Clinics in Oncology

Research Article
Published: 21 Oct, 2016

Delirium Improvement with Mianserin Suppositories in Cancer Patients

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Abstract

Delirium is a significant problem in palliative medicine, and its proper management and prevention is extremely important. In our cancer center, mianserin suppositories have been included in the hospital formulary and are prescribed for cancer patients who have dysphagia; however, previous studies have shown only limited data on the effect of mianserin suppositories. Therefore, in this study, we compared the therapeutic effect of mianserin suppositories with mianserin tablets for improvement of delirium.

Subjects were 66 cancer patients who had received either mianserin suppositories or mianserin tablets for delirium at our cancer center between April 2013 and March 2015. Delirium was evaluated using the Intensive Care Delirium Screening Check list (ICDSC). The improvement rates of delirium for 7 days were compared between the two groups using Fisher's exact test.

The dose of mianserin was 30-60 mg/day (median dose 30mg/day) in the suppository group (n=31) and 10-60 mg/day (median dose 20mg/day) in the tablet group (n=35). The improvement rates of delirium during the 7-day test period were 71.0% in the suppository group and 62.9% in the tablet group. There was no significant difference. (P=0.60)

Considering the results of this study, mianserin suppositories have an equal delirium improvement effect compared with mianserin tablets. These findings also suggest that mianserin suppositories can be effectively used to improve delirium in patients with dysphagia.

Keywords: Delirium; Mianserin; Suppositories; Hospital formulary; Cancer; Palliative care

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Received Date: *23 Sep 2016*
Accepted Date: *13 Oct 2016*
Published Date: *21 Oct 2016*

Citation:
Tanaka R, Ishikawa H, Sato T, Shino M, Matsumoto T, Omae K, et al. Delirium Improvement with Mianserin Suppositories in Cancer Patients. Clin Oncol. 2016; 1: 1127.

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Introduction

There are mainly 3 types of factors associated with delirium: direct causative factors such as encephalopathy and use of a psychotropic agent; predisposing factors, such as underlying physical conditions (e.g. age ≥60 years); and precipitating factors, such as stress and sleeping disorders, which aggravate the condition or help the condition to persist [1]. Cancer patients often have all 3 types of factors, and are likely to be at high risk of developing delirium. Thus, management and prevention of delirium are extremely important in care for patients with cancer. In addition to the removing these factors, conservative therapy with haloperidol [2,3], risperidone [4], lorazepam [5] and mianserin [6-8] were reported to be effective in the treatment of delirium.

Although the mechanism of action of mianserin for treating delirium remains unclear [9], it is a useful alternative to haloperidol, because of its milder antidopaminergic action and consequent lower risk of extra pyramidal side effects [10,11]. Mianserin is currently available only asoral tablets. However, the oral route is often unavailable in cancer patients with delirium, indicating the need for mianserin in suppository or injectable formulations for treating such patients. Our cancer treatment center includes 30mg mianserin suppositories in the hospital formulary for treatment of delirium (Figure 1), and these are used for treatment of delirium in cancer patients who have difficulty in taking oral medications. Because an anti-delirium agent needs to be administered for several days in cancer patients, mianserin suppositories are advantageous with their simple noninvasive route of administration, compared to haloperidol which is administered by intravenous infusion. Although benzodiazepines are available as suppositories, the therapeutic effect in delirium is reported to be

Formulation name	Mianserin suppository 30 mg			
Prescription composition	Mianserin oral tablet (30 mg)	1 tablet	70 tablets	280 tablets
	Witepsol (H-15)	1.1 g	77 g	308 g
	1.1 g/suppository (final product)	1 suppository	70 suppositories	280 suppositories
Preparation method	1. Preheat a mortar and a pestle at 50°C. 2. Put weighed witepsol (H-15) in a beaker, and melt it at ≤ 50°C in a water bath (typically around 45°C). 3. Crush mianserin tablets and pass through a 100 mesh sieve (150 μ). 4. Put the crushed tablets from step 3 in the mortar, and gradually add melted witepsol (H-15) to dissolve the mianserin. 5. Put 1.1 ml-aliquots of the mianserin suspension in 2.25-cc containers, allow to solidify at room temperature and then seal the containers. *Mix the mianserin suspension well before aliquoting. 6. Label the suppository packs and store in a cool dry place.			

