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Therapeutic Effects of Milnacipran (Serotonin Noradrenalin Reuptake Inhibitor) on Depression Following Mild and Moderate Traumatic Brain Injury

Kouichi Kanetani[1,2], Mahito Kimura[1] and Shunkichi Endo[1]

[1]Department of Neuropsychiatry, Nippon Medical School
[2] Matsue Hospital

Abstract

Background: The present study investigated the efficacy and safety of milnacipran, a serotonin noradrenalin reuptake inhibitor (SNRI), for the treatment of depression following mild and moderate traumatic brain injury (MMTBI). While other reports have been published on the use of antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and tricyclics for the treatment of depression following MMTBI, no previous study has examined the use of a SNRI for this condition.

Methods: A six-week open study was conducted using 10 patients (4 males and 6 females) of ages ranging from 28 to 74 years. DSM-IV (diagnostic statistical manual of mental disorders, 4 th Ed. American psychiatric association, 1994) was used to diagnose mood disorders. The severity of depression was measured with the 21-item Hamilton rating scale for depression (HAM-D). The cognitive state of the patients was assessed using the mini-mental state examination (MMSE).

Results: The maximum daily milnacipran dosage for the patients ranged from 30 to 150 mg. One patient experienced side effects, but none of the side effects were serious. On the basis of having a decrease in a final HAM-D score of more than 50%, the response rate for the nine patients was 66.7%, while in a final score of 7 or less, the remission rate for the nine patients was 44.4%. Furthermore, significantly greater improvement in cognitive function was seen in patients treated with milnacipran.

Conclusion: The results demonstrated that milnacipran is a safe and effective drug for depression following mild and moderate TBI and could be the first choice drug for the treatment of this condition. (J Nippon Med Sch 2003; 70: 313–320)

Key words: mild and moderate TBI, depression, antidepressant agents, milnacipran

Introduction

Since the 1970s, psychiatric and emotional disorders associated with traumatic brain injury (TBI) have been reported, and it is now clear that some individuals experience depression following such injuries[1–4]. Regarding the prevalence of depression following TBI, Kreutzer et al.[5] reported that 42% of 722 outpatients with TBI experienced

Correspondence to Kouichi Kanetani, MD, Matsue Hospital, 2–6–15 Matsue, Edogawa-ku, Tokyo 132–0025, Japan
E-mail: kanetani@k6.dion.ne.jp
Journal Website (http://www.nms.ac.jp/jnms/)

depression following the injury. Shoumitro et al. interviewed 164 patients following TBI and confirmed depression in 13.9%[6]. As to the risk factors for depression following TBI, some interesting reports on gender differences have been published. While women suffer depression following TBI twice as often as men[7], men suffer TBI twice as often as women[8]. In addition, several reports have documented the use of drugs, predominantly antidepressants, for the treatment of depression following TBI[4,9-12]. Furthermore, several reports have suggested a correlation between depression following TBI and Glasgow Outcome Scores (GOS)[13-16], while other studies have documented that anxiety and depression following severe head injury hinders rehabilitation[17]. However, many of these studies were conducted on patients with severe TBI in the subacute phase during rehabilitation[18-22], and few studies have examined psychiatric disorders following mild and moderate TBI (MMTBI)[7,23].

According to one epidemiological survey, MMTBI occurs at a rate of about 200 cases per 100,000 head injuries, and 81% of inpatients with TBI have MMTBI. In America, approximately 391,000 cases of MMTBI occur every year. These numbers suggest the importance of conducting clinical studies on psychiatric disorders following MMTBI[7,23]. In recent years, Fann et al.[24] used the selective serotonin reuptake inhibitor (SSRI) sertraline to treat depression following mild TBI and reported its effectiveness.

However, as we investigate, there seems to be no report regarding the treatment of depression following TBI in Japan, and since this condition is not well recognized, many patients with depression following TBI remain untreated. With some delay compared to Europe and America, the use of some SSRIs and serotonin noradrenalin reuptake inhibitors (SNRIs) has been approved in Japan. The antidepressant actions of SNRIs are comparable to that of existing antidepressants, but fewer drug interactions and adverse reactions have been encountered. SNRIs should therefore prove useful for the treatment of depression following MMTBI.

This present report describes an open study on the use and efficacy of the SNRI milnacipran for the treatment of depression following MMTBI.

Subjects and Methods

Subjects were 10 patients with depression following MMTBI who were patients at Matsue General Hospital in Tokyo between April 2001 and May 2002, and participated in the present study after obtaining informed consent.

