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ASSESSMENT OF THE INTERACTION BETWEEN MIANSERIN AND CENTRALLY-ACTING ANTIHYPERTENSIVE DRUGS

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1 The interaction between mianserin and centrally-acting antihypertensive drugs was evaluated in normal volunteers and in patients with essential hypertension receiving either clonidine or methyldopa.

2 The administration of the first dose of 20 mg mianserin to the normal volunteers was associated with a significant sedative effect and transient postural hypotension.

3 In the normal volunteers, the blood pressure responses to a single oral dose of 300 μg clonidine were not modified by pretreatment with mianserin. The bradycardia associated with clonidine alone, however, was significantly attenuated.

4 In the patient study, no significant changes in blood pressure control were observed, either after the first dose of 30 mg mianserin or after one and two weeks' continued treatment with mianserin.

5 There is no evidence from these studies that the addition of mianserin therapy results in a clinically significant impairment of the antihypertensive effects of clonidine or methyldopa.

Introduction

Depression and hypertension are relatively common clinical problems. The increasing prescription of psychoactive drugs and the increasing use of antihypertensive agents in recent years has invariably resulted in a substantial number of patients receiving both antidepressants and antihypertensives, with the attendant risk of potentially adverse drug interactions.

It has been shown that the antihypertensive effect of the adrenergic neurone blocking drugs guanethidine and bethanidine is antagonized in man by concurrent administration of tricyclic antidepressants (Leishman *et al.*, 1963; Mitchell *et al.*, 1970). This antagonism is a result of the action of tricyclic antidepressants to block the neuronal re-uptake mechanism ($Uptake_1$) for noradrenaline in the synaptic cleft, which also takes up and concentrates the adrenergic blocking drug at its site of action in the nerve ending (Mitchell *et al.*, 1970; Iversen, 1971).

Antagonism also occurs when tricyclic antidepressants are combined with the centrally-acting agents clonidine (Reid *et al.*, 1973; van Spanning & van Zwieten, 1973) and methyldopa (White, 1965; Finch *et al.*, 1975; van Spanning & van Zwieten, 1975). This interaction has been shown to result in a clinically significant reduction in clonidine's antihypertensive effect (Briant *et al.*, 1973) but, although clonidine may have peripheral effects, there is no evidence that its hypotensive effect is dependent upon uptake into peripheral nerves.

Alternatively, however, clonidine's hypotensive action appears to result from reduced central sympathetic outflow consequent upon activation of α-adrenoceptors in the brain stem (Kobinger & Walland, 1967; Schmitt *et al.*, 1968; Schmitt & Schmitt, 1969). These central receptors resemble peripheral presynaptic α-receptors (Langer, 1977) where clonidine acts as a relatively selective α_2-receptor agonist. There is evidence that tricyclic antidepressants have significant α-adrenoceptor blocking properties (Theobald *et al.*, 1964; Cairncross, 1965), affecting both α_1 and α_2-adrenoceptors, and so it has been proposed that their interaction with clonidine might result from actions on central α_2-adrenoceptors, with clonidine acting as a relatively selective agonist and the tricyclics as antagonists (Reid & Briant, 1977).

Mianserin is an antidepressant drug, with a tetracyclic structure, which has been reported to cause fewer side-effects and less cardiovascular disturbance than tricyclic compounds (Kopera, 1978) and which does not appear to interact adversely with the antihypertensive drugs guanethidine and bethanidine (Burgess *et al.*, 1978). However, mianserin also has been shown to have α-adrenoceptor blocking properties (Vargaftig *et al.*, 1971) and there are reports that it relatively selectively blocks α_2-receptors (Baumann & Maitre, 1977; Doxy *et al.*, 1978). Therefore, it might similarly interfere with clonidine's central hypotensive action by competitive antagonism at central α_2-adrenoceptors.

Two studies, therefore, have been undertaken to investigate the effects of treatment with mianserin on the blood pressure and other effects of clonidine and methyldopa.

