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The Effect of Mianserin Hydrochloride on Delirium

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Mianserin HCl (10–60 mg/day) was administered orally before bedtime to 46 patients (mean age: 63 years) with delirium at Kurume University Hospital. The therapeutic effects of mianserin were assessed pre- and post-treatment using the Delirium Rating Scale (DRS: Trzepacz *et al.*, 1988). The mean pre-treatment DRS score was 21. This score decreased significantly ($p < 0.05$) to 14 on treatment day 1 and 10 on day 3. Mianserin was observed to be effective in 85 per cent of the cases (marked improvement in 67 per cent of the patients and slight improvement in 17 per cent). Of the 46 patients, 28 were classified with delirium due to direct causes such as a brain tumour or cerebrovascular disease, and 18 due to facilitating factors such as hospitalization or physical restraint. In the former group, marked improvement was observed in 54 per cent of the patients, and slight improvement in 21 per cent. The latter group demonstrated marked improvement in 89 per cent of the patients, and slight improvement in 11 per cent. In control subjects receiving haloperidol, marked improvement was observed in 62 per cent of 17 delirious patients. The plasma concentration of mianserin reached a therapeutic level within 24 h of the initiation of treatment. Hence, based on these clinical results and on measurements of plasma mianserin concentrations, mianserin can be considered effective in the treatment of delirium in elderly patients due to its rapid onset and few side-effects. Mianserin may offer an efficacy similar to that of haloperidol in the treatment of delirium while being safer.

KEY WORDS—delirium; mianserin; haloperidol; plasma concentration; delirium rating scale

INTRODUCTION

The consultation liaison service (CLS) of Kurume University Hospital introduced the 'tradesman' system in May 1983, requiring two groups of two to three psychiatrists each to make rounds of all hospital wards (1200 beds) once a week with or without request. The most frequent diagnosis of patients referred to the CLS between May 1983 and June 1985 was neurosis (28·7 per cent), followed by delirium (15·2 per cent). However, between April 1985 and March 1989 referrals for delirium increased to 30 per cent of the total number of referrals (Tsujimaru *et al.*, 1992). The reason for this increase in the number of delirious patients may have been due to the increased number of elderly patients who were hospitalized and the increased need for hospitalization in emergency cases.

Delirium does not hinder the treatment of the basic disease, but it may cause secondary complications that adversely affect the prognosis. Until recently, neuroleptics such as haloperidol, tiapride and oxypertine were the principal drugs used in the treatment of delirium in Japan. However, the use of neuroleptics sometimes caused oversedation, extrapyramidal symptoms, and other adverse side-effects.

Delirious states are associated with a disturbance of sleep–wake rhythm and changes in the construction of sleep stages (Nakazawa *et al.*, 1981; Evans, 1987; Okawa *et al.*, 1991). Mianserin increases the duration of deep slow wave sleep (SWS) in humans and decreases the rapid eye movement (REM) periods (Dugovic and Adrien, 1991). We hypothesized that mianserin ameliorates delirium by normalizing the disturbed sleep–wake rhythm.

In the present study, the effects of mianserin on delirious patients evaluated by CLS were tested by assessing patients with the Delirium Rating Scale (DRS; Trzepacz *et al.*, 1988) as well as measurement of plasma concentrations of mianserin.

MATERIALS AND METHODS

This was an open study performed in CLS patients receiving mianserin. The presence of delirium was based on the DSM-III-R criteria (American

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Table 1. Clinical profiles of patients in a delirious state

A

Age (mean ± SD)	Male : Female	No. of postoperative cases
28–86 y (63·0 ± 12·4 y)	33 : 13	26 (56·4%)

Potential causative disease			
Malignant tumour	10 (6) *5*	Ophthalmopathy	3 (3)
Infection	7 (1) *2*	Heart failure	1 (0)
Cerebrovascular disease	6 (2) *6*	Renal failure	1 (0) *1*
Liver cirrhosis	6 (4) *6*	Multiple fractures	1 (1)
Intestinal bleeding	3 (2)	Others	8 (7) *8*

