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The Effect of Mianserin on Alpha-2 Adrenergic Receptor Function in Depressed Patients

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Summary: Recent clinical investigations have shown that long term treatment with the tricyclic antidepressants desipramine and amitriptyline reduces the sensitivity of the alpha-2 adrenergic autoreceptor. In order to determine whether the tetracyclic antidepressant mianserin also has this action, the effect of clonidine, an alpha-2 adrenergic receptor agonist, on plasma levels of the norepinephrine metabolite 3-methoxy-4-hydroxyphenlethyleneglycol (MHPG), blood pressure, and patient-rated sedation were measured in fifteen depressed patients before and during mianserin treatment. Postsynaptic alpha-2 adrenergic receptor function was assessed by measuring the growth hormone response to clonidine before and during treatment. Mianserin had little or no effect on the ability of clonidine to lower plasma MHPG and blood pressure, and to increase sedation and growth hormone secretion. The findings of this investigation indicates that long term mianserin treatment does not produce significant subsensitivity of the alpha-2 adrenergic receptor and suggests that a reduction in alpha-2 adrenergic autoreceptor sensitivity is not a necessary action for all effective antidepressant treatments.

Data from recent basic and clinical investigations suggest that the therapeutic mechanism of action of antidepressant drugs may involve alterations in the sensitivity of adrenergic and serotonergic receptor sensitivity. Chronic, but not acute, administration of a variety of antidepressant drugs to laboratory animals has been shown to decrease the sensitivity of alpha-2 and beta-adrenergic receptors and to increase the sensitivity of alpha-1 adrenergic and serotonergic receptors (Charney *et al*, 1981a). However, it has not been determined which, if any, of these changes are critical to the clinical effects.

One approach to this question is to develop paradigms capable of assessing these receptor systems in depressed patients before and during treatment with a spectrum of antidepressant drugs which have different biochemical and structural properties. These studies may lead to the identification of common drug induced alterations in receptor sensitivity which relate to antidepressant response. Such findings would have important implications regarding the aetiology of depression and the development of more specific antidepressant agents.

In this regard, determination of the effects of the antidepressant mianserin on adrenergic and serotonergic receptors are particularly important. In contrast to the commonly used tricyclic antidepressants, mianserin is tetracyclic in structure and has little or no effect on norepinephrine (NE) and serotonin reuptake in vivo (Baumann *et al*, 1977; Goodlet *et al*, 1977). On the other hand, mianserin has at least moderate affinity for alpha-2, alpha-1, and postsynaptic serotonin receptors (Tang and Seeman, 1980; Maggi *et al*, 1980; Hall and Ogren, 1981; Whitaker and Cross, 1980; Dumbrille-Ross *et al*, 1981). It has no affinity for beta adrenergic receptors. When given acutely, mianserin acts as an antagonist at the receptor sites for which it has affinity (Van Riezen, 1972; Maj *et al*, 1978; Robson *et al*, 1978; Harper and Hughes, 1979; Tang *et al*, 1979; Sugrue, 1980; Fludder and Leonard, 1978; Engberg and Svensson, 1980; Pommier *et al*, 1982; Clineschmidt *et al*, 1979; Delini-Stula *et al*, 1979). However, the effects of chronic mianserin treatment are less certain. Behavioural studies indicate that chronic mianserin treatment, in contrast to acute, may enhance the sensitivity of alpha-1 and serotonin receptors (Maj *et al*, 1979; Mogilnicka and Przewlocka, 1981; Mogilnicka and Klimek, 1979; Jones, 1980). There is evidence from binding and biochemical studies that chronic mianserin treatment reduces the sensitivity of beta adrenergic receptors (Clements-Jewery, 1978; Mishia *et al*, 1980). A few

(Fludder and Leonard, 1979; Tang *et al*, 1979) but not all (Sugrue, 1980; Cerrito and Raiteri, 1981; Scuvee-Moreau and Scensson, 1982; Sugrue, 1982) investigations, suggest that chronic mianserin treatment may continue to antagonize the alpha-2 adrenergic autoreceptor. The effects of mianserin on the alpha-2 adrenergic autoreceptors have been the most commonly hypothesized mechanism for mianserin's antidepressant efficacy.

