[**Original Research**]

A Clinical Survey of Gabapentin for Cancer Pain Management in a University Hospital

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Abstract: We conducted a clinical survey of gabapentin for cancer pain management at Osaka University Hospital. We collected data from the medical records of cancer patients who received gabapentin during the period from September 2006 to August 2008 retrospectively. We analyzed 69 patients in terms of demographic data, primary cancer sites, types of cancer pain, stable dosage of gabapentin, duration of use, and adverse effects. The types of cancer pain were 48 patients with neuropathic pain, 19 with somatic pain, and 2 with visceral pain. Analgesic effect was observed in the morning of the day after gabapentin administration among 58 patients (84%). The effectiveness was 93% with the mean stable dosage of 807.7 mg/day. The major adverse effects were drowsiness (36%) and staggering gait in 6 patients (9%). No serious adverse effect was observed. These results suggest that gabapentin may be an effective and safe drug with opioids and other adjuvants and the analgesic effect may be observed in the morning of the day after gabapentin administration.

Key words: gabapentin, cancer pain

INTRODUCTION

Pain associated with cancer greatly affects the quality of life (QOL) of the patients, and opioids have often been used for the treatment of cancer pain. However, there are several types of pain associated with cancer for which opioids do not appear to be very effective, such as neuropathic pain, and various drugs, including antidepressants, anticonvulsants and antiarrhythmics, have been used. Among these classes of drugs, anticonvulsants have been reported to be effective for paroxysmal pain and electric-shock-like pain.[1–4] However, the use of these drugs is associated with several problems, including adverse drug reactions and drug interactions.

Gabapentin (Gabapen®) is believed to exhibit its anticonvulsant actions via mechanisms different from those of other known anticonvulsants, i.e., through inhibition of the release of excitatory neurotransmitters via binding with the $\alpha_2\delta$ subunit of the voltage-dependent calcium channel,[5] and enhancing the activity of the gamma-aminobutyric acid (GABA) nervous system by increasing the levels of GABA in the brain.[6] In Japan today, gabapentin is covered by insurance only for use in the treatment of epilepsy, and adequate clinical data are not available regarding the efficacy and safety of gabapentin used for the relief of cancer pain, which is, therefore, not covered by insurance. In this study, we investigated the efficacy and safety of gabapentin in the early phase of administration for the treatment of cancer pain.

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MATERIALS AND METHODS

The subjects were 69 patients who were admitted to Osaka University Hospital and received gabapentin for the relief of cancer pain between September 2006 and August 2008. The patient background characteristics are shown in Table 1. The patient data recorded in the medical records from the day of start of administration of gabapentin through the day of completion of the drug administration or the day of discharge, including the total quantity of gabapentin administered, the degree of analgesic effect obtained, and the adverse effects of the treatment, were evaluated retrospectively. The degree of the analgesic effect was evaluated on the basis of the subjective report of relief by the patient, as well as mea-

Table 1 Demographic data

Gender		male 45	female 24
Age (average [range])		58.7 [7–80]	
Duration of use (day: average [range])		28.2 [2–125]	median: 18.0
Primary cancer sites			
	lung	17 (25%)	
	rectum	6 (9%)	
	uterine cervix	6 (9%)	
	pancreas	5 (7%)	
	liver	4 (6%)	
	multiple myeloma	4 (6%)	
	esophagus	3 (4%)	
	bladder	2 (3%)	
	others	2 (32%)	
Types of cancer pain			
	neuropathic pain	48 (70%)	
	somatic pain	19 (28%)	
	visceral pain	2 (3%)	
Patients already treated with opioids		58 (84%)	
Oral equivalent morphine dosage		111.5 ± 99.6 mg/day	

surements of the pain severity made by the medical staff, described in the medical charts. The treatment was considered to be effective if any improvement of the pain was seen as compared with the pain severity at baseline and the patient experienced no adverse effects or only adverse effects of an acceptable level of severity. Moreover, the analgesic effect was evaluated on the basis of comprehensive examination of the factors mentioned above. The drug was assessed as markedly effective when the pain was almost completely eliminated, and as unchanged when the pain remained almost unchanged in severity. Because the study was conducted in a retrospective manner, the evaluation scales employed were diverse. Therefore, each scale was converted into a 10-grade scale, and the treatment was regarded as effective in the cases exhibiting a decrease of the pain severity by 2 grades or more. In the statistical analysis, Fisher's exact test was used for comparison of the efficacy of the analgesic effect, and the square test was used for comparison of the incidence of adverse effects. Differences at a significance level of 0.05 or less were regarded as statistically significant. Microsoft office excel 2007 was used as the statistic software.