Figure 1: Formulation and preparation of mianserin suppositories at Shizuoka Cancer Center.

Table 1: Comparison of patients' background factors.

	Suppository group	Oral tablet group	*P* value
	n=31	n=35	
Median daily dose (range)	30 (30-60)	20 (10-60)	
Median age (range)	74 (36-90)	69 (58-89)	0.21[a)]
Sex, n (%) male female	 25 (80.6) 6 (19.4)	 25 (71.4) 10 (28.6)	0.41[b)]
PS, n (%) ≤ 2 ≥3	 10 (32.3) 21 (67.7)	 9 (51.2) 26 (48.8)	0.60[b)]
Disease stage, n (%) ≤ III IV	 14 (45.2) 17 (54.8)	 13 (37.1) 22 (62.9)	0.62[b)]
Presence of brain tumors and/or metastasis, n (%)	3 (9.7)	3 (8.6)	1.00[b)]
Presence of central nervous system disorders, n (%)	2 (6.5)	5 (14.3)	0.43[b)]
Presence of dementia, n (%)	1 (3.2)	2 (5.7)	1.00[b)]
Past history of alcohol intake, n (%)	13 (41.9)	16 (45.7)	0.81[b)]
Presence of renal insufficiency, n (%)	5 (16.1)	9 (25.7)	0.38[b)]
Presence of hepatic insufficiency, n (%)	9 (29.0)	11 (31.4)	1.00[b)]

[a)]: Student's t test; [b)]: Fisher's exact test

unsatisfactory [3]. Furthermore, there are associated risks of adverse events (e.g., aggravation of disease condition and over sedation) during treatment and upon withdrawal [12]. In clear contrast to benzodiazepines, mianserin suppositories are not associated with any risk of such adverse events, suggesting that they are readily usable in the treatment of delirium. The drug release profile and thermodynamic properties of mianserin suppositories have been reported [13], and the pharmacokinetics of mianserin have been compared between oral tablets and suppositories by Nawata et al. [14]. However, the effectiveness in clinical cases has not yet been fully compared between the oral tablet and suppository forms of mianserin; also, the dose conversion ratio of these 2 forms remains unclear. This study therefore investigated the effect of mianserin suppositories in the treatment of delirium in cancer patients, in comparison with therapeutic effect of mianserinoral tablets.

Methods

Subjects

We retrospectively examined 66 cancers in patients who started mianserin therapy with either oral tablets or suppositories to treat delirium between April 1, 2013 and March 31 2015 at our cancer center. All of the subjects who received suppositories had no options

Table 2: Comparison of incidence rates of adverse events.

	Suppository group	Oral tablet group	*P* value
	n=31	n=35	
Hypersomnia, n (%)	9 (29.0)	10 (28.5)	1.00
Constipation, n (%)	2 (6.4)	3 (8.6)	1.00
Dry mouth, n (%)	5 (16.1)	5 (14.3)	1.00
Urinary retention, n (%)	1 (3.2)	3 (8.6)	0.61
Nausea, n (%)	0 (0)	1 (2.9)	1.00
Fisher's exact test			

Table 3: Comparison of rates of delirium improvement by concomitant agents.

	Suppository group	Oral tablet group	*P* value
	n=31	n=35	
Psychotropic agents, n (%)	22 (71.0)	18 (51.4)	0.13
Opioids, n (%)	12 (38.7)	21 (60.0)	0.14
Benzodiazepines, n (%)	6 (19.4)	5 (14.3)	0.74
Antihistaminergics, n (%)	2 (6.5)	3 (8.6)	1.00
H_2 receptor antagonists, n (%)	4 (12.9)	2 (5.7)	0.41
Steroids, n (%)	3 (9.7)	8 (22.9)	0.20
Fisher's exact test			

for oral administration of mianserin and other medications.

Definition of patients' background factors associated with alleviation of delirium.

