Prevention of poststroke depression: 1 year randomised placebo controlled double blind trial of mianserin with 6 month follow up after therapy

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Abstract
Objectives—(1) To test whether early prophylactic antidepressive treatment by mianserin is able to prevent poststroke depression, and (2) to discover whether mianserin as an antidepressant has any beneficial influence on the outcome of ischaemic stroke.
Methods—A randomised, double blind, placebo controlled study involved 100 consecutive patients under 71 years old admitted to hospital for an acute ischaemic stroke; they were enrolled to receive 60 mg/day mianserin or placebo for 1 year. They were examined on admission, and at 2, 6, 12, and 18 months with depression, stroke, and functional outcome scales.
Results—According to DSM-III-R, the prevalence of major depression was 6% at the initial stage, 11% at 1 year, and 16% at 18 months. At no time point did prevalences differ between the treatment groups, nor were differences found in depression scales, although at 2 months a greater improvement from initial assessment on the Hamilton depression scale was evident in patients on mianserin (p=0.05). Some beneficial changes on the Hamilton depression scale and Beck depression inventory were found in patients older than 56 (median age) and in men treated with mianserin, but not in other subgroups. Mianserin treatment did not affect stroke outcome as measured by neurological status, nor did it have any influence on functional outcome as measured by Rankin scale or Barthel index.
Conclusion—It was not possible to show that early initiation of antidepressant therapy can prevent poststroke depression, because the prevalence of poststroke depression remained low even in patients on placebo. In this stroke population with a low rate of depressive patients, antidepressive medical treatment failed to affect stroke outcome.

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Keywords: depression; stroke outcome; treatment outcome

Depression is a major and often underrecognised problem after stroke. The prevalence of poststroke depression (PSD) ranges between 20% and 65%[1 2]; in a recent population based Finnish study it ranged between 41% and 51% during the first year.[2] It may be associated with reduced satisfaction with life[3] as well as with lowered functional ability of stroke patients,[4–6] and appropriate treatment of PSD might facilitate their rehabilitation and improve their quality of life.

The influence of antidepressive drug treatment on the outcome of stroke patients is still an open issue. Nortriptyline has been shown to relieve PSD, but its usefulness is limited because of frequent adverse effects.[7 8] Mianserin has been combined with either imipramine or desipramine in one study in which the first combination proved to be more effective in treatment of PSD.[9] Recently it was also shown that citalopram is both safe and effective.[10]

Mianserin is a tetracyclic antidepressant drug that is widely used. Its efficacy has been found comparable with that of tricyclic antidepressant drugs.[11 12] It has only minor anticholinergic activity[13] and no adverse cardiovascular effects,[14] and is relatively safe even in overdoses[15]; however, it does have some risk for causing leucopenia and agranulocytosis.[16]

The purpose of this study was to examine (1) whether prophylactic antidepressant treatment with mianserin is able to prevent PSD, and (2) whether mianserin as an antidepressant drug has a beneficial influence on the outcome of ischaemic stroke.

Patients and methods

The study covered 100 consecutive patients under 71 years of age and admitted to hospital for an ischaemic stroke in the Department of Neurology, University of Helsinki. Older patients were excluded because of a reported higher risk of leucopenia in elderly patients receiving mianserin.[16] Patients were eligible for the study if they had symptoms and signs of acute ischaemic stroke that had occurred not more than 30 days earlier, and if the CT or MRI was compatible with the clinical diagnosis. Patients were not included if they had other diseases severe enough to confound the assessments of stroke outcome (for example, severe cardiovascular or renal or liver disease, psychosis, alcoholism, or dementia). Those currently on antidepressive medication were also excluded.

The patients were randomised to mianserin or placebo groups of equal size, stratified according to location of lesion (right or left hemispheric infarction, brain stem infarction,

Table 1 Study flow chart

	0 Months	2 Months	6 Months	12 Months	18 Months
Ne	CGI[17]	CGI	CGI	CGI	CGI
	SSS[18]	SSS	SSS	SSS	SSS
	Rankin scale[19]	Rankin scale	Rankin scale	Rankin scale	Rankin scale
	DSM-III-R[20]	DSM-III-R	DSM-III-R	DSM-III-R	DSM-III-R
		Adverse events	Adverse events	Adverse events	Adverse events
Np	HDS[21]	HDS	HDS	HDS	HDS
	BDI[22]	BDI	BDI	BDI	BDI
			Strain on caregivers		Strain on caregivers
Nu	Life satisfaction (Viitanen)[23]		Life satisfaction (Viitanen)	Life satisfaction (Viitanen)	Life satisfaction (Viitanen)
			Nottingham health profile[24]	Nottingham health profile	Nottingham health profile
	Barthel index[25]	Barthel index	Barthel index	Barthel index	Barthel index
S	Language disorders (WAB)[26]		Language disorders (WAB)	Language disorders (WAB)	