The purpose of the present investigation was to evaluate the effects of long term mianserin treatment on the sensitivity of the alpha-2 adrenergic autoreceptor and the postsynaptic alpha-2 adrenergic receptor in depressed patients. The alpha-2 adrenergic receptor, located somatodendritically and on noradrenergic nerve terminals, functions as an autoreceptor by regulating the release of NE through a negative feedback mechanism (Cedarbaum and Aghajanian, 1977). Acute stimulation of the alpha-2 adrenergic autoreceptor by norepinephrine in the synaptic cleft, or by an alpha-2 adrenergic receptor agonist such as clonidine, decreases NE impulse flow and turnover (Anden *et al*, 1976; Cedarbaum and Aghajanian, 1976; 1977; Leckman *et al*, 1980; Charney *et al*, 1981b; Charney *et al*, 1982a); and induces behavioural sedation (Drew *et al*, 1979; Strombom and Svensson, 1980). The ability of alpha-2 adrenergic receptor agonists to reduce blood pressure appears to be due to effects on both presynaptic (Robson *et al*, 1978; Rockhold and Caldwell, 1980) and postsynaptic (Timmermans *et al*, 1981) alpha-2 adrenergic receptors. Conversely, the alpha-2 adrenergic antagonists, yohimbine, mianserin and piperoxane, acutely increase NE impulse flow and turnover (Anden *et al*, 1976; Cedarbaum and Aghajanian, 1976; Cedarbaum and Aghajanian, 1977; Scatton *et al*, 1980; Charney *et al*, 1982b); and cause behavioural activation (Holmberg and Gershon, 1961; Lang and Gershon, 1963). Consequently, it has been suggested that measurements of the effect of alpha-2 adrenergic receptor agonists (eg clonidine) and antagonists (eg yohimbine) on NE turnover, sedation, and blood pressure may provide an index of alpha-2 adrenergic autoreceptor sensitivity.

The function of the postsynaptic alpha-2 adrenergic receptor has not been determined; however evidence exists that activation of this receptor may result in the stimulation of growth hormone release (Terry and Martin, 1981). There is data suggesting that the sensitivity of postsynaptic alpha-2 adrenergic receptors is decreased in depressed patients. The ability of clonidine to increase growth hormone secretion, which is due primarily to stimulation of postsynaptic alpha-2 adrenergic receptors, is blunted in depressed patients in comparison to healthy controls (Matussek *et al*, 1980; Checkley *et al*, 1981b; Charney *et al*, 1982a). Long term treatment with amitriptyline, desipramine, and clorgyline fail to potentiate the growth hormone response to clonidine in treatment responders and nonresponders (Charney *et al*, 1982c; Glass *et al*, 1982; Siever *et al*, 1982). It is of interest whether long term mianserin treatment alters the effect of clonidine on growth hormone levels since short term mianserin administration antagonizes alpha-2 adrenergic receptors.

In the present study, alpha-2 adrenergic autoreceptor sensitivity was examined before and during long term mianserin treatment by measuring changes in plasma free MHPG and patient sedation in response to challenge doses of clonidine and placebo. Plasma-free MHPG was used as an index of central NE turnover because it has been shown to reflect brain MHPG, the major metabolite of brain NE (Maas *et al*, 1976; Maas *et al*, 1979; Elsworth *et al*, 1982). Post synaptic alpha-2 adrenergic function was determined before and during long term mianserin tratment by assessing the effect of clonidine on growth hormone levels.