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Methods

Volunteer study

A randomized double-blind cross-over assessment in six healthy male volunteers, aged 20–38 years, of the acute α_2-adrenoceptor mediated responses (hypotension, bradycardia, dry mouth, sedation), to a first dose of 20 mg mianserin (or placebo) by mouth and the effect of pretreatment with mianserin 20 mg t.i.d. (or placebo) for three days on the responses to a single oral dose of clonidine 300 μg.

Patient study

A randomized double-blind cross-over study was undertaken in 11 patients with essential hypertension, aged 47–70 years, on maintenance treatment with clonidine (five patients) or methyldopa (six patients). The responses to a first dose of 30 mg mianserin (or placebo) were measured and then the cardiovascular effects of continued treatment with mianserin 20 mg t.i.d. (or placebo) were measured after one and two weeks.

In both studies, at intervals throughout the study days, blood pressure was measured by an automatic recorder (Roche Arteriosonde 1225) after a minimum of 10 min supine rest and for up to 5 min standing. Corresponding heart rates were measured by 1 min radial pulse counts. The degree of sedation was assessed on a visual analogue scale and saliva production was measured using pre-weighed dental rolls (Dollery *et al.*, 1976). Blood and urine samples were collected for catecholamine measurements (Henry *et al.*, 1975).

For the repeated measurements throughout the study days the statistical evaluation was by repeated measures analysis of variance.

All subjects, volunteers and patients, gave witnessed informed consent for participation in the studies, which were approved by the local Ethical Committee.

Results

Volunteer study

In the supine position there were no significant differences in blood pressure or heart rate between mianserin and placebo. On standing, however, mianserin 20 mg caused acute cardiovascular effects, as shown in Figure 1. The systolic blood pressure at 5 min erect fell significantly ($P<0.05$) by a maximum of 25 ± 15 mmHg at 2 h. There was an

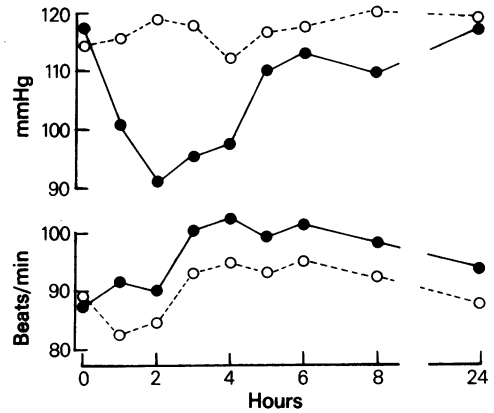

Figure 1 The mean 5 min erect systolic blood pressure and heart rate responses to a first dose of 20 mg oral mianserin in six normal volunteers. ○ Placebo, ● mianserin 20 mg.

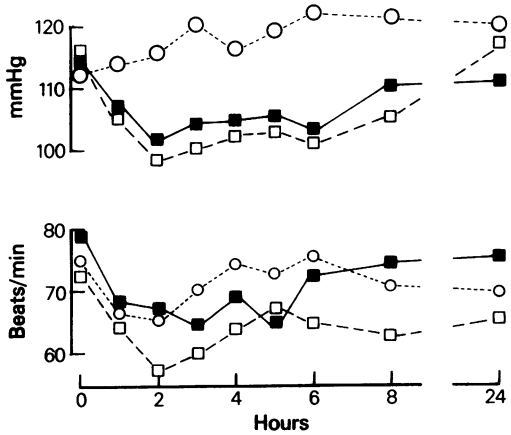

Figure 2 The mean supine systolic blood pressure and heart rate in six normal volunteers following a single dose of 300 μg clonidine, combined with pretreatment with mianserin 20 mg t.i.d. or placebo. ○ Placebo, □ clonidine, ■ clonidine + mianserin.

associated significant increase in standing heart rate ($P<0.05$). These cardiovascular effects were transient, however, and no significant difference in blood pressure or heart rate was detected after three days treatment with mianserin, compared to placebo.