Ne=neurologist; Np=neuropsychologist; Nu=nurse; S=speech language pathologist; CGI=clinical global impression of depression (separately also CGI of stroke severity and CGI of depression and stroke severity combined); SSS=Scandinavian stroke scale (total score); DSM-III-R=Diagnostic and statistical manual of mental disorders, edition 3, revised; HDS=Hamilton depression scale (21 items); BDI=Beck depression inventory (21 items); WAB=Western aphasia battery.

or severe aphasia as a separate group; the last group was expected to include patients who could not reliably be assessed with all depression measures at the acute stage). For each stratum, the test drugs were provided in numbered vials containing tablets of identical appearance. The initial dose was 10 mg mianserin or placebo at bedtime. Within 10 days, dosage was increased to the maintenance level, 60 mg mianserin or placebo. Treatment was continued for 12 months; then drug administration was withdrawn gradually during 4 weeks. The last follow up assessment was done 18 months after the initial stage. Because of the small risk of agranulocytosis related to mianserin, blood counts were analysed 3 and 6 to 8 weeks after the start of the treatment. Patients were requested immediately to contact the attending physician if any developed a sore throat with high fever. To determine serum mianserin concentrations, blood samples were collected at 2, 6, and 12 months. After the code was broken at the end of the study, mianserin concentrations were measured for all patients, including those on placebo. The randomisation codes were kept in sealed envelopes.

During the study, several rating scales were completed by a team of investigators including a neurologist (HP), a study nurse (RL), a neuropsychologist (AB), and a speech language pathologist (ML) (table 1).

Depression was assessed by HP and AB; before starting the study and during its execution the neurologist was guided by a psychiatrist (JL) in the use of the depression scales. Informed consent was obtained from the patient or a caregiver. The study protocol followed the guidelines of the National Board of Health, Finland, and the Declaration of Helsinki. The ethics committee of the Department of Neurology, University of Helsinki accepted the study protocol.

DATA ANALYSIS
We used BMDP statistical programs in the analyses.[27] Analyses were completed for both the intention to treat analysis including all randomised patients, and explanatory analysis. The second analysis included only patients on mianserin presenting serum concentrations of at least 100 nmol/l (lowest therapeutic concentration),[28] and those on placebo showing concentrations of 0 nmol/l. Patients using other antidepressant medical treatment during

Table 2 Characteristics before and at entry into the trial

	Placebo (n=49)	Mianserin (n=51)
Mean age (SD)	54.7 (10.1)	55.7 (11.1)
Men	32 (65.3%)	36 (70.6%)
Previous diseases:		
Stroke	11 (22.4%)	12 (23.5%)
Hypertension	24 (49.0%)	25 (49.0%)
Heart disease*	10 (20.8%)	17 (34.0%)
Diabetes mellitus	10 (20.4%)	10 (19.6%)
Peripheral arterial disease	6 (12.5%)	6 (12.0%)
Status on admission:		
Mean SSS (SD)	42.8 (10.9)	44.4 (12.4)
Stratified subgroup:		
Left hemisphere	14 (28.6%)	15 (29.4%)
Right hemisphere	19 (38.8%)	18 (35.3%)
Brain stem	9 (18.4%)	11 (21.6%)
Severe aphasia	7 (14.3%)	7 (13.7%)
Mean Barthel index (SD)	13.9 (4.4)	14.9 (4.6)
Mean Rankin scale (SD)	3.7 (1.0)	3.6 (1.1)

*Includes coronary heart disease, atrial fibrillation, heart failure, and other signs of significant heart disease.
SSS=Scandinavian stroke scale. One aphasic patient had a right sided hemispheric lesion, others had a left hemispheric lesion.

the study were excluded from the explanatory analysis. For comparisons between continuous variables, the Mann-Whitney U test was used. For categorical variables we used Fisher's exact test, or the χ^2 test.

Results
Characteristics before and at entry into the study are presented in table 2. No significant differences were found between the treatment groups. Mean interval from stroke to the beginning of the therapy was 14.3 (range 4 to 30) days. Explanatory analysis included 82 patients at 2 months (39 on mianserin, 43 on placebo), 71 at 6 months (31 and 40), and 64 at 12 months (27 and 37), when medication was withdrawn. At 18 months, explanatory analysis included 91 patients.