Method

Fifteen depressed patients (eleven women and four men; age-groups 31 to 61 years; mean 43 ± 11 years) gave voluntary, informed written consent for their participation in this study prior to being treated at the Clinical Research Unit of the Connecticut Mental Health Center, New Haven, where the study was conducted. All patients met criteria for a major depressive episode, according to the Diagnostic and Statistical Manual of Mental disorders (3rd edition) of the American Psychiatric Association. On the basis of a complete medical and neurological evaluation (including ECG, EEG, chest X-ray and laboratory tests of renal, hepatic, pancreatic, haemopoietic, and thyroid function), each patient was found to be physically healthy.

The patients were studied during a double-blind placebo-controlled treatment with mianserin. Each patient received placebo mianserin for a minimum of two weeks, and active mianserin itself for a minimum of four to six weeks. During the first week of mianserin administration, the dose was increased to a minimum of 60 mg per day. Thereafter, the dose was titrated according to clinical state and side effects to a maximum of 120 mg per day. The mean daily mianserin dose after four weeks of treatment was 116 ± 15 mg with a range from 90 to 120 mg.

Throughout the study, the patients were maintained on a vanilymandelic acid (3-methoxy-4-hydroxymandelic acid)-exclusion diet. A modified Hamilton Depression Scale of 30 items was completed on each patient shortly after admission, and again following

four or six weeks of mianserin treatment (Hamilton, 1960). The mean pretreatment Hamilton Depression Scale was 36 ± 11 with a range from 20 to 50.

After having been free of all psychotropic medication for at least two weeks, and having taken placebo for at least ten days, each patient was studied on two clonidine test days. They received (in orange-flavoured solutions) placebo clonidine on the first test day, and 5μg/kg of clonidine hydrochloride one to three days later. After a minimum of four weeks and maximum of six weeks of mianserin treatment, each patient was again studied on two clonidine test days in the same sequence and spacing as the clonidine test days during placebo treatment.

For each test day, the patients fasted overnight for ten hours and remained in the fasting state during the test day until approximately 3 p.m. Subjects were in the supine position with the head elevated during most of the six-hour test day. They stood to micturate and to permit recording of standing blood pressure (BP) and pulse. They were not permitted to sleep. Blood was sampled from an intravenous (iv) cannula in a forearm vein that was kept patent with a normal saline solution. Blood samples were obtained for plasma-free MHPG at 15 and 0.5 minutes prior to the clonidine dose, and at 180, 210, and 240 and 300 minutes after the clonidine dose. Blood samples for plasma growth hormone were taken at 15 and 0.5 minutes prior to the clonidine dose, and 60, 120, 180, 210, and 240 minutes after clonidine in ten of the fifteen patients studied. These time points were chosen because of previous findings, so as to include the time of maximum clonidine effect. At similar intervals all of the patients completed analogue scales, designed to evaluate the change of ten different mood states (happy, sad, drowsy, anxious, irritable, energetic, calm, fearful, high, mellow) following clonidine administration. The scales were scored in millimetres (mm) from the left hand side of a 100 mm line to a perpendicular mark made by the patient at the point corresponding to the feeling state at the time. Therefore, the score could range from 0 (not at all) to 100 (most ever). The patients, research nurse, and research technicians were blind to the composition of the clonidine dose.

Biochemical methods

Blood samples were kept on ice for a maximum of one hour before separation of plasma in a refrigerated centrifuge. Each blood sample yielded three 1-ml aliquots of plasma. Sodium metabisulfite (0.5 mg) and deuterated MHPG (200 ng) were added to each plasma aliquot. The plasma specimens were then frozen at −70°C until assay. Preparation of the sample was carried out according to a modified version of the method of Dekirmenjian and Maas (1974). Quantification of the plasma-free MHPG was carried out by selected ion monitoring, as described elsewhere (Maas *et al*, 1976) using a quadrupole mass spectrometer equipped with a gas chromatographic inlet system. To reduce the variance in method, plasma specimens were assayed in duplicate. The individual values reported are the means of the two values obtained from these specimens. Growth hormone was assayed with a homologous double-antibody method with materials provided by the National Institute for Arthritis, Metabolism, and Digestive Diseases (NIAMDD) (Schlach and Parker, 1964).

