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ORIGINAL ARTICLE

Efficacy and adverse effects of olanzapine in the treatment of moderate to severe refractory neuropathic pain*

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Abstract

Objective The aim of the study was to investigate the efficacy and adverse effects of olanzapine in the treatment of moderate to severe refractory neuropathic pain.

Methods Forty patients with digestive system cancer were enrolled, who had moderate to severe refractory neuropathic pain; the patients were treated with olanzapine for 2 weeks at a daily dosage of 5 mg to 10 mg per night according to patients' response and tolerability, combined with conventional analgesic therapy. Pain intensity was evaluated by using a Numeral Rating Scale (NRS) at baseline, 3 days, and 2 weeks after therapy. The Pittsburg Sleep Quality Index (PSQI) was evaluated at baseline and 2 weeks after therapy. Data on adverse events were recorded. The dosage of conventional analgesics was adjusted over time based on the severity of pain.

Results The mean pain score decreased by 2.575 ± 1.318 ($P < 0.000$) at 3 days and by 3.400 ± 1.614 ($P < 0.000$) at 2 weeks; 30% of the patients experienced significant pain relief at 3 days and 50% at 2 weeks. The PSQI decreased by 4.725 ± 2.828 ($P < 0.000$) at 2 weeks. The adverse events induced by olanzapine included sleepiness, weight gain, dizziness, fatigue, dry mouth, and constipation; all the side effects were mild.

Conclusion When combined with conventional analgesic therapy, olanzapine was effective in relieving pain and sleep disturbance, and was well-tolerated among patients with refractory neuropathic pain.

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Key words: Olanzapine; refractory cancer pain; neuropathic pain; efficacy; adverse effect

According to a review of the published literature [1], the incidence of pain ranges from 33% to 59% in the patients with cancer who are undergoing radical treatment, and reaches up to 64% in patients with metastatic, advanced, or terminal phase cancer. Under the guidance of the WHO cancer pain relief program, the control of cancer pain has become increasingly more pro-active and standardized; however, cancer pain does not appear to be effectively controlled in almost half of patients.

For patients with neuropathic pain, the control of symptoms is much more difficult. Neuropathic pain results from injury to the peripheral or central nervous system; this type of pain may be described as burning, sharp, or shooting. Studies have suggested that 69% of neuropathic pain is tumor-related, whereas up to 43% may be treatment-related [2]. Opioid-based analgesic therapy is recommended for both tumor- and treatment-related neuropathic pain. The use of a combination of tricyclic antidepressants (e.g., amitriptyline and nortriptyline) and anticonvulsants (e.g., gabapentin and pregabalin) in addition to the basic use of opioids can improve pain control [3–6]. Despite of, the treatment of moderate and severe cancer pain, especially when combined with neuropathic pain, remains very difficult.

Olanzapine is a thiophene benzodiazepine derivative; as a newer atypical antipsychotics, it has been identified as useful for the management of several symptoms commonly encountered in palliative care and it is used

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widely for chemotherapy-induced nausea and vomiting [7]. This paper retrospectively analyzed the efficacy and adverse reaction of 40 patients with refractory neuropathic pain admitted to the Department of Digestive Oncology, Cancer Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science & Technology, Wuhan, China, and these patients were all treated with olanzapine on the basis of conventional analgesia.

Materials and methods

Clinical materials

In total, 40 patients with cancer were admitted to the Department of Digestive Oncology, Cancer Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science & Technology, Wuhan, China, were enrolled. The median age of patients was 57 years of age (range: 26–69 years). There were 26 males and 14 females. The ECOG score of 40 patients was 1–2 (that of 10 was 2 and the rest was 1). There were 19 patients with rectal cancer, 3 patients with esophageal cancer, 7 patients with pancreatic cancer, 2 patients with anal cancer, and 9 patients with liver cancer; 26 had advanced-stage disease. All 40 patients experienced refractory pain, defined as pain symptoms that could not successfully be relieved after analgesic drug treatment for 1–2 weeks, all of which met the diagnostic criteria for neuropathic pain, that is, at least met the first and second criteria of the grading system of IASP 2008 [8]. All patients scored ≥ 2 on the ID Pain scale [9]. The clinical characteristics of the 40 patients are shown in Table 1.

Methods

For enrolled patients, the self-control method was used, and all Numeral Rating Scales (NRS) scores was recorded for all patients. The initial dose of olanzapine was 5 mg orally, once per night. Changes in the NRS score and adverse events were recorded. The Pittsburg Sleep Quality Index (PSQI) was used to assess the patients' sleep status before and 2 weeks after treatment.

In accordance with the principle of the WHO analgesia ladder, opioids should be adjusted at any time in parallel with changes in pain.