The following background factors of the patients influencing the onset of delirium were examined and compared between 2 treatment groups: daily dose of mianserin (either the oral tablet or suppository form); age; sex; symptoms; the presence of brain tumors and/or brain metastasis; the presence of Central Nervous System (CNS) disorders; the presence of dementia; the presence of renal insufficiency; the presence of hepatic insufficiency. Patients with CNS disorders were defined as those with the history of dementia, Alzheimer's disease, and cerebrovascular disorder. In accordance with CTCAE (Common Terminology Criteria for Adverse Events) ver.4.0, Grade ≥1 for blood creatinine elevation (≥1.04 mg/dl in men, ≥0.79 mg/dl in women) was defined as renal insufficiency, and Grade ≥1 for blood AST or ALT elevation (an AST level ≥40 U/L or an ALT level ≥40 U/L) as hepatic insufficiency. The Student's t test was used for dose and age comparisons, while the Fisher's exact test was used for comparisons of the other background factors of the patients.

Comparison of the response rate to therapy

Delirium was diagnosed based on the retrospective examination of medical records in accordance with the Intensive Care Delirium Screening Checklist (ICDSC) [15]. Responders to therapy were defined as those who showed decreases in the ICDSC score (maximum score of 8) from a pre-treatment score ≥4 to a post-treatment score ≤3 [16]. The first author of this study (R.T) was solely responsible for ICDSC scoring. Response rates to mianserin by the 7th day of treatment were compared between the oral tablet group and the suppository group using Fisher's exact test.

Comparison of adverse event incidence rates

Incidence rates of adverse events (hypersomnia, constipation, dry mouth, urinary retention and nausea) at Grade 3 or higher according to the CTCAE ver. 4.0, observed during a 1-week mianserin treatment period were compared between the suppository group and the oral tablet group using Fisher's exact test.

Comparison of use of concomitant agents

Concomitant use of delirium-affecting agents, such as psychotropic agents, opioids, benzodiazepines, steroids, H_2 receptor antagonists, and antihistaminergics [17], in a 2-week period (1 week before and 1 week after the start of mianserin therapy) were compared between the oral tablet group and the suppository group using Fisher's exact test.

Ethical issues

This study adhered to the "Ethical Guidelines for Medical and Health Research Involving Humans" and conducted after approval by the institutional ethics committee (approval number 27-J154-27-1-3).

Results

Among 66 subjects, 31 were in the suppository group, while 35 were in the oral tablet group. The daily doses of mianserin were 30-60 mg (median, 30 mg) and 10-60 mg (median 20 mg) in the suppository group and in the oral tablet group, respectively (Table 1). There were no significant differences in the following between the groups: age, sex, symptoms, and the presence of brain tumors/brain metastasis, CNS disorders, dementia, past history of alcohol intake, renal insufficiency, and hepatic insufficiency.

Overall response rates were 71.0% and 62.9% in the suppository and in the oral tablet groups, respectively (Table 2), but the difference was not statistically significant (Figure 2, *P*=0.60). The lowest possible daily dose in the suppository group was 30 mg due to the formulation, but a daily dose of 10-20 mg was administered in some patients in the oral tablet group. The response rate in the oral tablet subgroup receiving a daily dose ≥30 mg was 69.2%, which was very close to that in the suppository group (Figure 3, *P*=1.00).

Regarding a comparison of adverse event incidence rates, there were no significant differences in hypersomnia, constipation, dry mouth, urinary retention, and nausea between the groups (Table 2).

Use of the following concomitant agents were examined: psychotropic agents (haloperidol, chlorpromazine, levomepromazine, risperidone, quetiapine, and mirtazapine); opioids (morphine, oxycodone and tramal); benzodiazepines (etizolam, brotizolam, flunitrazepam, alprazolam, lorazepam and diazepam), steroids (prednisolone, hydrocortisone, dexamethasone and betamethasone),