Data analysis

An analysis of variance (ANOVA) with repeated measures was used to evaluate overall main effects and interactions of mianserin treatment, dose of clonidine, and time of measurement before and after clonidine administration. Paired t-tests were used to evaluate changes across time. Two tailed levels of significance were used.

Effects of mianserin treatment and clonidine on plasma MHPG levels

The ANOVA assessing the effects of clonidine on plasma MHPG levels before and during long term mianserin treatment revealed a significant main effect of clonidine administration on MHPG ($P < .02$), and a significant interaction of clonidine and time of sampling ($P < .003$). The interaction of mianserin treatment with clonidine and time of sampling showed a trend toward significance (see Table I).

The effect of clonidine on plasma MHPG before and during mianserin treatment is shown in Table II. During placebo mianserin administration clonidine resulted in modest but significant decreases in plasma MHPG 180 ($P < .01$), and 210 ($P < .05$) and 240 ($P < .01$) minutes following the dose compared to

TABLE I

*Effect of mianserin treatment on response of plasma MHPG level to clonidine**

ANOVA	F ratio	P
Main factors		
Mianserin	4.1	.06
Clonidine	6.8	.02
Time of sampling	1.1	.36
Interactions		
Mianserin and clonidine	.7	.42
Mianserin and time	.4	.77
Clonidine and time	5.5	.003
Mianserin and clonidine and time	2.7	.06

*The values were obtained by analysis of variance with repeated measures (two tailed)

TABLE II

Effect of clonidine on plasma MHPG level during placebo and mianserin treatment

Treatment	Clonidine Dose μg/kg	MHPG level* (ng/ml) (mean ± SE) Time (minutes) Base	180	210	240
Placebo	0	3.3 ± .2	3.4 ± .2	3.5 ± .2	3.5 ± .2
	5	3.3 ± .3	3.1 ± .2[2]	3.0 ± .3[1]	3.0 ± .2[2]
Mianserin					
	0	3.0 ± .2	3.1 ± .2	3.0 ± .2	3.0 ± .2
	5	3.0 ± .2	2.7 ± .2[1]	2.7 ± .2	3.0 ± .2

*Paired t-tests were used and the probability values are two tailed.
[1]P <.05 difference (time point – base), 0 vs 5μg/kg dose of clonidine
[2]P <.01 difference, 0 vs 5μg/kg dose of clonidine
At none of the time points was the effects of clonidine on plasma MHPG significantly different during placebo vs mianserin treatment.

TABLE III

*Effect of mianserin on blood pressure (mmHg) responses to clonidine**

	Sitting				Standing			
	Diastolic		Systolic		Diastolic		Systolic	
ANOVA	F	P	F	P	F	P	F	P
Main factors								
Mianserin	.82	.38	.02	.95	.42	.53	.12	.74
Clonidine	56.6	.0001	94.3	.0001	151.3	.0001	159.5	.0001
Time of sampling	18.1	.0001	33.7	.0001	19.5	.0001	34.1	.0001
Interactions								
Mianserin & clonidine	3.2	.09	3.5	.08	5.4	.04	2.9	.11
Mianserin & time	1.9	.12	.04	.99	1.0	.40	1.4	.24
Clonidine & time	18.6	.0001	38.7	.0001	26.7	.0001	37.2	.0001
Mianserin & clonidine & time	1.3	.30	2.6	.04	.94	.45	.67	.62

*The values were obtained by analysis of variance with repeated measures (two tailed)

placebo clonidine. Mianserin treatment slightly attenuated the decrease in plasma MHPG levels induced by clonidine, but this did not reach significance. During mianserin treatment clonidine significantly decreased plasma MHPG 180 minutes after the dose compared to placebo clonidine (P <.05). At none of the time points was the effect of clonidine on plasma MHPG significantly different during the placebo mianserin administration compared to mianserin treatment. Mianserin treatment resulted in a non-significant reduction in baseline plasma MHPG levels.