B

Age (mean ± SD)	Male : Female	No. of postoperative cases
40–92 y (67·7 ± 15·0 y)	12 : 5	10 (58·8%)

Potential causative disease			
Malignant tumour	8 (6)	Ophthalmopathy	1 (1)
Infection	2 (0) *1*	Fractures	2 (2)
Heart failure	1 (1)	Others	2 (0)
Intestinal bleeding	1 (0)		

A indicates the background profiles of delirious patients who received mianserin.
B indicates the background profiles of delirious patients who received haloperidol.
Figures in parentheses indicate the number of postoperative cases. Italics indicate the number of cases caused by direct factors.

Psychiatric Association, 1987) and the study included 46 patients who met the symptom severity criterion of a baseline DRS total score of 16. The Appendix illustrates the items of the DRS.

The average age of the patients was 63·0 ± 12·4 years (mean ± SD), 93·5 per cent of the patients were over 50 years of age and 39·1 per cent were in their sixties. Of the potentially causative diseases of the patients with delirium, malignant tumours (21·7 per cent) ranked first, followed by infection (15·2 per cent) cerebrovascular disease (13·0 per cent), liver cirrhosis (13·0 per cent), gastrointestinal bleeding, ophthalmopathy and others (28·3 per cent).

Initially, mianserin (10–60 mg) was administered orally once daily prior to bedtime. To evaluate the clinical course of the delirium, the DRS was used to determine scores and the DRS prior to and following treatment with mianserin were compared. The DRS was scored as 1 unit per 24 h, and total scores regarded from 0 to 32. The higher the score, the more severe the delirium.

On the same day as the clinical ratings, blood sampling was performed ~12 h (between 11 and 13 h) following the administration of the bedtime dose. Plasma concentrations of mianserin were measured in duplicate using the high-performance liquid chromatography (HPLC) method of Suckow *et al.* (1982).

As a control study, 17 patients with delirium were enrolled into an open-label study in which they received 2 to 6 mg of oral haloperidol once a day. The method and evaluation of the haloperidol administration were the same as those used for the mianserin administration. The background profiles of the subjects who received haloperidol were similar to those of patients who received mianserin (Table 1B). Eleven (64·7 per cent) of the control subjects were postoperative patients. Only one case of delirium in those subjects was caused by a direct factor (encephalitis).

Informed consent was obtained from each patient and/or a member of his/her family.

Statistical analysis were performed using one-way ANOVA, the Kruskal-Wallis test, and the Scheffe's test. A p value of $<0·05$ was regarded as statistically significant.

RESULTS

Effects of mianserin on delirium

The average DRS scores prior to treatment, and for days 1, 3, 5, 7 and 14 of mianserin treatment

