded in a standing position.

Side-effects

These were recorded during an interview at each session. All measurements were made by the same investigator in each volunteer at the same time, before intake of the first test preparation and on trial days 2, 4, 6 and 8; with the exception of intraocular pressure, which was only determined before the trial and on day 8.

Statistical methods

Statistical analysis was carried out using an analysis of co-variance, the pretreatment assessment being used as a co-variable and the results obtained on days 2, 4, 6 and 8 of treatment being the response variables. The number of interruptions in urinary flow (which was almost always zero) and the side-effects were not statistically analyzed.

Results

Parameters

Clinical investigations The post-study physical examination did not show any drug effects.

Urinary flow Apart from a significant difference in delay between mianserin and placebo at day 2 (more rapid initiation of micturition in the mianserin group), no significant differences could be demonstrated.

Intraocular pressure No significant differences between mianserin and amitriptyline and between mianserin and placebo could be demonstrated.

Accommodation No significant difference between mianserin, amitriptyline and placebo was found in either eye at any assessment day. In both the mianserin and the amitriptyline group, however, the mean distance of the near point tends to increase (not statistically significant) with increased duration of treatment.

Pupil diameter A significant difference in pupil diameter between mianserin and placebo was observed on days 2 and 4 for the left eye and on days 4 and 6 for

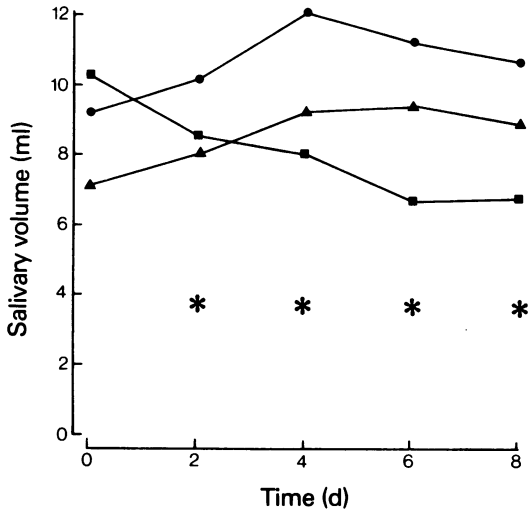

Figure 1 Mean saliva production (ml) of healthy male subjects, each treated with either mianserin (●), amitriptyline (■) or placebo (▲) (method of Kingsley & Turner, 1974). *Significant difference between amitriptyline and placebo, and between amitriptyline and mianserin.

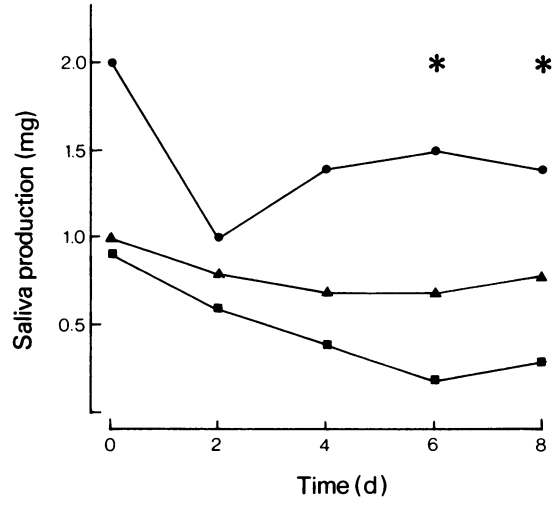

Figure 2 Mean saliva production (g) of 18 healthy male subjects, each treated with either mianserin (●), amitriptyline (■) or placebo (▲) (method of Dollery *et al.*, 1976). *As in Figure 1.

the right eye. There was also a significant difference between amitriptyline and placebo for the left eye on day 2 and the right eye on day 6. The mean pupil diameter in both groups was smaller than the mean diameter in the placebo group. No significant differences in mean pupil diameter between the mianserin group and the amitriptyline group could be observed (Table 1).