Effects of mianserin treatment and clonidine on blood pressure and pulse

The ANOVA of the blood pressure data indicated no significant main effect of mianserin treatment on either systolic or diastolic blood pressure. In contrast, there were significant main effects of clonidine administration and time of sampling on both diastolic and systolic blood pressure. Significant interactions were noted for mianserin and clonidine (sitting systolic and standing diastolic blood pressure) and clonidine and time (all blood pressures). The interaction of mianserin treatment with clonidine and time of sampling was not significant for standing systolic and diastolic and sitting diastolic blood pressure. There was a significant (P <.05) interaction with sitting systolic blood pressure (see Table III).

Clonidine produced significant decreases in systolic and diastolic blood pressures at all time points

measured, with the most robust effects occurring 120 and 180 minutes after the dose. Mianserin treatment did not significantly alter the blood pressure response to clonidine for any of the blood pressures at any of the time points, except for sitting systolic blood pressure 120 ($P < .05$) and 180 ($P < .01$) minutes folowing the clonidine dose (Fig). Mianserin treatment did not change base line systolic or diastolic blood pressure.

The ANOVA examining the effects of mianserin and clonidine on pulse rate revealed a significant main effect of mianserin ($F = 18.2$, $P < .001$) and clonidine ($F = 11.2$, $P < .01$) on sitting pulse rate. A significant main effect of time was observed for both sitting ($F = 4.4$, $P < .01$) and standing ($F = 3.1$, $P < .05$) pulse rate. A significant interaction of clonidine and time was also seen for both sitting ($F = 6.3$, $P < .001$) and standing ($F = 3.1$, $P < .05$) pulse rate. The interaction of mianserin treatment with clonidine and time of sampling was not significant for either sitting or standing pulse rate.

Mianserin treatment produced a significant increase in base-line sitting pulse (77 during placebo, compared to 82 during mianserin treatment ($P < .05$)). Clonidine resulted in significant decreases in sitting pulse rate 120 ($P < .05$), 180 ($P < .01$), 210 ($P < .05$), and 240 ($P < .001$) following the dose, during placebo mianserin treatment; and 180 ($P < .01$), 210 ($P < .01$), and 240 ($P < .05$) minutes following the dose, during active mianserin treatment. Clonidine induced significant decreases in standing pulse 120 ($P < .01$), 180 ($P < .01$), 210 ($P < .01$), and 240 ($P < .05$) minutes following the dose, during placebo mianserin treatment. At none of the time points was the effect of clonidine on sitting or standing pulse significantly different during placebo mianserin administration compared to mianserin treatment.

Effects of mianserin treatment on clonidine induced changes in growth hormone levels

The growth hormone response to clonidine during placebo and long term mianserin treatment is illustrated in Table IV. Although statistically significant ($P < .01$), clonidine did not robustly increase growth secretion in the depressed patients and this response was not altered by mianserin treatment. Mianserin treatment did not change the ability of clonidine to increase growth hormone in either treatment responders or nonresponders (see below).

Behavioural effects

The effect of clonidine on the severity of depressed mood, anxiety, drowsiness, energy, and several other mood states was assessed using visual analogue scales. The ANOVA revealed no significant effects of clonidine or any significant interaction between