RESULTS

Gabapentin was administered to 69 patients with cancer. Fifty-eight patients (84%) had already received strong opioids, and the status of concomitant drug use is shown in Table 2. Addition of gabapentin relieved the pain during the study period in most patients (effectiveness, 93%). Of the 69 patients administered gabapentin, 48 had neuropathic pain, 19 had somatic pain, and 2 had visceral pain, and effectiveness of gabapentin for the three types of pain during the study period were 92%, 95%, and 100%, respectively (difference not significant, Fisher's exact test; Table 3).

The starting dose of gabapentin was 485.5±240.1 mg/day (median, 400 mg/day). Analgesic effect was observed in 58 of the 69 patients (84%) on the day after gabapentin administration. When analyzed by the type of pain, analgesic effect was seen on the day after gabapentin administration in 85%, 79%, and 100% of the patients with neuropathic pain, somatic pain, and visceral pain, respectively (Table 4). No significant differences in the onset or degree of the analgesic effect were observed in relation to the dosage. The results of examination of the analgesic effect in individual patients were as follows: markedly effective, 25 patients; effective, 33 patients; unchanged, 9 patients; unknown, 2 patients.

Adverse effects to gabapentin observed on the day after gabapentin administration included drowsiness in 25 patients (36%), staggering gait in 6 patients (9%), and fatigue in 1 patient (1%) (Table 5); in 6 patients who developed drowsiness as an adverse effect, the drug needed to be discontinued.

When the incidence of drowsiness on the day after gabapentin administration was examined according to the dose, the incidence tended to increase in a dose-dependent manner. Comparison of the incidence between patients in whom gabapentin was started at the dose of 400 mg once daily after supper or at bedtime and those in whom the drug was administered at the dose of 400 mg/day in two divided doses or 600 mg in three divided doses showed that the incidence of drowsiness on the day after gabapentin administration tended to be higher in the latter groups (Fig. 1).

Examination of the laboratory data before and after gabapentin administration revealed abnormalities of hematologic and biochemical parameters during the study period; however, none of these necessitated discontinuation of the drug. In particular, no patients exhibited unfavorable changes of the serum creatinine values, which

Table 2 Concomitant drugs and their effectiveness

Concomitant drugs	*n*	Effectiveness (%)
Opioid + NSAIDs + another analgesic adjuvant	20	100
Opioid + NSAIDs	29	93
Opioid + another analgesic adjuvant	5	80
NSAIDs + another analgesic adjuvant	2	100
Only opioids	4	100
Only NSAIDs	2	100
Only another analgesic adjuvant	6	67
No concomitant drugs	1	100
Total	69	93

Table 3 Types of cancer pain, dosage of gabapentin and effectiveness

	n	Stable dosage (mg/day)	Effectiveness (%)
Neuropathic pain	48	823.5 ± 457.6	92
Somatic pain	19	771.4 ± 372.9	95
Visceral pain	2	800.0 ± 565.7	100
Total	69	807.7 ± 425.1	93

NS, Fisher's exact test.

Table 4 Effectiveness on the day after gabapentin administration

	Effectiveness (*n*)
Neuropathic pain	85% (48)
Somatic pain	79% (19)
Visceral pain	100% (2)

NS, Fisher's exact test.

Table 5 Adverse effects on the day after gabapentin administration

	Adverse effects (*n*)	Average age
Drowsiness	36% (25)	59
Staggering gait	9% (6)	60
Fatigue	1% (1)	28
Nausea	1% (1)	65
Vomiting	1% (1)	65
Headache	1% (1)	55

is an indicator of renal function. Among the patients who received gabapentin continuously for at least 1 week, the hematologic and biochemical parameters (AST, ALT, BUN, serum creatinine) measured 1 month before the start of gabapentin administration and 1 month after the start of the administration were compared; the results revealed no significant differences in the values between the two measurement points.

DISCUSSION

The results of this study suggested that in most patients with cancer pain, the analgesic effect of gabapentin begins to be manifested on the day after gabapentin administration. Since 81% of the patients with cancer pain were also receiving opioids, it was considered that concomitant use of opioids with gabapentin probably resulted in a synergistic effect. When patients who re-

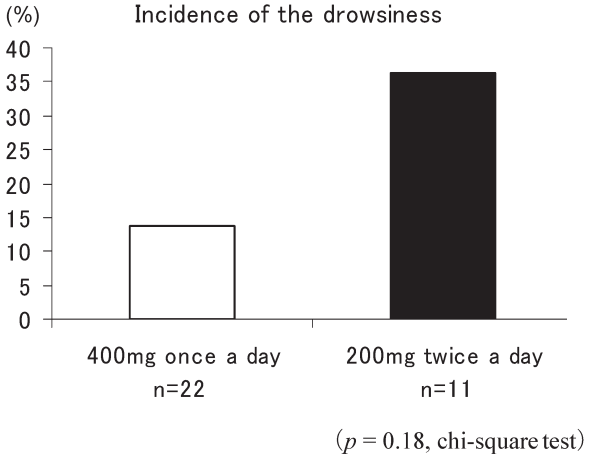

Fig. 1 Drowsiness on the day after gabapentin administration in relation to the dosage.