Saliva production

According to Kingsley & Turner (1974) A significant difference ($P<0.05$) between mianserin and amitriptyline, and between amitriptyline and placebo, could be demonstrated on days 2, 4, 6, and 8 (Figure 1 and Table 2). There was no significant difference between mianserin and placebo. The mean saliva production in the mianserin group was similar to that in the placebo group, whereas a lower mean saliva production was observed in the amitriptyline group. All estimated differences in mean saliva production (ml) between two treatments are corrected for existing pretreatment differences.

According to Dollery et al. *(1976)* A significant difference in saliva production between mianserin and amitriptyline, and between amitriptyline and placebo, could be demonstrated on days 6 and 8. The mean saliva production in the amitriptyline group was lower than that in the mianserin and the placebo groups. No significant difference between mianserin and placebo could be demonstrated (Figure 2 and Table 3).

Blood pressure No significant differences between mianserin and amitriptyline, and between mianserin and placebo, could be demonstrated for the measurements of the systolic recumbent and for the diastolic standing BP.

A significant difference in diastolic BP in recumbent subjects was found on day 8, the values in the mianserin group being higher than those in the amitriptyline group. A similar trend (although not

Table 1 Mean pupil diameter (mm)

	Day 0		*Day 2*		*Day 4*		*Day 6*		*Day 8*	
	L	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*
Mianserin	6.7	7.3	6.0	6.3	5.7	6.2	6.2	6.3	6.3	6.2
Amitriptyline	6.8	6.8	6.2	6.3	6.3	6.5	6.3	6.3	6.4	6.7
Placebo	7.0	6.9	7.4	6.8	7.3	7.2	7.0	7.2	6.9	7.0

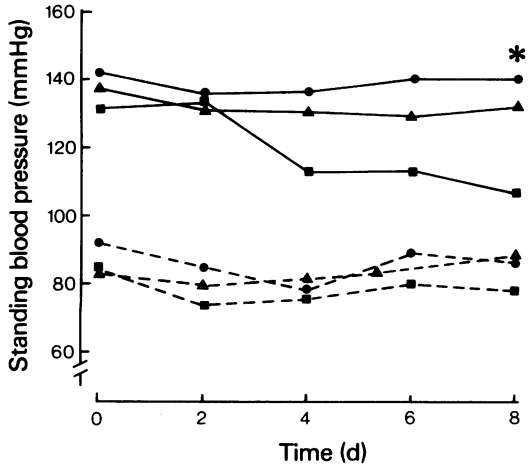

Figure 3 Mean standing BP of 18 healthy male subjects, each treated with either mianserin (●), amitriptyline (■) or placebo (▲). —, Systolic; – – – –, diastolic. *As in Figure 1.

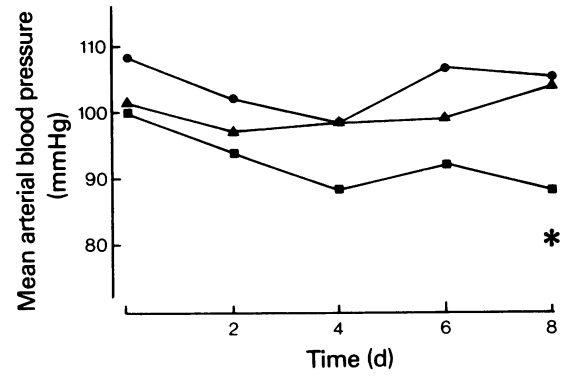

Figure 4 Mean arterial standing BP. Values represent means of each group of six healthy male subjects treated with either mianserin (●), amitriptyline (■) or placebo (▲). Mean arterial BP was calculated by approximation (diastolic BP + one-third of the BP amplitude). *Significant difference between amitriptyline and placebo.

statistically significant) was observed on day 6. No significant differences between mianserin and placebo could be demonstrated.

A significant difference in systolic standing BP between mianserin and amitriptyline was found on days 6 and 8. Significance was found on day 8 between amitriptyline and the placebo. The mean values in the amitriptyline group were lower than in both the mianserin and the placebo groups. There was no significant difference between the mianserin and placebo groups (Figure 3). This effect on the circulatory regulation is also reflected in the BP amplitude and the mean arterial BP, the latter being significantly lower in the amitriptyline group than in the placebo group on day 8. (Figure 4 and Table 4).