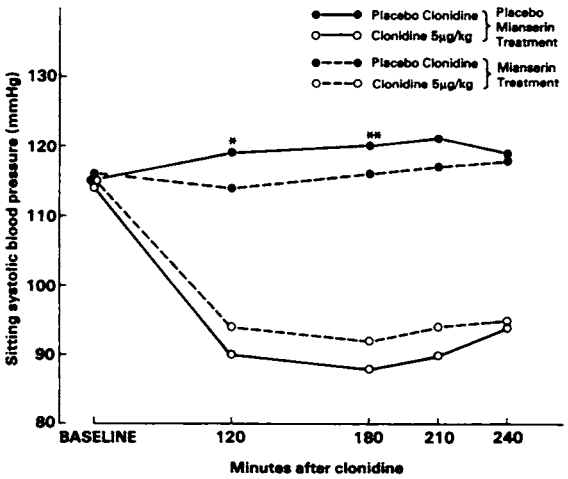

Fig.—The effect of long term mianserin treatment on the clonidine induced decreases in mean sitting systolic blood pressure in fifteen patients. Mianserin treatment significantly attenuated the clonidine induced decreases in sitting systolic blood pressure observed 120 and 180 minutes following the dose during placebo mianserin treatment. *($P < .05$), **($P < .01$).

clonidine and mianserin treatment on these variables except for the sedation measure. The ANOVA did reveal significant main effects of mianserin ($F = 7.9$, $P < .01$), clonidine ($F = 30.4$, $P < .001$), and time of sampling ($F = 10.8$, $P < .001$) on patient rated drowsiness. A significant interaction was identified for clonidine and time ($F = 7.2$, $P < .001$). The interaction of mianserin treatment with clonidine and time of sampling was not significant.

Mianserin treatment resulted in a significant decrease in the base line drowsiness rating (21 mm during placebo administration compared to 10 during mianserin treatment ($P < .05$). Clonidine produced a significant increase in drowsiness 60 ($P < .05$), 120 ($P < .01$), 210 ($P < .05$) and 240 ($P < .05$) minutes following the dose, during placebo mianserin treatment. During mianserin treatment treatment clonidine caused significant increases in sedation 60 ($P < .05$), 120 ($P < .001$), 180 ($P < .001$), 210 ($P < .001$), and 240 ($P < .01$) minutes following the dose. At none of the time points was the ability of clonidine to induce sedation significantly different during placebo administration in comparison to mianserin treatment (Table V).

Relationship to treatment response

Three of the 15 patients were classified as treatment responders because they had 50 per cent or greater decrease in scores on the Hamilton Depression Scale, were discharged on mianserin, and were judged by the

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TABLE IV

Growth hormone (GH) response to clonidine during placebo and long term mianserin treatment

Treatment	Clonidine Dose (μg/kg)	Mean GH,* ng/ml (±SE) Base	Peak	Difference
Placebo	0	.8 ± .5[1]	1.3 ± .4	.5 ± .5
	5	.4 ± .1	5.2 ± 2.8[1]	4.8 ± 2.8[2]
Mianserin	0	.3 ± .1	1.2 ± .3	.0 ± .3
	5	.3 ± .1	5.7 ± 2.3[1]	5.4 ± 2.3[2]

*Indicates peak GH concentration 60, 120, 180, and 240 minutes after clonidine dose. Paired t-tests were used and the probability values are two tailed

[1]P <.01 base vs peak

[2]P <.01, difference, 0 vs 5 μg/kg clonidine dose

At none of the time points was the effect of clonidine on GH significantly different during placebo vs mianserin treatment

TABLE V

Effects of mianserin on clonidine induced sedation

Treatment	Clonidine dose μg/kg	Sedation Rating*, (mean ± SE) Time (minutes) Base	60	120	180	210	240
Placebo	0	22 ± 7	28 ± 6	37 ± 6	35 ± 5	29 ± 6	23 ± 5
	5	20 ± 7	50 ± 9[1]	73 ± 8[2]	63 ± 8[1]	58 ± 8[1]	48 ± 7[1]
Mianserin	0	10 ± 4	24 ± 7	19 ± 5	21 ± 5	20 ± 5	20 ± 5
	5	10 ± 3	48 ± 8[1]	55 ± 6[3]	53 ± 6[3]	48 ± 6[3]	40 ± 5[2]