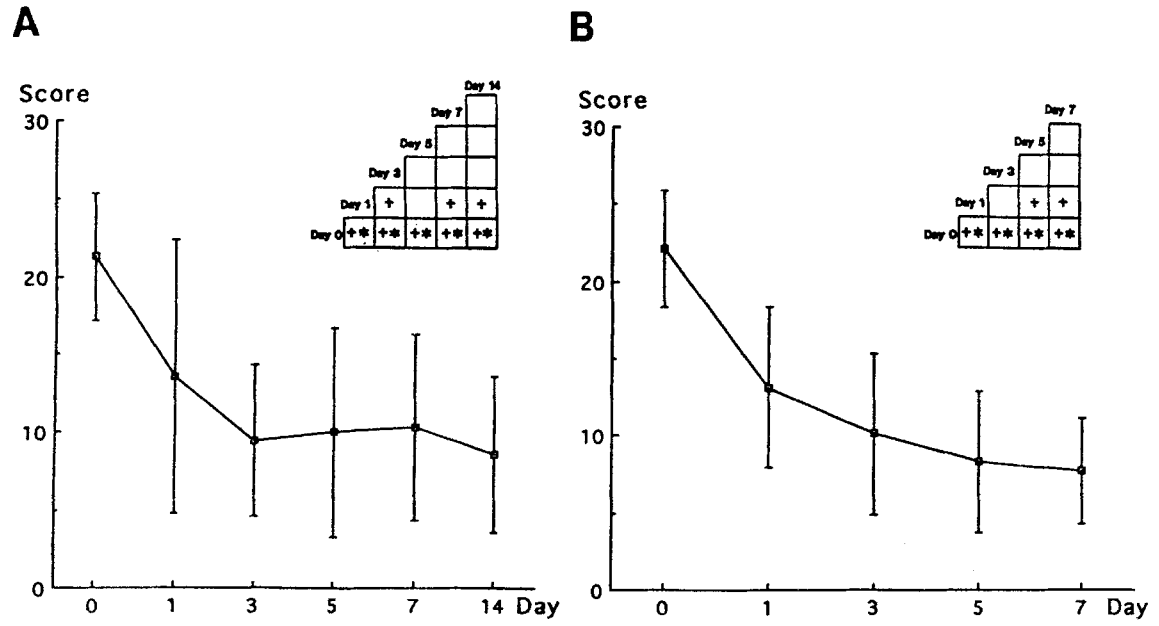

Figure 1. (A) Time course of clinical effects of mianserin represented as scores determined using the Delirium Rating Scale (DRS) by Trzepacz *et al.* ($n = 46$). Each vertical bar represents the DRS score. Each horizontal bar represents the number of days after treatment. One-way factor ANOVA measures for day 0 to day 5. Significant difference ($*p<0.05$) by Kruskal-Wallis test, significant difference ($+p<0.05$) by Scheffe's test. (B) Time course of clinical effects of haloperidol represented as DRS scores ($n = 17$)

are shown in Figure 1A. The average pre-treatment DRS score was 21.3 ± 4.1 (mean $\pm$ SD, $n = 46$), this decreased significantly to 13.6 ± 8.8 ($n = 46$) following the first day of mianserin treatment, and 9.5 ± 4.9 ($n = 30$) on the third day of treatment. Thereafter, the score remained at approximately the same level. The average scores on the 5th, 7th, and 14th days of treatment were 10.0 ± 6.7 ($n = 23$), 10.3 ± 6.0 ($n = 37$) and 8.6 ± 5.0 ($n = 18$), respectively. The average dose of mianserin was 25.3 ± 11.8 mg/day (mean $\pm$ SE) on the first day, 27.2 ± 13.7 mg/day on the third day, 26.9 ± 14.1 mg/day on the 5th day, and 27.5 ± 13.6 mg/day on the 7th day, respectively. These results suggest that the therapeutic effect of mianserin appears early within the first three days of treatment.

The effects of haloperidol on delirium are shown in Figure 1B. The average pre-treatment DRS score was 22.1 ± 3.8 (mean $\pm$ SD, $n = 17$), which decreased significantly to 13.1 ± 5.2 ($n = 17$) after the first day of haloperidol treatment. The average scores on the third, 5th, and 7th days, of treatment were 10.1 ± 5.2 ($n = 17$), 8.3 ± 4.6 ($n = 15$) and 7.7 ± 3.4 ($n = 12$), respectively.

We compared the pre-treatment scores with the scores from the final assessment period, and found that mianserin treatment was effective in approximately 85 per cent of the treated patients. It was markedly effective (DRS score decreased by >50 per cent) in 67.4 per cent of the patients, slightly effective (DRS score decreased by 20 to 50 per cent) in 17.4 per cent, and ineffective (DRS score decreased by <20 per cent) in 10.9 per cent, the treatment was discontinued in two patients (4.3 per cent). We found that treatment with haloperidol was effective in approximately 82 per cent of the patients who served as controls. It was markedly effective (DRS score decreased by >50 per cent) in 70.6 per cent ($n = 12$) of these subjects, slightly effective (DRS score decreased by 20 to 50 per cent) in 11.8 per cent, and ineffective (DRS score decreased by <20 per cent) in 11.8 per cent, the treatment was discontinued in one patient (5.6 per cent).