Subjective and other side-effects recorded during the trial are summarized in Table 5. Amitriptyline clearly produced most of the adverse effects. The severity of the side-effects generally increased with the dose of the drug.

Discussion

The results of this trial indicate that neither the tricyclic antidepressant amitriptyline nor the tetracyclic compound mianserin influence intraocular pressure in healthy subjects. The observation that mianserin reduced latency to initiation of micturition was confined to day 2, when treatment had only just

Table 2 Result of analysis of co-variance of salivary production measured using the method of Kingsley & Turner (1974)

Day	*Comparison*	*Difference*	*95% confidence interval*
2	M–P	0.0	−2.3 to 2.4
	A–P	−2.7	−0.2 to −5.1
	M–A	2.7	0.4 to 4.9
4	M–P	0.9	−1.8 to 3.6
	A–P	−4.0	−1.2 to −6.8
	M–A	4.9	2.3 to 7.5
6	M–P	0.3	−2.8 to 3.3
	A–P	−4.9	−1.8 to −8.1
	M–A	5.2	2.3 to 8.2
8	M–P	0.5	−1.8 to 2.8
	A–P	−4.0	−1.6 to −6.4
	M–A	4.5	2.3 to 6.7

M, Mianserin; P, placebo; A, amitriptyline.

Table 3 Result of analysis of co-variance of salivary production measured using the method of Dollery *et al.* (1976)

Day	*Comparison*	*Difference*	*95% confidence interval*
2	M–P	−0.1	−0.5 to 0.3
	A–P	−0.08	0.3 to −0.4
	M–A	0.0	−0.4 to 0.3
4	M–P	0.3	−0.4 to 0.9
	A–P	−0.2	0.4 to −0.8
	M–A	0.5	−0.2 to 1.2
6	M–P	0.3	−0.1 to 0.7
	A–P	−0.4	−0.1 to −0.7
	M–A	0.7	0.3 to 1.1
8	M–P	0.0	−0.5 to 0.5
	A–P	−0.5	−0.1 to −1.0
	M–A	0.5	0.1 to 1.0

M, Mianserin; P, placebo; A, amitriptyline.

Table 4 Results of analysis of co-variance of mean arterial BP

Day	*Comparison*	*Difference*	*95% confidence interval*
2	M–P	−0.3	11.9 to −12.5
	A–P	−2.0	9.6 to −13.6
	M–A	−1.7	14.2 to −10.9
4	M–P	−5.9	5.9 to −17.7
	A–P	−8.4	2.8 to −19.7
	M–A	2.6	14.7 to −9.6
6	M–P	2.0	15.4 to −11.5
	A–P	−5.5	7.3 to −18.3
	M–A	7.5	21.3 to −6.4
8	M–P	−4.5	5.0 to −14.0
	A–P	−14.0	−5.0 to −23.1
	M–A	9.5	19.3 to −0.3

M, Mianserin; P, placebo; A, amitriptyline.

Table 5 Side-effects

	Mianserin	*Amitriptyline*	*Placebo*
Drowsiness			
Slight	3	1	3
Pronouced	3	5	—
Feeling of unreality	2	1	—
Impaired concentration	1	2	3
Dizziness	—	4	—
Blurred vision	—	2	—
Finger tremor	1	4	—
Dry mouth			
Slight	1	1	—
Pronounced	—	4	—
Diarrhoea	1	1	—
Constipation	1	—	—
Orthostatic collapse	—	1	—

started. It therefore can be regarded as a chance finding rather than a true effect. There was a non-significant trend for the distance of the near point to increase during both amitriptyline and mianserin treatment.

The significant reduction in pupil diameter found on some occasions in both the mianserin and the amitriptyline group compared with placebo, is the opposite effect to that which would be expected of an anticholinergic agent.

Amitriptyline clearly diminishes saliva production. Mianserin was not only devoid of such an effect, but on the contrary tended to increase saliva production compared with placebo, although this effect did not reach the level of statistical significance. Ghose *et al.* (1976) have also reported that salivary production increases during mianserin treatment of depressive patients. Since salivary production is known to be reduced in depressive patients (Palmai *et al.* (1967), it was thought that this increase could be related to improvement in the depressive state. The present finding in healthy volunteers indicates that increased salivary production could be a direct and possibly desirable pharmacological effect of mianserin. Undoubtedly, lack of this anticholinergic effect of mianserin is responsible for the distinctly fewer side-effects produced in therapeutic practice as well as in this study.