Matsue General Hospital has about 2,000 traumatic patients a year, and the 15～20% of these patients were admitted, the 15% of outpatients besides inpatients received regular treatment over 4 times a month. Subjects have diagnosed in such a background.

The semistructured interview of the Mini-International Neuropsychiatric Interview (MINI)[25] was used for diagnosing post-stroke depression (PSD). All subjects required having a diagnosis of mood disorder based on DSM-IV[26] criteria for "depression due to TBI with major depressive like episodes" or "minor depression" (ie, DSM-IV research diagnosis). The severity of depression was measured with the 21-item Hamilton rating scale for depression (HAM-D)[27]. The cognitive state of patients was assessed using the mini-mental state examination (MMSE)[28].

Initially, 30 mg/day of milnacipran was administered twice daily initially in the morning and at night, and dosage was adjusted weekly according to clinical symptoms. The maximum milnacipran dosage ranged from 30 to 150 mg.

An efficacy analysis (ie, exclusion dropout; the last observation was extended in the case of patients who did not complete the planed treatment period of 6 weeks) was performed, and the paired t-test was used to compare HAM-D scores and MMSE scores between before treatment (weeks 0) and after treatment (weeks 2, 4, 6).

Results

Table 1 shows the background characteristics of all patients who received milnacipran. The patient group was comprised of 4 males and 6 females,

Table 1 Characteristics of the patients

No.	Type of TBI	Age	Sex	Type of depression	GCS scores at the time of injury	HAM-D baseline	MMSE baseline	Milnacipran Maximum Dose (mg)
1	TSAH, C.C.	74	F	Minor	15	19	30	60 mg
2	TSAH, C.C.	67	M	Major	15	24	27	75 mg
3	concussion	33	F	Major	15	57	27	150 mg
4	AECHx	62	M	Minor	12	8	30	60 mg
5	TSAH, C.C.	70	M	Minor	12	11	20	60 mg
6	concussion	65	F	Major	15	27	26	60 mg
7	ASDHx	51	M	Major	14	38	26	120 mg
8	TSAH, C.C.	68	F	Major	12	55	14	150 mg
9	concussion	28	F	Major	15	39	27	60 mg
10	ASDHx, C.C.	65	F	Major	15	26	28	30 mg

TSAH: traumatic subarachnoid hemorrhage, C.C.: cerebral contusion, ASDHx: acute subdural hematoma, AEDHx: acute epidural hematoma

ranged in age from 28 to 74 years (mean age 57.5 years). With regards to the type of TBI, four patients experienced either traumatic subarachnoid hemorrhage or cerebral contusion; three experienced concussion; two experienced acute subdural hematoma; and one experienced acute epidural hematoma. Computed tomography (CT) revealed organic brain lesions in 7 patients. The lesion location was left hemisphere only in two patients, right hemisphere only two patients, and both hemispheres in three patients. Seven patients were diagnosed with major depression, and three with minor depression. GCS scores at the time of injury ranged from 12 to 15. Two of ten patients (20%) had gait disturbance, and one of ten patients (10%) had sensory deficit, but no patients had dysarthria. The length of time from TBI to treatment ranged widely from 21 to 510 days, with a mean of 152.8 days. In addition, maximum milnacipran dosage ranged from 30 to 150 mg.

One of the ten patients dropped out from the study. This patient was a 28 year-old woman who satisfied the diagnostic criteria for DSM-IV major depression (HAM-D 35 points): after receiving 30 mg/day of milnacipran for one week, the patient complained of nausea. She dropped out from the study because she did not wish to take the drug any longer, but she did not experience any other adverse reactions, and the nausea was not severe.

Fig. 1 shows changes in HAM-D scores for the nine patients to whom milnacipran was continuously administered for duration of the study. Although HAM-D scores were not assessed at one week, improvements were seen in many patients after only one week of treatment. On the basis of having a decrease in a final HAM-D score of more than 50%, the response rate for the nine patients was 66.7%, while on the basis of having a decrease in a final HAM-D score of below 7 and no longer meeting criteria for major or minor depression (remission), the remission rate for the nine patients was 44.4%.

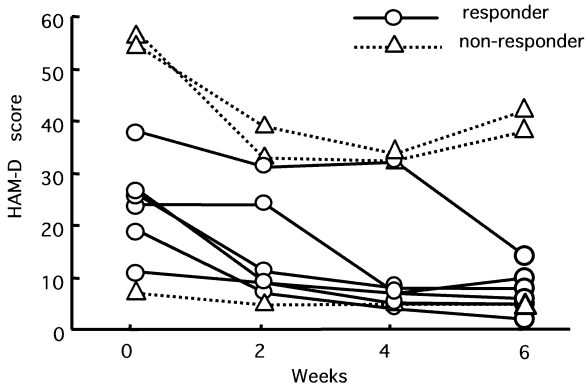

Fig. 1 Changes in HAM-D scores for treatment responder (n=6) and non-responder (n=3) groups. The response rate was 66.7%, and the remission rate was 44.4%.