If we classify the delirium according to its aetiology, approximately 60 per cent of the patients ($n = 28$) manifested symptoms of an acute disturbance of consciousness such as a metabolic encephalopathy, epilepsy, encephalitis, or trauma

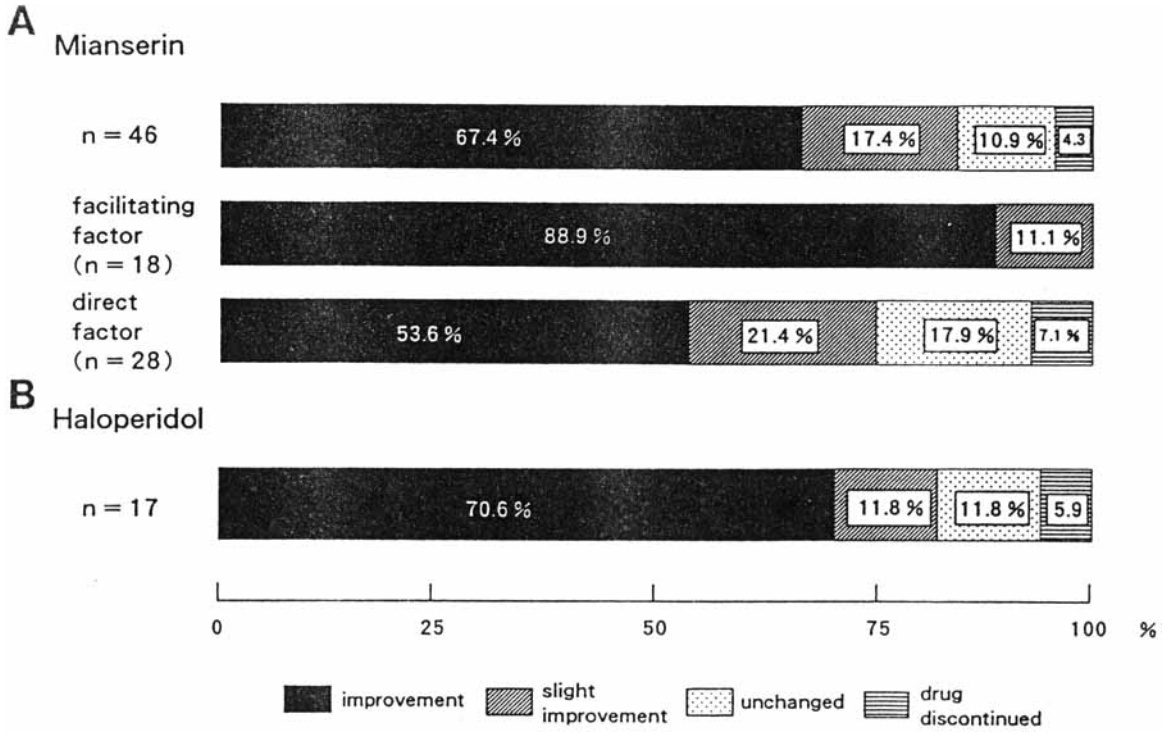

Figure 2. Summary of the clinical efficacy of mianserin (n = 46) and haloperidol (n = 17)

due to underlying diseases including brain tumours, cerebrovascular disease, renal dysfunction and hepatic diseases. Improvement in the rating of delirium due to direct precipitating factors was marked in 53·6 per cent of the patients, slight in 21·4 per cent, and absent in 17·9 per cent, the treatment was discontinued in 7·1 percent (n = 2) of the patients. In 40 per cent (n = 18) of the delirious patients, the delirium was due to facilitating factors including environmental changes secondary to hospitalization, physical stress due to pain, environmental changes secondary to a visual disturbance, sensory deprivation due to isolation in a private room, or forced bed rest due to physical restraint, fracture or prior surgery. Improvement in the rating of delirium due to these facilitating factors was marked in 88·9 per cent of the patients and slight in 11·1 per cent; hence, improvement was noted in all cases (Figure 2). Final assessment of the clinical effects of mianserin on delirium revealed DRS scores similar to those for haloperidol.