Observation indices

Assessment of pain

Pain levels were measured by self-reporting on a 0–10 NRS, where 0 is no pain and 10 is the worst pain the patient can imagine. The three levels of pain intensity referred to in the algorithm are mild pain (1–3), moderate pain (4–6); and severe pain (7–10). The clinical grading of pain was as follows. (1) Mild pain: the pain was tolerable, and the patient could live normally without the disturbance of sleep; (2) Moderate pain: the pain was obvious and unbearable, requiring the use of analgesics, and sleep was disturbed; (3) Severe pain: the pain was intolerable and sleep was seriously disturbed, which may have been accompanied by the disturbance of vegetative nervous system or passive body posture.

According to the changes in NRS score before and after medication, the degree of pain relief was evaluated as mild (< 25%), moderate (25%–49%), and obvious (≥ 50%).

Patients chose a number that represented their pain level, based on their individual experience of pain, and the pain score was registered by the medical staff. Pain score was recorded three times per day from the start of medication. If breakthrough pain occurred, it was evaluated and recorded at any time.

Assessment of sleep quality

The PSQI was used to evaluate the patients' sleep status [10]. PSQI is a widely used sleep quality scale. Patients filled in 18 self-rating items before and after 2 weeks treatment. There were seven evaluation items for PSQI: sleep quality, time to fall asleep, sleep time, sleep efficacy, sleep disorders, hypnotic drugs, and daytime function. The sum of the seven items was the total score of PSQI, and a total score of greater than seven could be diagnosed as insomnia.

Adverse reactions

The adverse reactions of patients treated with

Table 1 Clinical characteristics of 40 patients with refractory cancer pain

	n	%
Gender		
Male	26	65.0
Female	14	35.0
Age (years)		
> 60 y	14	35.0
≤ 60 y	26	65.0
Pain causes		
Tumor	26	65.0
Surgery	6	15.0
Radiotherapy	4	10.0
Surgery + radiotherapy	4	10.0
Stage		
II	1	
III	13	
IV	26	
ECOG score		
0	3	7.5
1	27	67.5
2	10	25.0
Cancer type		
Rectal cancer	19	47.5
Esophageal cancer	3	7.5
Pancreatic cancer	7	17.5
Anal cancer	2	5.0
Liver cancer	9	22.5

olanzapine were recorded, and the degree of adverse reactions was closely observed. Vital signs were measured at least once per day.

Statistical methods

SPSS 22.0 statistical software was used for data processing. A paired *t*-test was used to analyze changes in the NRS score and PSQI score before and after treatment for each patient, and $P < 0.05$ was considered to represent a statistically significant difference.

Results

Analysis of analgesic effect

The enrolled patients all experienced moderate or severe pain: 22 patients (55.0%) had moderate pain (NRS 4–6) and 18 patients (45.0%) with severe pain (NRS 7–10).

After 3 days treatment with added olanzapine, 90% (36/40) of patients experienced pain relief, and the pain relief rate reached 92.5% (37/40) after 2 weeks of treatment. The PSQI score of all 40 patients after 2 weeks of treatment was lower than before treatment.

The mean NRS of the 40 patients was 6.675 ± 1.328 at baseline, 4.100 ± 1.008 after 3 days with the addition of olanzapine treatment, and 3.275 ± 0.988 after 2 weeks.

The proportion of pain relief after 3 days and 2 weeks are shown in Table 2.

Assessment of sleep status

The PSQI score was 13.700 ± 3.566 before olanzapine treatment and 8.975 ± 2.486 after 2 weeks of treatment. The changes in NRS and PSQI score after the addition of olanzapine treatment are shown in Table 3.

Summary statistics were compared by using a paired *t*-test. Compared with the baseline values, the NRS score after 3 days of medication decreased by 2.575 ± 1.31 (*t*-value, 12.354; $P < 0.000$), and the NRS score decreased by 0.825 ± 0.747 (*t*-value, 6.983; $P < 0.000$) after 2 weeks of administration compared to that after 3 days. Compared with the baseline values, the PSQI score decreased by 4.725 ± 2.283 (*t*-value, 10.566; $P < 0.000$) after 2 weeks of treatment. All differences were statistically significant.

Adverse reaction

The patients were continuously monitored for adverse reactions during treatment. Fifteen patients (37.5%) experienced somnolence after olanzapine medication, 3 patients (7.5%) reported weight gain after 2 weeks of drug administration, 6 patients (15.0%) experienced dizziness, 7 patients (17.5%) experienced fatigue, 1 patient (2.5%) experienced a mild extrapyramidal reaction, which manifested as dysphoria and fidgeting for unknown reasons, 2 patients (5.0%) experienced grade I transaminase elevation, 2 (5.0%) patients experienced nausea but no vomiting, and 14 (32.5%) patients complained of mild xerostomia after treatment. All the above adverse reactions were mild and tolerable, and no drug withdrawal or reduction treatment was given.