The results of the BP measurements confirm the known effects of amitriptyline and related compounds. They cause postural hypotension through peripheral vasodilatation and by a negative inotropic effect on the heart muscle (Lamarche *et al.*, 1966; Sacks *et al.*, 1968). Similar effects are claimed for all tricyclic antidepressants (Moccetti *et al.*, 1971). The tetracyclic mianserin has no detectable adverse influence on BP; and does not differ from a placebo in this respect. Presumably orthostatic hypotension produced by tricyclic antidepressants contributes to some of the unpleasant side-effects of these drugs such as drowsiness, dizziness, tendency to postural collapse and perhaps also blurred vision.

Apart from the side-effects mentioned in Table 5, no adverse reactions or findings were recorded in any of the 18 treated volunteers.

I thank Ir. S. Stulemeijer for carrying out the statistical analysis and Dr M. Peet for assistance in preparing this paper.

References

COPPEN, A.J., GUPTA, R., MONTGOMERY, S., GHOSE, K., BAILEY, J., BURNS, B. & RIDDER, J.J. DE (1976). Mianserin hydrochloride: a novel antidepressant. *Br. J. Psychiat.* **129**, 342–345.

DOLLERY, C.T., DAVIES, D.S., DRAFFAN, G.H., DARGIE, H.J., DEAN, C.R., REID, J.L., CLARE, R.A. & MURRAY, S. (1976). Clinical pharmacology and pharmacokinetics of clonidine. *Clin. pharmac. Ther.* **19**, 11–17.

GHOSE, K., COPPEN, A.J. & TURNER, P. (1976). Autonomic actions and interactions of mianserin hydrochloride (Org GB94) and amitriptyline in patients with depressive illness. *Psychopharmacology*, **49**, 201–204.

JASKARI, M.O., AHLFORS, U.G., GINMAN, L., LYDECKEN, K. & TIENARI, P. (1977). Three double-blind comparative trials of mianserin (Org GB94) and amitriptyline in the treatment of depressive illness. *Pharmakopsychiat. Neuro-Psychopharmak.*, **10**, 101–103.

KINGSLEY, P.J. & TURNER, P. (1974). Class experiment

in clinical pharmacology with benzilonium bromide, an anticholinergic drug. *Eur. J. clin. Pharmac.*, **7**, 141–143.

LAMARCHE, M., ROYER, R., WEILLER, M. & DENIS, P. (1966). Etude pharmacodynamique de la toxicité cardiaque de l'amitriptyline. *Thérapie*, **21**, 59–71.

MOCCETTI, T., LICHTLEN, P., ALBERT, H., MEIER, E. & IMBACH, P. (1971). Kardiotoxizität der trizyklischen Antidepressiva. *Schweiz. med. Wschr.* **101**, 1–10.

PALMAI, G., BLACKWELL, B., MAXWELL, A.E. & MORGENSTERN, F. (1967). Patterns of salivary flow in depressive illness and during treatment. *Br. J. Psychiat.* **113**, 1297–1308.

SACKS, M.H., BONFORTE, R.J., LASSER, R.P. & DIMICH, J. (1968). Cardiovascular complications of imipramine intoxication. *J. Am. med. Assoc.*, **205**, 588–590.

TAYLOR, N.B. (1950). The special senses. In *The Physiological Basis of Medical Practice*, ed. Best, C.H. & Taylor, N.B., 1139. London: Baillière, Tindall & Cox.

VOGEL, H.P., BENTE, D., FEDER, J., HELMCHEN, H., MÜLLER-OERLINGHAUSEN, B., BOHACEK, N., MIHOVILOVIC, M., BRÄNDLI, A., FLEISCHHAUER, J. & WALCHER, W. (1976). Mianserin versus amitriptyline. A double-blind trial evaluated by the AMP system. *Int. Pharmacopsychiat.*, **11**, 25–31.