No correlation between the pre-treatment DRS score and the initial dose of mianserin was observed. However, the DRS scores were elevated in the two patients who received 60 mg of mianserin. The initial dose was determined not only on the basis of the DRS score, but also on the age and general physical condition of the patients. A significant correlation between the dose of mianserin and the improvement rate of delirium on the 7th day of treatment also was not observed; however, the improvement rate was high in those patients who received greater than 40 mg of mianserin. In addition, a significant correlation between the final DRS score and the maximum dose of mianserin was not observed. Although the final improvement rate was high in those patients who received a maximum dose of greater than 40 mg the improvement rate of patients who received 10 mg, of mianserin was also relatively high.

Oversedation occurred in two patients, but no other side-effects were observed. One case involved a 75-year-old man with thalamic bleeding, to whom 60 mg of mianserin was administered. Since difficulty in arousal was observed in this patient the next day, the dose of mianserin was reduced to 30 mg. As a result, this side-effect resolved and his delirium significantly improved. The other case involved a 59-year-old man with a subarachnoid

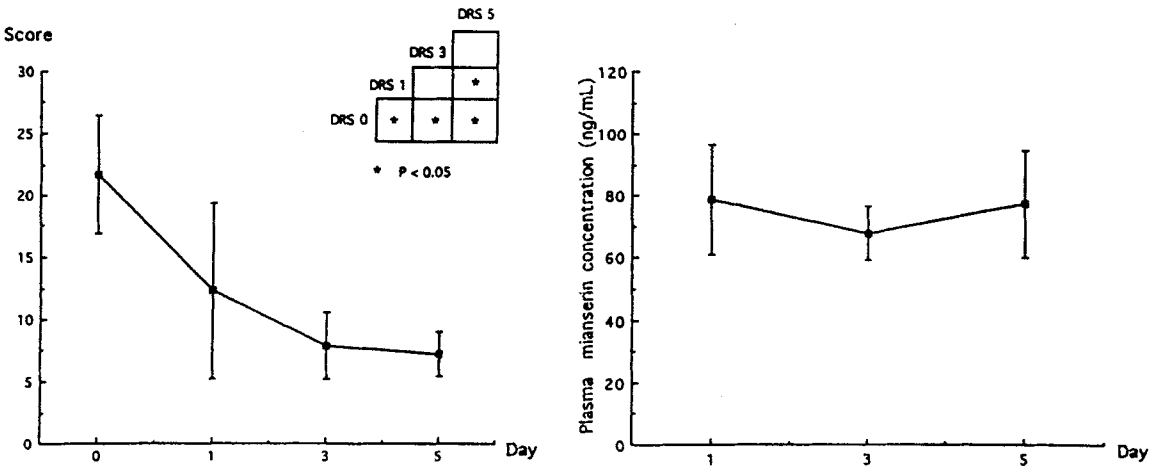

Figure 3. (A) Clinical effects of mianserin represented as DRS scores in 14 cases where plasma mianserin concentrations were assessed. Each point represents a mean. One-way factor ANOVA measures for day 0 to day 5. Significant difference ($*p<0.05$) by Scheffe's test. (B) Time course of the effects of plasma mianserin concentration on delirium ($n = 14$). Clinical effects of mianserin at a therapeutic plasma concentration were observed early

hemorrhage who received 30 mg of mianserin. Since difficulty in arousal was subsequently observed, the dose of mianserin was reduced to 20 mg and the patient improved.