Table 6 Changes of laboratory data before and after gabapentin administration

	Baseline data	Data after one month
AST	31.8 ± 24.9 U/*l*	34.7 ± 21.1 U/*l*
ALT	33.5 ± 34.1 U/*l*	41.7 ± 37.7 U/*l*
BUN	16.8 ± 5.9 mg/dl	19.5 ± 11.2 mg/dl
Scr	0.83 ± 0.36 mg/dl	0.89 ± 0.54 mg/dl

NS, *t*-test.

sponded to continuation of treatment with gabapentin were also included, cancer pain was relieved in 93% of the patients, suggesting the excellent analgesic effect of gabapentin against cancer pain. Moreover, good efficacy rates were not only seen in patients with neuropathic pain but also in those with non-neuropathic pain. In recent years, progress in basic research on analgesics has brought about a deeper understanding of pain, and analgesic adjuvants have come to be believed to be effective even for pains other than neuropathic pain. The results of our study support this belief. Thus, the analgesic effect of gabapentin was seen in a relatively large percentage of the patients in this study. This could be attributable, at least in part, to the involvement of a palliative care team in the treatment, and the availability of an accurate diagnosis for a large number of the patients.

Serious hepatic and blood disorders have occasionally posed problems during treatment with carbamazepine and phenytoin, which have been widely used for the treatment of cancer pain. On the other hand, concerning the laboratory test abnormalities associated with gabapentin use, there were no cases in this study in which the drug could clearly be concluded as being the cause of the laboratory abnormalities, suggesting that it was reasonably safe. Moreover, no noteworthy drug interactions were observed. While the present study covered a period of 2 years, examination of adverse drug reactions, including laboratory data abnormalities, during long-term administration of gabapentin is also necessary.

Since drowsiness occurred at a high incidence as an adverse effect, and necessitated discontinuation of the drug in some cases, further study is needed to determine the optimal starting dose and the dose escalation method that might result in a reduced incidence of drowsiness. In the present study, the incidence of drowsiness tended to be higher in patients in whom the drug administration was started at the dose of 400 mg/day in two divided doses (200 mg per dose) or 600 mg/day in three divided doses (200 mg per dose) than when it was administered at the dose of 400 mg once daily after supper or at bedtime. This suggests the possibility that administration of gabapentin in the morning increases the incidence of drowsiness during the daytime. Therefore, it may be possible to reduce daytime drowsiness and improve the patient's QOL by once-daily administration of gabapentin after supper or at bedtime. However, according to the report of Robert H. et al., gabapentin is excreted via the kidneys. Thus, administration needs to be started at a reduced dose in patients with impaired renal function, and the recommended starting dose for neuropathic pain in patients with impaired renal function is 100 to 300 mg administered at bedtime or in three divided doses.[7] In Japan, gabapentin is available only as 200 mg and 400 mg tablets. During the target investigation period, only 400-mg tablets were used at our hospital. For these reasons, individual doses were 400 mg or 200 mg, different from the standard starting dose in foreign countries. The target population for this study did not include patients with impaired renal function, and none of the patients fell during nighttime. However, we believe that in patients with impaired renal function and have risk factors for falls, administration needs to be started carefully at a smaller starting dose. On the other hand, in patients who have been bed-ridden for a long time and have no risk of falling, the analgesic effect should be given priority, and administration can be started at higher doses, such as 400 mg/day. Thus, it may be possible to change the dose depending on the clinical situation. No other subjective adverse reactions, which are not mentioned in the package insert, were observed.

Some reports suggest that gabapentin is less effective than tricyclic antidepressants against neuropathic pain.[7] However, since gabapentin causes fewer adverse reactions and the interactions with drugs metabolized by cytochrome P450 do not pose a problem,[8] it is regarded as the preferable drug to use in patients with terminal cancer. Studies conducted overseas have accumulated evidence of the efficacy of gabapentin against various types of pain, including neuropathic pain,[9] postherpetic neuralgia,[10, 11] cancer pain,[12, 13] pain associated with diabetic neuropathy,[14] complex regional pain syndrome,[15] pain after spinal cord injury,[16] and migraine.[17] The results of this study yielded new findings regarding the efficacy and safety of gabapentin for the treatment of cancer pain in Japanese patients on the day after administration, not reported until date. Further examination of the optimal administration method and confirmation of the safety of the drug during long-term administration is still awaited.

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