The effects on supine and erect blood pressure and heart rate of combining mianserin or placebo with a single dose of clonidine are shown in Figures 2 and 3. The significant reductions in blood pressure, both supine and standing, caused by clonidine alone were not significantly different from those obtained by the mianserin-clonidine

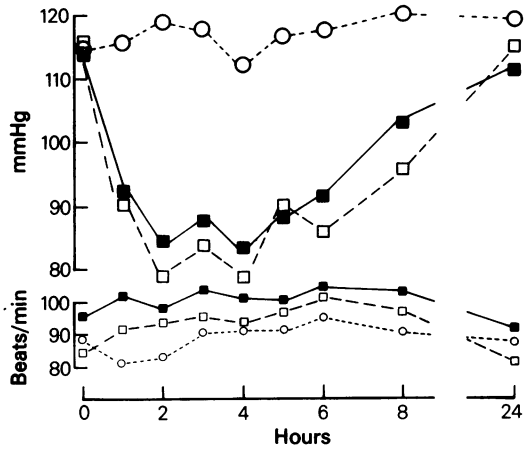

Figure 3 The mean 5 min erect systolic blood pressure and heart rate in six normal volunteers following a single dose of 300 µg clonidine, combined with pretreatment with mianserin 20 mg t.i.d. or with placebo. Symbols as in Figure 2.

combination. There was no significant difference in the standing heart rate associated with clonidine alone and the mianserin-clonidine combination, both being significantly greater than placebo. However, in the supine position, clonidine alone induced a significant reduction in heart rate compared to placebo ($P<0.001$). No significant change in heart rate (compared to placebo) was observed when the mianserin-clonidine combination was administered and it was noted that clonidine alone caused a significant reduction in heart rate compared to the mianserin-clonidine combination ($P<0.05$).

The effects of the different treatments on salivary flow and sedation are summarized in Figure 4. Both clonidine alone and the mianserin-clonidine combination produced significant reductions ($P<0.05$) in salivary flow, but no significant effect was associated with mianserin itself. Mianserin, clonidine and the mianserin-clonidine combination all caused comparable sedative effects. It was additionally noted that a mild but significant ($P<0.05$) sedative effect was associated with mianserin, compared to placebo, after 24 h and after four days.

Clonidine alone was associated with significant reductions in plasma and urinary catecholamines. These changes were not significantly altered by mianserin pretreatment (Elliott *et al.*, 1981).

Patient study

The blood pressure and heart rate responses to the

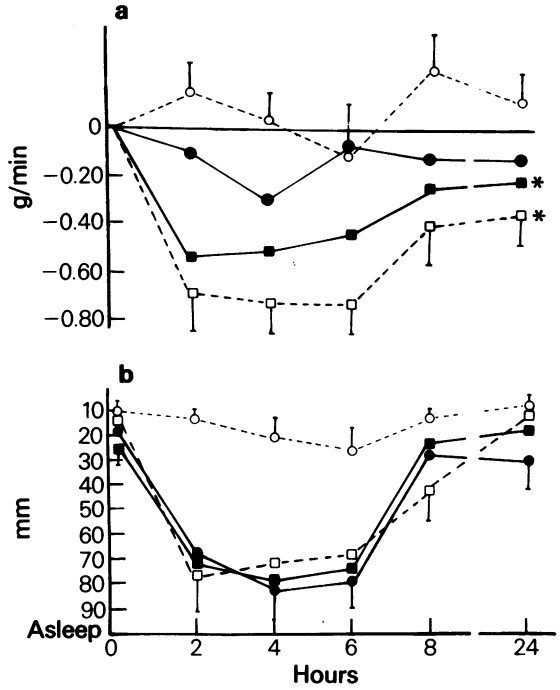

Figure 4 The mean effects of the different treatments in normal volunteers on (a) salivary flow and (b) sedation scales (mean scores—mm from 'wide awake'—on visual scale). ○ Placebo, ● mianserin, □ clonidine. ■ clonidine + mianserin. *$P<0.05$.

first dose of 30 mg mianserin in patients established on antihypertensive therapy are illustrated in Figures 5 and 6.

Symptomatic postural hypotension occurred in two patients, but overall the addition of mianserin was not associated with an additional hypotensive effect, either supine or erect, and similarly there were no significant changes in heart rate.

The effects of continued treatment for two weeks with mianserin 20 mg t.i.d. in addition to the patients' usual doses of clonidine or methyldopa are shown in Figure 7.

There were no significant changes in the level of blood pressure control in either group.