Table 2 Pain relief after introduction of olanzapine [*n* (%)]

	No relief (%)	Mild relief (%)	Moderate relief (%)	Obvious relief (%)
After 3 days	4 (10.0)	5 (12.5)	19 (47.5)	12 (30.0)
After 2 weeks	3 (7.5)	7 (17.5)	10 (25.0)	20 (50.0)

Table 3 NRS and PSQI changes before and after introduction of Olanzapine

	Before medication	Three days after medication	Two weeks after medication
NRS score	6.675 ± 1.328	4.100 ± 1.008	3.275 ± 0.988
PSQI score	13.700 ± 3.566		8.975 ± 2.486

Discussion

Psychiatric drugs have been used for the treatment of pain for more than 30 years [11]. Phenothiazine drugs such as chlorpromazine and propofol are used for the treatment of headache, and psychoactive drugs, such as haloperidol and fluphenazine, are reported to be used in the treatment of neuropathic pain, especially for patients with mood disorders, anxiety, depression, and other adverse emotions [11–12].

It has been reported that the incidence of insomnia in patients with cancer is as high as 20%–90% [13–16], especially in patients with pain. Apart from the psychological inducement of fear and anxiety caused by disease and treatment, pain caused by disease and treatment, and adverse reactions caused by drugs, are important factors affecting sleep [17]. Sleep dysfunction can induce different levels of anxiety and depression, which will significantly affect the quality of life of patients with cancer. Studies have shown that patients with sleep disorders often also experience a decrease in central 5-hydroxytryptamine (5-HT) content [18], and that changes in central 5-HT level can significantly affect the emotional state of patients, resulting in anxiety, depression, and other symptoms.

Olanzapine, as a new atypical psychotropic drug, has been used widely in various fields, such as antiemetic therapy for cancer patients and treatment for depression [7, 19] owing to its affinity for a variety of neurotransmitters [19–20], including the dopamine (D) D1, D2, D3, D4, 5-hydroxytryptamine (5-HT) 5-HT2A, 5-HT2C; histamine H1; adrenal α1 and M1 receptors. Olanzapine acts on the 5-hydroxytryptamine/dopamine receptor, downregulates

the 5-HT2 receptor and its antagonism to the dopamine receptor is relatively weak, which may be the key effect through which olanzapine improves sleep and alleviates depressive symptoms in patients [21]. Many studies have suggested that olanzapine can improve sleep in healthy people [22–23]. A small study showed that when opioid drugs were used to treat moderate and severe cancer pain, the addition of 2.5–7.5 mg olanzapine daily, which can effectively control pain, reduce the use of opioids, relieve pain-related anxiety, depression, delirium, and cognitive impairment, improve the patients' sleep, and improve the quality of life of patients with pain.

In this study, all 40 enrolled subjects were patients with refractory cancer pain that could not be satisfactorily controlled by conventional analgesic therapy for 1–2 weeks. There were 26 patients with advanced cancer, and 13 patients with stage IIb and IIIb rectal cancer were enrolled because of the poor control of anal pain caused by surgery and radiotherapy. One patient with stage III esophageal cancer had poor control of symptoms of chest wall pain after surgery. For the patients with refractory pain, we added olanzapine on the premise of basic analgesic treatment; after 3 days, only 4 patients (10.0%) showed no improvement in pain symptoms, after 2 weeks, 37 patients (92.5%) showed varying levels of relief in pain symptoms. After 3 days administration of olanzapine, pain symptoms were relieved slightly in 9 cases (22.5%), moderately in 19 cases (47.5%), and significantly in 12 cases (30%). However, after 2 weeks of medication, 50% of the patients' pain has been significantly improved. The overall pain improvement is obvious.

The total average score of PSQI before medication was 13.700 ± 3.566; the lowest score was 7 and the highest score was 20. All 40 patients in the group had sleep disorders of different levels and all met the diagnostic criteria for insomnia. After the administration of olanzapine for 2 weeks, the overall mean score of the PSQI re-evaluation was 8.975 ± 2.486; the lowest score was 4, and the highest score was 12. This was a statistically significant decreased. The PSQI total score of in 8 (20%) patients was lower than 7. This suggests that the sleep condition of patients with olanzapine was significantly improved. After severe pain was controlled, the use of opioids also decreased.

Conclusion

This study showed that the incidence of adverse reactions to low-dose olanzapine for the treatment of refractory pain in patients with cancer was low, and that most of the adverse reactions were mild and well-tolerated. Olanzapine is cheap, only 8 yuan per day for 5 mg, and administered once per day orally. In summary, in patients with cancer with refractory neuropathic pain, a low dose of olanzapine added to the conventional analgesic therapy, which has clear analgesic effect, results in mild adverse reactions, can be well tolerated, and a low price, can be considered for selected cases.

Conflicts of interest

The authors indicate no potential conflicts of interest.

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