*Sedation was rated on 100 mm visual analogue scale for drowiness

Paired t-tests were used and the probability values are two tailed

[1]P <.05 difference (time point-base), 0 vs 5 μg dose of clonidine during placebo or mianserin treatment

[2]P <.01 difference, 0 vs 5 μg dose of clonidine placebo or mianserin treatment

[3]P <.001 difference, 0 vs 5 μg dose of clonidine during mianserin treatment

At none of the time points was the effect of clonidine on sedation significantly different during placebo vs mianserin treatment

treating psychiatrist as having a good treatment response. The rest of the patients were classified as treatment non-responders since they had less than a 20 per cent decrease in scores on the Hamilton Depression Scale and were judged to show no benefit from mianserin treatment. For the entire group, there was no correlation between the change in the base line Hamilton Depression Score following a minimum of four weeks of mianserin treatment and base line MHPG or clonidine effects on MHPG, blood pressure, growth hormone, and sedation during placebo or mianserin treatment. The values for the three treatment responders and twelve non-responders were overlapping on these parameters.

Discussion

Long term mianserin treatment only slightly attenuated the ability of clonidine to decrease plasma MHGH and blood pressure and did not alter the clonidine induced increase in patient rated sedation. The ANOVA of the effects of clonidine on plasma MHPG levels before and during long term mianserin treatment revealed only a trend toward a significant interaction of mianserin treatment with clonidine and time of sampling. In addition, at none of the time points was the effect of clonidine on plasma MHPG significantly affected by mianserin treatment. The ANOVA assessing the interaction of mianserin treatment with clonidine and time of sampling on blood pressure identified a significant interaction only for sitting systolic blood pressure. Mianserin treatment did not change the blood pressure response to clonidine except for sitting systolic blood pressure 120 and 180 minutes following the clonidine dose. The action of clonidine to induce sedation was not significantly affected by mianserin treatment. These findings suggest that long term mianserin, in contrast to desipramine (Checkley *et al*, 1981a, Charney *et al*,

1981b) and amitriptyline (Charney *et al,* in press) only weakly reduces the function of alpha-2 adrenergic autoreceptors when administered to depressed patients. The inability of mianserin to raise plasma MHPG levels, as would be expected if alpha-2 adrenergic autoreceptor function was substantially decreased by mianserin, also indicates inconsequential effects of mianserin treatment on this receptor. It should be noted, however, that most of the patients were mianserin non-responders (12 out of 15 patients). Thus it is possible that the negative results of this study may be related to lack of clinical response and that if larger numbers of treatment responders were studied, significant alpha-2 adrenergic receptor subsensitivity might have been observed.

The findings of the present investigation are consistent with two previous studies in laboratory rats. Sugrue (1980) using a similar experimental paradigm reported that mianserin (10 mg/kg) administered once daily for 9 and 15 days failed to alter the brain MHPG response to clonidine (.1 mg/kg). Scuvee-Moreau and Svensson (1982) found that two weeks of mianserin administration (10 mg/kg once daily) did not decrease the responsiveness of locus coeruleus neurones to iontopheoretically applied clonidine. The results of these two studies would appear to be at variance with the findings of Tang *et al* (1979) and Fludder and Leonard (1979). The daily administration of mianserin (10 mg/kg) to rats for 21 days blocked the reduction in brain MHPG induced by clonidine (.35 mg/kg) (Tang *et al,* 1979). The simultaneous administration of mianserin (15 mg/kg) and clonidine (2.5 mg/kg) for 14 days resulted in an attenuation of the ability of the latter to lower the concentration of the norepinephrine metabolite, normetanephrine, in rat amygdaloid cortex (Fludder and Leonard, 1979). However, these discrepant observations are probably due to the higher doses of clonidine and mianserin used in the latter two studies. The selectivity of these doses of clonidine for the alpha-2 adrenergic autoreceptor is open to question. High doses of clonidine do interact with postsynaptic alpha-1 adrenergic receptors (Maj *et al,* 1979).