Discussion

These studies were designed primarily to investigate a possible interaction between mianserin and centrally-acting antihypertensive drugs, with particular regard to cardiovascular effects. Hypotension, bradycardia and a fall in plasma noradrenaline are effects which wholly or partly result from reduced sympathetic activity and in

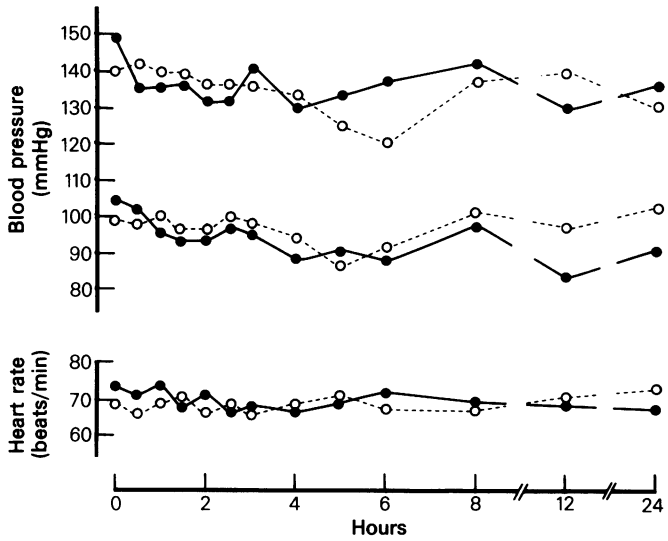

Figure 5 The mean erect blood pressure and heart rate following 30 mg mianserin in patients receiving clonidine. ○ Clonidine + mianserin, ● clonidine + placebo.

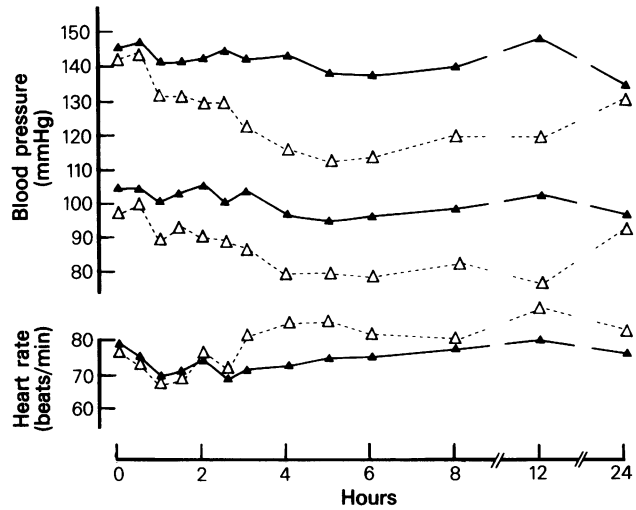

Figure 6 The mean erect blood pressure and heart rate following 30 mg mianserin in patients receiving methyldopa. △ Methyldopa + mianserin, ▲ methyldopa + placebo.

addition sedation (Delbarre & Schmitt, 1971) and dry mouth (Rand *et al.*, 1969) also appear to be α_2-adrenoceptor mediated. Mianserin has been reported to act as an antagonist at α_2-adrenoceptors but in normal volunteers there was no evidence of a clinically relevant interference with those effects of clonidine which are thought to be mediated by its agonist action at central α_2-adrenoceptors.

Mianserin pretreatment did not modify sedation or dry mouth due to clonidine, or its antihypertensive action, erect or supine. Only clonidine's heart rate-slowing effect was attenuated by mianserin pretreatment. Clonidine-induced bradycardia results from the reduced central sympathetic activity and increased vagal reflex activity (Robson *et al.*, 1969) and the failure of the combination to increase vagal tone may reflect an