Fig. 2 shows changes in HAM-D scores following milnacipran treatment. The results of an efficacy analysis (ie, excluding dropout case) showed significant improvements after two weeks ($p=0.0044$), after four weeks ($p=0.005$) and after six weeks ($p=0.0002$).

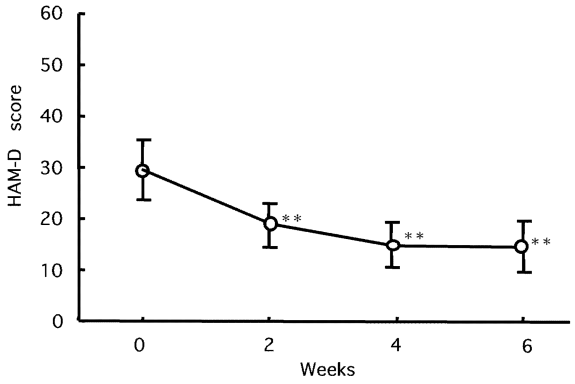

Fig. 2 Change of HAM-D scores in patients with post-TBI depression during treatment study. The result of efficacy analysis showed significant improvement after 2 weeks ($p = 0.0044$), 4 weeks ($p = 0.005$), and 6 weeks ($p = 0.0002$). Error bars represent standard errors of the mean (SE).

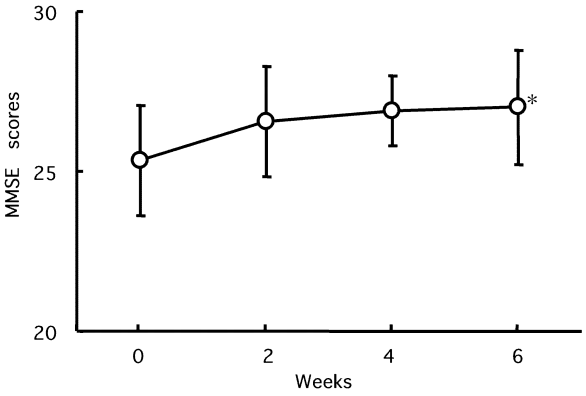

Fig. 3 Change of MMSE scores in patients with post-TBI depression during treatment study. The result of efficacy analysis showed significant improvement after 6 weeks ($p = 0.005$). Error bars represent standard errors of the mean (SE).

Fig. 3 shows changes in MMSE scores following milnacipran treatment. The results of an efficacy analysis showed significant improvements in MMSE scores after six weeks ($p = 0.0167$).

Case

A patient in whom milnacipran was markedly effective is presented below:

The patient was a 65-year-old woman. In November 2001, she experienced a traffic accident; while riding her bicycle, she collided with a moving motorcycle. She had mild transient amnesia when she was brought to hospital, but she was conscious and no remarkable neurological deficits were observed. The patient had mild acute subdural hematoma in the right frontal region revealed by her head CT scan, but the hematoma disappeared after a few days following conservative treatment. The patient experienced dizziness and headache after admission, but these conditions improved gradually, and the patient was discharged in December 2001. Starting in January 2002, the patient began to experience lethargy, depression, anxiety, irritation, insomnia and anorexia. When she experienced nocturnal palpitations, she became afraid that her heart would stop beating, and as a result began frequently visiting a local doctor and using an isosorbide dinitrate patch every night. In March 2002, the patient visited the Matsue Hospital. The patient did not exhibit any signs of neurological deficit and walked on her own to the hospital. The patient complained that she did not feel like going shopping or visiting her friends, and in fact, she did not feel like doing anything and she complained that her husband did not understand what she was going through. In addition, she had severe sleep disorder (HAM-D: 26 points). Consequently, 30 mg/day of milnacipran was administered twice daily, in the morning and at night, and the patient took 0.25 mg of triazolam as needed for sleep. Since the patient was on antihypertensive and antiplatelet agents before the start milnacipran therapy, these medications were continued for the duration of the study. After one week of milnacipran administration, the patient stated that that she was feeling much better, and improvements were seen in facial expression, depression mood and anxiety. At two weeks after the start of milnacipran therapy, the patient was more vital and smiled more, but was sleep disorder still persisted (HAM-D: 11 points). As a result, the dosage of milnacipran was maintained at 30 mg. At four weeks after the start of milnacipran therapy, the patient was experiencing minimal depression (HAM-D: 6 points). As she no longer experienced palpitations at night, she often forgot to use isosorbide dinitrate patches and eventually stopped using them all together. At six

weeks after the start of milnacipran therapy, the patient complained of constipation, and the dosage of milnacipran was reduced to 15 mg/day. The patient still visits Matsue Hospital regularly and takes 15 mg/day of milnacipran. Her condition has been stable, with no recurrence of depressive symptoms.