Thirteen patients on placebo and 17 on mianserin reported side effects. These included tiredness (five and seven respectively), gastrointestinal complaints (one and two), dry mouth (one and two), mental irritability (none and two), dizziness (none and one), dysuria (one each), rash (none and one), and other complaints (five and one). Ten patients on placebo and nine on mianserin discontinued the treatment prematurely. Reasons for stopping medication were lack of efficacy (three on placebo, one on mianserin), lack of compliance (three and one), side effects (three and six), and death (one each). Among those six patients treated with mianserin who refused

Table 3   Depression and outcome of ischaemic stroke in patients treated with mianserin (m) or with placebo (p)

	0 Months		2 Months		6 Months		12 Months		18 Months	
	m	p	m	p	m	p	m	p	m	p
No of patients (%):										
DSM-III-R major depression	3 (6.7)	2 (4.4)	2 (4.3)	5 (10.6)	4 (8.3)	3 (6.8)	5 (10.9)	5 (11.4)	7 (16.3)	7 (15.9)
Mean score:										
HDS	5.3*	4.6	4.1*	4.7	4.1	4.1	4.3	3.7	4.6	4.2
BDI	8.6	8.1	7.1	7.5	6.4	7.3	6.9	7.3	6.5	7.5
CGI	1.9	1.8	1.6	1.8	1.8	1.6	1.9	1.7	2.1	1.9
SSS	44.4	42.8	49.3	49.5	50.9	51.7	50.4	52.2	50.4	52.4
Rankin scale	3.6	3.7	2.6	2.6	2.4	2.2	2.3	2.2	2.4	2.0
Barthel index	14.9	13.9	17.6	18.0	18.7	19.0	18.9	19.1	18.9	19.3

DSM-III-R=Diagnostic and statistical manual of mental disorders, edition 3, revised; HDS=Hamilton depression scale (21 items); BDI=Beck depression inventory (21 items); CGI=clinical global impression of depression; SSS=Scandinavian stroke scale (total score).
*$p=0.05$ (change from initial assessment to 2 months).

the medication due to side effects, three experienced tiredness, and one of these also experienced weight gain. The three remaining reasons were dry mouth, cheek smarting, and rash. No blood dyscrasias occurred. Two patients died during the follow up, one because of myocardial infarct, and another from subarachnoid haemorrhage.

For clinical reasons, the patient's family physician replaced the trial medication by another antidepressant medication in four cases of placebo and in two of mianserin during the first year. In three cases, antidepressant medication was started after withdrawing the trial medication at 12 months.

OUTCOME OF PATIENTS

Main outcome variables are presented in table 3. Of 90 patients, only five (5.6%) had major depression at the initial stage (DSM-III-R). Due to their aphasia, reliable assessment was impossible for 10 patients. To avoid patient selection, those who were initially aphasic were later included in the analyses whenever their PSD was possible to assess with certainty. No significant differences occurred between treatment groups in the frequencies of major depression at any time point. The same was true of dysthymia, which was found in only 4.5% to 6.5% of all patients during 18 months. According to the clinical global impression of depression (CGI), 21% of the patients presented with some degree of depression at the initial stage. The percentages of patients in the stratified subgroups having at least mild depression in CGI at the initial stage were 16 (right hemisphere), 21 (left hemisphere), 15 (brain stem), and 50 (severe aphasia). The aphasic patients were depressive more often than the others ($p<0.05$). However, in four aphasic patients (29%) CGI of depression was not assessable. At 18 months, the prevalence of patients with at least mild depression according to CGI had increased to 29 of 91 (32%).

Table 3 presents the total scores on the Hamilton depression scale (HDS), Beck depression inventory (BDI), and CGI of depression at different time points. In general, the scores were low in both treatment groups at all stages of the study. Because of the few depressive patients we computed the differences between treatment groups using the total scores from depression scales with no cut off points. No significant differences were noticed in any of the scales. However, in intention to treat analysis covering all randomised patients, a marginally greater improvement in HDS was found in patients treated with mianserin at two months ($p=0.05$, table 3). The difference was slightly more prominent in the explanatory analysis at the same time point ($p=0.03$). To increase the proportions of depressive patients in the analyses, we also computed the differences in HDS and BDI between treatment groups including only patients having their initial scores above the median values. No significant differences emerged.

In male patients, a difference was found in BDI in favour of mianserin at 6 months, the mean BDI scores being 5.7 for mianserin, and 9.1 for placebo patients on the intention to treat analysis ($p=0.05$). On the explanatory analysis, a significant difference occurred both at 6 ($p=0.04$), and at 12 months ($p=0.04$). In patients older than 56 (median age) treated with mianserin, a significant improvement in both HDS and BDI was seen at 2 months compared with placebo on the intention to treat analysis ($p=0.02$ and 0.05, respectively). Conversely, women on mianserin showed an unfavourable outcome on the BDI at 6 months ($p=0.02$, intention to treat analysis and explanatory analysis), and patients younger than 56 years treated with mianserin presented higher HDS at 12 months on the intention to treat analysis ($p=0.03$).