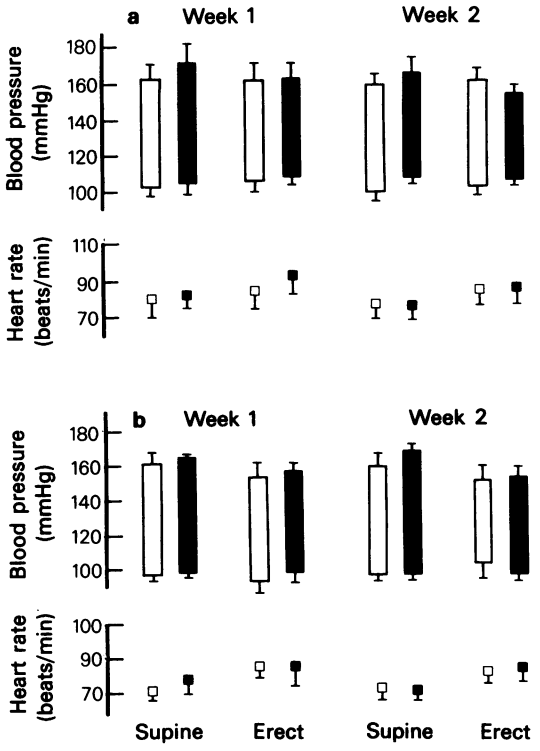

Figure 7 Summary of blood pressures and heart rates after one and two weeks' treatment with mianserin 20 mg t.i.d. (a) in patients receiving clonidine ($n=5$), and (b) in patients receiving methyldopa ($n=6$). □ Placebo, ■ mianserin.

underlying antagonistic interaction in brainstem control centres. While this interaction is comparable to that reported with α-blocking drugs, including the tricyclic antidepressant, desipramine (Scriabine & Stavorski, 1977), it may alternatively be due to an unidentified effect which is directly modifying heart rate control, although insufficient to produce an increase in supine heart rate when mianserin alone is administered. On standing, mianserin alone was associated with an increase in heart rate which might simply reflect the reflex response to its hypotensive effect. However, the mianserin-clonidine combination was associated with the greatest increase in heart rate—with a hypotensive effect which was certainly not greater than clonidine alone—again suggesting that mianserin has direct (i.e., non-reflex-mediated) positive chronotropic activity.

Mianserin alone caused no reduction in supine systolic blood pressure but was associated with a significant early hypotensive effect on standing. Postural hypotension has not been a prominent feature reported in previous studies of mianserin's side-effects and cardiovascular actions (Burgess *et al.*, 1978; Kopera, 1978). The postural fall in blood pressure on standing was not associated with orthostatic symptoms and was not observed after four days treatment with mianserin. It is possible that acute postural hypotension and tachycardia reflect peripheral α_1-antagonism by mianserin and that the haemodynamic disturbance is thus analogous to that induced by the α_1-antagonist prazosin, with a profound first dose hypotensive effect which is modified by continued treatment.

With regard to the other effects studied, the most obvious side-effect of mianserin was its pronounced sedative effect. In fact, the sedative effect of all three active treatments was comparable and did not appear to be additive when mianserin and clonidine were combined. Mianserin did not significantly reduce saliva production when compared to placebo and this is consistent with reports (Kopera, 1978), that mianserin is relatively free of anticholinergic activity. This contrasts with the significant reduction in salivary flow caused by desmethylimipramine when given to normal subjects in a comparable study (Reid *et al.*, 1979).

In the study of patients on established therapy for essential hypertension the most important finding was that there was no loss of blood pressure control. In fact, an augmented fall in standing blood pressure was observed in two patients. Neither after the first dose of 30 mg mianserin nor during two weeks treatment with 20 mg t.i.d. were there significant alterations to blood pressure or heart rate. Thus there is no evidence that mianserin, at doses commonly encountered in clinical practice, interferes with the action of clonidine or methyldopa at central α_2 adrenoceptors.

In summary, there is no evidence from these studies that an immediate loss of blood pressure control or a gradual increase in blood pressure will result from adding mianserin to the therapy of patients already receiving clonidine or methyldopa. The hypotension, sedation, xerostomia and reduced sympathetic activity, which are thought to be mediated by central α_2 adrenoceptors, were not significantly antagonized by the addition of single or multiple doses of mianserin, either in the volunteers or in the patients receiving clonidine or methyldopa. Mianserin, therefore, appears to differ from tricyclic antidepressants and would appear to be the preferred agent if antidepressant therapy is required in patients already receiving centrally-acting antihypertensive drugs.

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