Discussion

The results of the present study suggest that milnacipran is effective drug for treatment of depression following MMTBI and is very safe, as only one of ten patients experienced non-serious side effects (non-severe nausea). Also, relatively low doses of milnacipran (30～75 mg/day) were effective in treating depression following MMTBI after one or two weeks, suggesting that this is a fast-acting drug.

Since the introduction of CT, acute head injury has been classified according to systems established by Adams et al.[29, 30] and Gennarelli et al.[31－33], and our understanding of head injury has been greatly advanced. Gennarelli introduced the term "diffuse injury" to describe severe head injuries in which GCS≤8 lasts more than 6 hours and CT scans do not reveal any localized space occupying lesion, differentiating this phenomenon from focal injuries such as acute epidural hematoma, acute subdural hematoma and brain contusion. Based on subsequent animal and clinical studies, they then divided TBI into focal and diffuse brain injuries, subdividing diffuse brain injury with respect to the severity of neurological symptoms and consciousness disorders, as follows:

Ⅰ) Mild concussion: transient neurological symptoms unaccompanied by loss of consciousness.

Ⅱ) Classical cerebral concussion: transient neurological symptoms accompanied by less than 6 hours loss of consciousness.

Ⅲ) Prolonged coma (diffuse axonal injury)

ⅰ) Mild diffuse axonal injury: loss of consciousness immediately following injury, and consciousness disorders lasting 6 to 24 hours.

ⅱ) Moderate diffuse axonal injury: consciousness disorders lasting for 24 hours after injury, in the absence of persisting brainstem symptoms.

ⅲ) Severe diffuse axonal injury: coma exceeding 24 hours after injury, with brainstem symptoms present.

This classification system shows that head injury can be viewed as a condition comprising two components: location of focal brain injury, and severity of diffuse brain injury. Compared to conditions such as cerebrovascular disease, the location and severity of culprit lesions for brain injury are thus more difficult to identify.

Interestingly enough, Jorge et al.[34] studied 66 patients with TBI and reported that while major depression unaccompanied by generalized anxiety disorder (GAD) was correlated with right cerebral hemisphere injury, major depression accompanied by GAD was correlated with left cerebral hemisphere injury, thus shedding some light on the localization of brain functions and culprit lesions for emotional disorders accompanying organic brain injury.

Furthermore, because the prognosis for TBI correlates well to clinical factors such as the severity of consciousness disorders at the time of injury, loss of consciousness, and duration of coma. TBI is classified as mild, moderate or severe based on the severity of these clinical factors. Mild TBI was determined by using the criteria set forth by the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine[35] and is defined as manifested by at least one of the follows: a) any period of loss of consciousness of 30 minutes or less, b) any posttraumatic amnesia lasting not more than 24 hours, c) any alteration of mental status at the time of the accident (e.g., feeling dazed, disoriented, or confused), and d) any focal neurological deficits, which may or may not be transient, resulting in initial Glasgow Coma Scale score of 13 to 15[24, 35].

In the present study, subjects included with more severe TBI cases than mild TBI, but no subjects displayed severe TBI with GCS scores≤8 on admission. In other words, subjects in the present study displayed depression following MMTBI[7]. Regarding background factors and current state for the treatment of depression following TBI, patients with severe TBI are frequently admitted to acute

care wards and then transferred to other facilities to undergo rehabilitation. Depression is one of the major factors that delay and hinder rehabilitation. Several studies have confirmed the efficacy of the following drugs for the treatment of depression following severe TBI: desipramine (tricyclic antidepressant (TCA)) (n=6) vs. placebo (n=4)[9]; moclobemide (short-acting monoamine inhibitor) (18 men, 8 women)[11]; paroxetine (SSRI) (n=13) vs. citalopram (SSRI) (n=13)[10]; and citalopram combined with carbamazepine (mood stabilizer) (n=20)[12].