Changes in DRS scores and plasma mianserin concentrations due to mianserin treatment

A summary of the 14 cases in which the plasma mianserin concentration was measured is presented in Figure 3. The average DRS score prior to treatment was $21{\cdot}7 \pm 4{\cdot}5$ (mean $\pm$ SD), $12{\cdot}9 \pm 7{\cdot}1$ on day 1, $8{\cdot}6 \pm 4{\cdot}5$ on day 3, and $8{\cdot}2 \pm 4{\cdot}1$ on day 5. Hence, scores on days 1, 3, and 5 decreased significantly from those obtained prior to treatment, and a significant difference also was observed in the DRS scores obtained on days 1 and 3. On the other hand, the plasma concentration of mianserin was $79{\cdot}0 \pm 5{\cdot}9$ ng/mL (mean $\pm$ SE) on day 1, $67{\cdot}9 \pm 8{\cdot}5$ ng/mL on day 3, and $77{\cdot}4 \pm 17{\cdot}3$ ng/mL on day 5. In other words, the plasma mianserin concentration reached a therapeutic level within 24 h of the initiation of treatment.

Relationship between clinical effects and plasma concentration of mianserin

The correlation between the severity of delirium and the plasma concentration of mianserin was examined. A positive correlation ($r = 0{\cdot}67$, $p<0{\cdot}01$) was obtained between the DRS score on day 3 and the plasma concentration of mianserin (Figure 4).

DISCUSSION

On the CLS of Kurume University Hospital, the number of patients with delirium has increased in

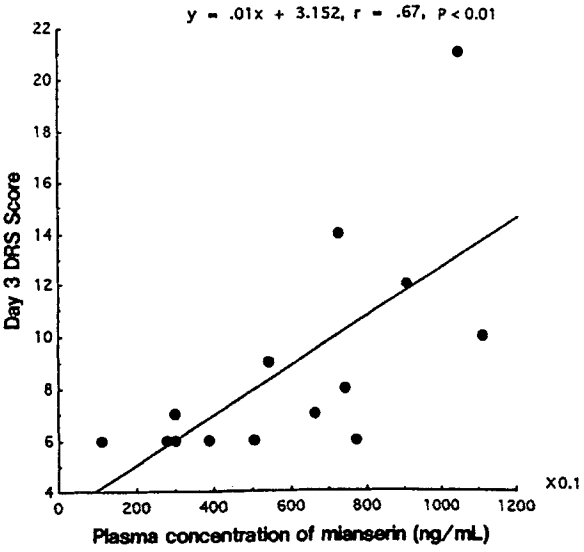

Figure 4. Relationship between the DRS scores and the plasma mianserin concentration 3 days following mianserin treatment (day 3)

the last 10 years. The reasons for this increase include the number of patients of advanced age and requiring hospitalization in the intensive care unit who are referred to the CLS. Actually, 93·5 per cent of the patients with delirium who were referred to the CLS for this study were older than 50 years old; the largest population was of patients in their sixties, followed by patients in their seventies, fifties, and eighties in that order. Nineteen patients in the emergency unit developed delirium comprising 41·3 per cent of the patients with delirium referred to the CLS. The two factors most responsible for the incidence of delirium in these patients were aging and disorders of the CNS due to acute somatic diseases. In general, neuroleptics such as haloperidol, oxypertine, and tiapride are used for treatment of delirium in Japan. At present, haloperidol is the standard treatment in most parts of the world for delirium other than when delirium was caused by alcohol or minor tranquilizer withdrawal. However, in senile patients neuroleptics frequently cause oversedation. As a result, a patient may suffer a fracture from falling, an aspiration pneumonia, or extrapyramidal symptoms. In addition, daytime activity of the patient may decrease or a disturbance of the sleep–wakefulness rhythm may occur.