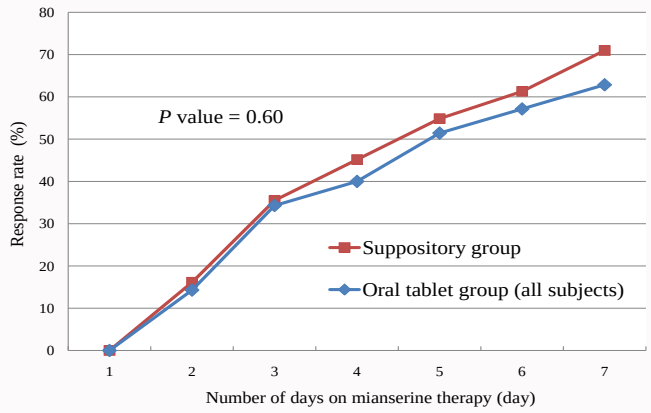

Figure 2: Comparison of overall response rates.

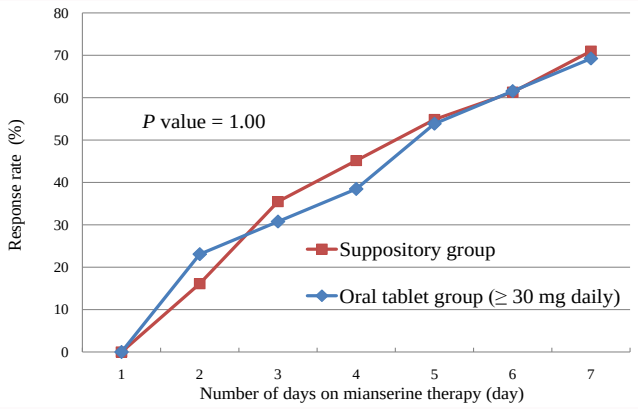

Figure 3: Comparison of response rates in subjects receiving mianserin ≥30 mg daily.

H_2 receptor antagonists (famotidine, ranitidine and lafutidine), and antihistaminergics (chlorpheniramine, promethazine and hydroxyzine). Use of the above agents with mianserin was not significantly different between the groups (Table 3). Also, none of the subjects consumed an over-the-counter product, health-enhancing food, or an herbal product during the observation period.

Discussion

This study showed that the response rate to mianserin in the suppository and the oral tablet forms were 71.0% and 62.9% respectively, which were not significantly different. These rates were consistent with the response rate in a previous study examining delirium in Japanese patients (67.4%) [18], indicating that both the suppository and oral tablet forms of mianserin exert a satisfactory therapeutic effect in cancer patients with delirium. Mianserin suppositories were offered selectively when the oral route was unavailable, suggesting that mianserin suppositories will benefit patients who are unable to take oral medications. It was also suggested that a daily dose of 10-60 mg is appropriate clinically in cases of delirium. However, in this study, the starting dose in each patient was determined by the attending physician, and this may affect therapy outcomes.

The results of the subgroup analysis comparing the 2 formulations of mianserin in the matching dosing range showed that the conversion ratio of an oral tablet to a suppository is probably 1:1. The pharmacokinetics of mianserin suppositories showed a longer T_{max} and a lower AUC than that of the corresponding dose of mianserin oral tablets [14]. However, this study did not find any significant differences in therapeutic effect and the incidence rates of adverse events in clinical cases.

Although many of the patients in this study used sleep-inducing agents (e.g., psychotropic agents, opioids, and benzodiazepines) in combination with mianserin, the incidence of hypersomnia was similar to that previously reported for mianserin oral tablets (23.4%) [10]. Also, some of the subjects received a psychotropic agent (haloperidol, chlorpromazine, levomepromazine, risperidone, quetiapine, and mirtazapine) for treatment of delirium. Although the rates of use of concomitant agents were not significantly different between the 2 groups, confounding factors (doses and frequencies of administration) might have existed.

Furthermore, because this was a retrospective study, some background factors that might have influenced the study results, such as the presence of complications (e.g., abnormal levels of blood electrolytes (e.g., Na^+, K^+, and Ca^{2+}), hypoxemia, dehydration, nutritional deficiency and endocrine disorders), were missing in some patients, and thus were not examined.

Taken together, mianserin suppositories are comparable to mianserinoral tablets in the treatment of delirium, and can bein valuable for cancer patients when the oral route is unavailable.

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