On the other hand, patients with MMTBI are typically treated at general hospitals equipped with an emergency room, and many of these patients successfully rehabilitate[36,37]. Unfortunately, it is not rare for outpatients to experience depression or emotional disorders later, thus hindering rehabilitation[38]. Depression can also delay the recovery of physical symptoms such as headache and neck pain. If depression is not diagnosed and appropriate therapy is not administered, patients can suffer and quality of life can be markedly reduced.

Patients with TBI are often followed as outpatients to monitor symptoms associated with whiplash (e.g., post-concussive symptoms, traumatic cervical syndrome, and neck sprain) by orthopedic and neurosurgery departments. Patients may receive drugs such as analgesics or anxiolytics. However, these patients are rarely diagnosed with emotional disorders such as depression and are thus not treated using antidepressants.

This represents a very important issue for traffic accidents, where the clinical course of patients is an important piece of data for lawsuits involving monetary compensations[39]. When depression, an emotional disorder, is not recognized subjectively or objectively, delays in the recovery of symptoms such as headache, neck pain, depressive mood, loss of energy, insomnia and poor appetite can make patients appear somewhat lazy, further isolating them and exacerbating their psychological state.

Patients with MMTBI are often treated at general hospitals. Medical personnel at these hospitals therefore need to both recognize emotional disorders such as depression following MMTBI, and treat these disorders promptly[7,23].

With regard to overseas systemic reports on treatment of depression following TBI, efficacy of the TCA amitriptyline has been documented[23]. In 2000, Fann et al.[24] confirmed the efficacy of SSRIs, which display fewer adverse reactions. They administered sertraline to patients (n=18) with depression following mild TBI and followed them for 8 weeks. Therapeutic response and remission rates were favorable at 86.7% and 66.7%, respectively.

Cognitive disorder is another important problem associated with TBI. In 2001, Fann et al.[35] performed neuropsychological tests such as Wechsler Memory Scale (WNS)-logical memory test and Benton Visual Retention Test (BVRT), on patients with depression following mild TBI before and after sertraline therapy. They reported a significant difference in cognitive function between patients who underwent sertraline therapy and those who did not.

In the present study, patients treated with milnacipran showed significantly greater improvement on cognitive function assessed by the MMSE. The findings suggest that the impairment in cognitive function associated with MMTBI can be significantly improved by the treatment of depression with MMTBI.

Milnacipran is a SNRI developed by the French pharmaceutical company, Pierre-Fabre. Its effect on depression is comparative to tricyclic antidepressants[40], and several comparative studies have shown that this drug could work faster than imipramine[41], or mianserin[42]. Also, the results of meta-analysis have revealed that milnacipran (50 mg twice a day) was more effective in treating depression than fluoxetine (20 mg once a day) or fluvoxamine (100 mg twice a day). Furthermore, because the affinity of milnacipran towards various receptors is low and the anticholinergic activity is extremely low, fewer side effects are expected with milnacipran than with conventional antidepressants[43], such as the gastroenterological symptoms and sexual dysfunction associated with SSRIs. However, due to the potential for urinary disturbance, use of milnacipran is contraindicated for patients with

prostatic hypertrophy[44]. Furthermore, milnacipran does not inhibit any subtypes of cytochrome P 450, thus causing fewer drug interactions when compared to other antidepressants, including SSRIs[45]. The symptoms associated with depression closely correlate to monoamines such as noradrenalin, serotonin and dopamine. As a result, there is a close correlation between serotonin and impulse, mood and anxiety, and between noradrenaline and vigiliance, motivation or energy[46]. The biological mechanisms for monoamines are complex, and although SSRIs alleviates depression by activating serotonin, noradrenaline is probably involved in improving spontaneity and energy. As a result, milnacipran could be more effective in treating depression because it acts on both serotonin and noradrenaline re-uptake. Consequently, milnacipran could be useful for the treatment of apathy following TBI.

In Japan, no systemic study on the treatment of depression following TBI has been conducted, and to the best of our knowledge, the present study is the first report anywhere in the world to ascertain the efficacy of milnacipran for the treatment of depression following MMTBI. In future, comparisons between milnacipran and SSRIs using randomized double blind studies, and investigation of the effects of milnacipran on apathy following TBI using tools such as the apathy scale[47] will be necessary.

Conclusions

1. Preliminary results demonstrate that milnacipran is effective and safe as a treatment of depression following MMTBI. In addition, low doses of milnacipran (30～75 mg) were shown to be effective, and some degree of improvement was seen only 1 to 2 weeks after initiating therapy.
2. Although the number of reports on psychiatric symptoms associated with MMTBI is low, appropriate diagnosis and treatment of psychiatric symptoms following MMTBI is particularly important because there are given the frequency of depression following this condition.

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