Several factors contribute to the pathogenesis of delirium, especially in senile patients (Trzepacz *et al.*, 1985). Lipowski (1983) has classified the various causative factors of delirium into three classes: (1) precipitating factors: diseases such as brain tumours, cerebrovascular diseases, and head trauma which cause disturbance in consciousness; (2) facilitating factors: stress, sleep disturbances, or physical restraint which may act as a mental burden, and (3) predisposing factors: non-specific factors which cause dementia or a chronic state of cerebrovascular disease. If we classify the factors which caused the delirium in the patients who were referred to the CLS, 60 per cent were direct factors and 40 per cent were facilitating factors. However, the relationship between these factors was complex and patients also had predisposing factors including aging. This classification also may be the result of the unique characteristics of the patients referred to the CLS. Improvement was observed in all patients with facilitating factors, and in 75 per cent of the patients in whom the delirium was attributable to direct factors.

Analysis of DRS items showed that mianserin was especially effective in treating sleep disturbances and psychomotor excitement.

The clinical effects of mianserin and its therapeutic plasma concentration were assessed on the first day of treatment. The initial dose of mianserin was determined on the basis of DRS scores, patient age, and general conditions such as hepatic, renal, and pulmonary function, however, principally, we administered an initial dose of 10–30 mg/day, and, the dose was gradually increased up to 60 mg/day, if no improvement was observed. For determining an appropriate dosage regimen, it is important to establish whether there is a relationship between the clinical effects of mianserin and its plasma concentration. A significant correlation between the plasma concentration of mianserin and the rate of improvement of the delirium was not observed in this study. However, when we studied each case individually, improvement in the delirious state was dose-dependent in most patients, and improvement was observed in all of the patients who received more than 40 mg/day of mianserin. Generally, plasma concentration of mianserin reached a therapeutic level within 12 h. A therapeutic effect was observed at a concentration of 80 ng/mL at a mianserin dosage of 30 mg/day. The therapeutic plasma concentration of mianserin in delirious patients was greater than twice that of depressed patients: however, this difference could be because the mean age of the delirious patients was more than 20 years older than that of the depressed patients (Montgomery *et al.*, 1978; Yokoyama *et al.*, 1986; Otani *et al.*, 1991).

Difficulty in arousal as a side-effect of mianserin was observed in only two patients (4·3 per cent) whose delirium was due to precipitating factors, and resolved after a reduction in the mianserin dosage. Side-effects such as extrapyramidal symptoms, respiratory depression, oversedation which sometimes occurs in patients receiving neuroleptics such as haloperidol, and liver dysfunction were not observed. This suggests that the side-effects of mianserin are less than those associated with neuroleptics, hence mianserin treatment is safer.

Mianserin is a tetracyclic antidepressant, with a pharmacological profile characterized by potent antagonism of presynaptic α_2 receptors and postsynaptic 5-HT_2 receptors, and weak antagonism of D_2 receptors (Coppen *et al.*, 1976; Marshall, 1983; Pinder, 1983). Antagonists which act at presynaptic nerve terminals of α_2 receptors serve to increase the release of norepinephrine (NE). Therefore, mianserin increases the release and turnover of NE. However, since the biological

mechanism of delirium is unknown, the mechanism of action of mianserin in delirious patients is not clear. It is possible that the sedative and hypnotic actions of mianserin are induced by inhibition of histamine (H_1) and α_1 norepinephrine receptors, resolution of disturbances in the sleep–wake rhythm through the inhibiting actions of mianserin on 5-HT_2 may contribute to clinical improvement in delirium. In fact, mianserin exerts stronger histamine H_1- and H_2-receptor-blocking actions that haloperidol (Richelson, 1982; Kanba and Richelson, 1983, 1984) which may account for its sedative effects. In addition, it may offer advantages over neuroleptics treatment with regard to fewer side-effects.