In this study the antidepressive treatment had no beneficial influence on recovery from ischaemic stroke. We found no differences in severity of stroke at any time point nor in the functional outcome as measured by Rankin scale or Barthel index (table 3). Nor did mean duration of hospital stay differ (18.3 and 24.6 days for patients on placebo and mianserin, respectively; $p=0.9$). No differences were noticed either, in dysthymia, in adjustment disorder, in CGI for depression and stroke combined, or in the rate of strain on the caregivers.

Compared with HDS including all 21 items, no unambigious additional differences between treatment groups emerged when only 17 items were considered.[21] In a separate analysis we also included only six HDS items (Nos 1, 2, 7, 8, 10, and 13), but this did not significantly affect the results. These items have been suggested to constitute an interval scale for the severity of depression.[17]

Discussion

Of patients with ischaemic stroke, 6% had major depression according to DSM-III-R at the acute stage, 11% at 1 year, and 16% at the 18 month follow up when they had been 6 months with no antidepressant medical treatment. In the literature, prevalences have been reported of PSD of up to more than 60%.[1 2 6 29–33] Accordingly, the small proportion of depressive patients in our study was less than expected, although it is comparable with low prevalences of poststroke major depression ranging between 8.8% and 12% in some earlier studies.[34 35] One reason for the low rate of depression at the acute stage was probably the early recruitment of patients with no selection bias (mean interval since stroke 14.3, range 4 days to 30 days), and the patients' relatively young mean age.

Only a few eligible patients refused to enter the trial. It is therefore unlikely that the proportion of depressive patients in our study was significantly different from the proportion of all eligible patients admitted to hospital at the Department of Neurology.

Some studies have shown depressive symptoms to be more common in patients with left hemispheric lesions.[1 5 29] In our study half of the patients in the stratified group of severe aphasia were depressive according to CGI at the initial stage. This was significantly more than the prevalence of depression among other patients. The assessment of CGI of depression was, however, impossible in a large proportion of aphasic patients at the initial stage (29%).

For this study, the neurologist was guided by a psychiatrist in the use of depression scales. Evaluation of DSM-III-R and CGI by the neurologist and of HDS and BDI by a neuropsychologist gave very similar depression rates. Regardless of the assessors involved, the proportions of depressive patients in both patient groups remained low. At the early stage of the study, depression scores seemed to recover more rapidly in patients treated with mianserin (table 3). With HDS, the change from the initial score was marginally significant, favouring active treatment, but no differences existed after 2 months in the changes of scores between successive assessments nor in the total scores between treatment groups. Beneficial changes of small magnitude were noticed in older patients and in men treated with mianserin but not in women or in younger subjects. In future studies, prophylactic antidepressive treatment might therefore be targeted to older male stroke victims. Concerning severity of stroke and functional outcome in terms of Rankin grade and Barthel index, mianserin had no influence.

In the literature, clinical depression occurring soon after stroke has been shown to be associated with impaired recovery of functional status and cognitive performance, and early intervention has been considered.[4] Depressed mood after stroke has also been related to an increased risk for subsequent mortality, even independent of several other risk factors.[37] Regardless of several outcome variables in this study, mianserin treatment failed to differentiate clearly between actively treated patients and those on placebo. The most reasonable explanation for these negative results was low prevalence of depression that prevented meaningful assessment of whether mianserin had an effect on recovery of patients.

We assume that an effective management of stroke including early rehabilitation in our department probably had an influence on the low rate of depression. The efficacy of medical treatment including the comprehensive rehabilitation programme tailored for each patient in our neurological departments and executed after discharge at our outpatient clinic for stroke rehabilitation was shown to be effective in our earlier radomised study comparing stroke treatment in medical and in neurological departments.[38] That study was carried out in the same hospital as the present one. Self estimated life satisfaction was among factors favouring well organised care.[38] Recently, Kotila *et al*[2] found lower depression rates in stroke patients on active rehabilitation programmes compared with those without such programmes. Depression scores have been shown to decrease during the rehabilitation process, even though initial scores were relatively low.[39] Good medical care and comprehensive and individually planned early rehabilitation programmes in our study may have abolished the possibility of mianserin influencing PSD and stroke outcome.

The proportion of patients treated with mianserin discontinuing the treatment because of side effects was low (12%), and most of the side effects were mild and well tolerated. No serious adverse events related to medication occurred. The single most frequent complaint related to mianserin was its sedative effect.

In earlier studies, patients with PSD have been shown to benefit from antidepressant medical treatment.[12 13] In the present study, we were unable to show that early initiation of antidepressant medical treatment after stroke can prevent PSD in an unselected stroke population, because the prevalence of PSD even in patients on placebo remained low. In this stroke population with a low rate of PSD stroke outcome was not affected by antidepressant medical treatment.

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