In contrast to the lack of effect of long term mianserin on alpha-2 adrenergic autoreceptor sensitivity, single doses of mianserin and short term mianserin treatment clearly antagonize the function of this receptor. Mianserin has been shown to have moderate affinity for the cortex alpha-2 adrenergic receptor (Sugrue, 1982) and to block central alpha-2 adrnergic receptors in vitro (Baumann and Maitre, 1977). The ability of single doses of mianserin to activate locus coeruleus neurones and increase brain MHPG are evidence of mianserin's alpha-2 autoreceptor antagonist properties. In addition, single doses of mianserin and five days of mianserin treatment significantly attenuate the clonidine induced decrease in brain MHPG (Sugrue, 1980), locus coeruleus firing rate (Engberg and Svensson, 1980), and blood pressure (Robson *et al,* 1978).

Abrupt withdrawal of chronic mianserin treatment appears to result in a functional supersensitivity of alpha-2 adrenergic receptors. Cerrito and Raiferi (1981) evaluated alpha-2 adrenergic receptor sensitivity four days following the discontinuation of two weeks of once daily mianserin (10 mg/kg) administration. The inhibitory effect of extracellular norepinephrine on norepinephrine release from hypothalamic synaptosomes was significantly potentiated in comparison to saline treatment. No potentiation was observed in animals who had received a single dose of mianserin (10 mg/kg).

These studies of the effects of acute and chronic mianserin administration and withdrawal of chronic mianserin administration suggest that long term mianserin may increase alpha-2 adrenergic autoreceptor sensitivity via compensatory changes in receptor function resulting from prolonged receptor blockade. These changes are not evident when mianserin levels are high during long term treatment but are seen when drug levels are reduced following discontinuation.

Effect of mianserin on postsynaptic alpha-2 adrenergic receptor sensitivity

Mianserin treatment did not affect the growth hormone response to clonidine. Clonidine stimulates growth hormone secretion by activating postsynaptic alpha-2 adrenergic receptors (Terry and Martin, 1981), therefore, this finding suggests that long term mianserin treatment fails to change the function of this receptor.

There is now evidence that four different antidepressant drugs, desipramine (Charney *et al,* 1982c), amitriptyline (Charney *et al,* 1982c; Glass *et al,* 1982; Charney *et al,* 1983), clorgyline (Siever *et al,* 1982) and mianserin do not enhance the growth hormone response to clonidine. This failure suggests that the blunted growth hormone response to clonidine in depressed patients represents a trait abnormality that is not reversed by antidepressant treatment.

Implications

The findings of this investigation have implications regarding the current understanding of the mechanism of action of antidepressant treatments. An important question has been whether the ability to reduce alpha-2 adrenergic autoreceptor sensitivity is a necessary condition for antidepressant efficacy. Previous clinical studies have shown that amitriptyline (Charney *et al,* 1983) and desipramine (Charney *et al,* 1981b) both

reduce the sensitivity of the alpha-2 adrenergic autoreceptor. It has been widely hypothesized that mianserin, because of its acute effects, may be therapeutically effective by antagonizing the function of this receptor. The results of this study, that long term mianserin treatment does not alter, to a major extent, alpha-2 adrenergic autoreceptor sensitivity in depressed patients, suggest that other biochemical effects of mianserin are responsible for its antidepressant efficacy; and that the reduction of alpha-2 autoreceptor sensitivity is not an effect common to all antidepressant treatments. Long term treatment of laboratory rats with a spectrum of antidepressant drugs, including mianserin have been shown to reduce beta adrenergic receptor sensitivity and to increase postsynaptic alpha-1 and serotonin receptor sensitivity. Clinical investigations in which the functional sensitivity of these receptors are assessed before and during treatment with a spectrum of antidepressants are necessary. It is possible that the effects of antidepressants on one or more of these receptors represent a "final common pathway" for antidepressant activity.

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