In summary, mianserin may not only improve delirium due to predisposing factors, but also that due to precipitating and facilitating factors. The clinical effects and therapeutic plasma concentrations of mianserin are observed in the early stages of treatment. Mianserin offers a similar efficacy to haloperidol in the treatment of delirium, and is associated with less side-effects.

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APPENDIX

THE DELIRIUM RATING SCALE (DRS) (TRZEPACZ *ET AL.*, 1988)

Item 1: Temporal onset of symptoms

0. No significant change from longstanding behaviour, essentially a chronic or chronic-recurrent disorder
1. Gradual onset of symptoms, occurring within a 6-month period
2. Acute change in behaviour or personality occurring over a month
3. Abrupt change in behaviour, usually occurring over a 1- to 3-day period

Item 2: Perceptual disturbances

0. None evident by history or observation
1. Feelings of depersonalization or derealization
2. Visual illusions or misperceptions including macropsia, micropsia; e.g. may urinate in wastebasket or mistake bedclothes for something else
3. Evidence that the patient is markedly confused about external reality; e.g. not discriminating between dreams and reality

Item 3: Hallucination type

0. Hallucinations not present
1. Auditory hallucinations only
2. Visual hallucinations present by patient's history or inferred by observation, with or without auditory hallucinations
3. Tactile, olfactory, or gustatory hallucinations present with or without visual or auditory hallucinations

Item 4: Delusions

0. Not present
1. Delusions are systematized, i.e. well-organized and persistent
2. Delusions are new and not part of a pre-existing primary psychiatric disorder
3. Delusions are not well circumscribed; are transient, poorly organized, and mostly in response to misperceived environmental cues; e.g., are paranoid and involve persons who are in reality caregivers, loved ones, hospital staff, etc.

Item 5: Psychomotor behaviour

0. No significant retardation or agitation
1. Mild restlessness, tremulousness, or anxiety evident by observation and a change from patient's usual behaviour
2. Moderate agitation with pacing, removing i.v.'s, etc.
3. Severe agitation, needs to be restrained, may be combative; or has significant withdrawal from the environment, but not due to major depression or schizophrenic catatonia

Item 6: Cognitive status during formal testing

0. No cognitive deficits, or deficits which can be alternatively explained by lack of education or prior mental retardation
1. Very mild cognitive deficits which might be attributed to inattention due to acute pain, fatigue, depression, or anxiety associated with having a medical illness
2. Cognitive deficit largely in one major area tested, e.g. memory, but otherwise intact
3. Significant cognitive deficits which are diffuse, i.e.,affecting many different areas tested; must include periods of disorientation to time or place at least once each 24-h period; registration and/or recall are abnormal; concentration is reduced
4. Severe cognitive deficits, including motor or verbal perseverations, confabulations, disorientation to person, remote and recent memory deficits, and inability to cooperate with formal mental status testing

Item 7: Physical disorder

0. None present or active
1. Presence of any physical disorder which might affect mental state
2. Specific drug, infection, metabolic, CNS lesion, or other medial problem which can be temporally implicated in causing the altered behaviour or mental status

Item 8: Sleep–wake cycle disturbance

0. Not present; awake and alert during the day, and sleeps without significant disruption at night

1. Occasional drowsiness during day and mild sleep continuity disturbance at night
2. Frequent napping and unable to sleep at night
3. Drowsiness prominent, difficulty staying alert during interview
4. Drifts into stuporous or comatose periods

Item 9: Lability of mood

0. Not present; mood stable
1. Affect/mood somewhat altered and changes over the course of hours; patient states that mood changes are not under self-control
2. Significant mood changes which are inappropriate to situation, including fear, anger or tearfulness; rapid shifts of emotion, even over several minutes
3. Severe disinhibition of emotions, including temper outbursts, uncontrolled, inappropriate laughter, or crying

Item 10: Variability of symptoms

0. Symptoms stable and mostly present during daytime
1. Symptoms worsen at night
2. Fluctuating intensity of symptoms, such that they wax and wane during a 24-h period

Total score 32