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ORIGINAL ARTICLE

Low-dose gabapentin as useful adjuvant to opioids for neuropathic cancer pain when combined with low-dose imipramine

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Abstract
Purpose Painful neuropathic conditions of cancer pain often show little response to nonopioid and opioid analgesics but may be eased by antidepressants and anticonvulsants. Although gabapentin is effective in the treatment of neuropathic pain in patients with cancer, some patients experience intolerable side effects sufficient to warrant discontinuation. The aim of this study was to see whether low-dose gabapentin is effective in treating cancer-related neuropathic pain when combined with low-dose imipramine.
Methods Fifty-two cancer patients diagnosed as having neuropathic pain were allocated into four groups: G400-I group took gabapentin 200 mg and imipramine 10 mg every 12 h orally; G400 group took gabapentin 200 mg every 12 h orally; G800 group took gabapentin 400 mg every 12 h orally; I group took imipramine 10 mg every 12 h orally.
Results Low-dose gabapentin–imipramine significantly decreased the total pain score and daily paroxysmal pain episodes. Several patients developed mild adverse symptoms in the four groups, and three patients discontinued treatment due to severe adverse events in the G800 group.
Conclusion Low-dose gabapentin–antidepressant combination with opioids was effective in managing neuropathic cancer pain without severe adverse effects.

Keywords Cancer pain · Neuropathic pain · Antidepressant and anticonvulsants · Gabapentin

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Introduction

Neuropathic pain, producing a burning, shooting, or aching sensation with or without paresthesia, results from dysfunction of peripheral and central nerves [1, 2]. Opioid analgesics show good response in the treatment of neuropathic pain of nonmalignant origin [3]. However, painful neuropathic conditions of cancer pain often show little response to nonopioid and opioid analgesics but may be eased by adjuvants such as antidepressant and anticonvulsants [4–6].

Gabapentin is an anticonvulsant that binds to the a2-d subunit of voltage-gated calcium channels, decreasing the release of glutamate, norepinephrine, and substance P [1, 6]. Although it is effective in treating not only noncancer- but also cancer-related neuropathic pain [7, 8], some patients experience intolerable side effects sufficient to warrant discontinuation [1]. The incidence of side effects warranting its discontinuation is about 10–45% [1, 9]. We experienced some patients reporting somnolence and dizziness even when doses <800 mg are used, thereby discontinuing gabapentin in our daily clinical practice. However, a review article suggests that combination pharmacotherapy provide greater benefits [10]. In fact, when doses <600 mg are combined with antidepressants, gabapentin is effective in treating cancer-related neuropathic pain without severe side effects in our experience.

Table 1 Demographics and baseline characteristics of patients

	G400-I ($n = 14$)	G400 ($n = 14$)	G800 ($n = 12$)	I ($n = 12$)	p value
Age (year)	65 (58–73)	67.5 (64–70)	69 (65.5–71.5)	65 (60.5–79)	0.872
Sex (M/F)	9/5	10/4	9/3	6/6	0.573
Weight (kg)	51.5 (46–61)	52 (50–60)	55 (48.5–60)	54 (50–61.5)	0.921
Diagnosis (n)					
Breast	0	0	0	1	
Lung	5	1	3	3	
Gynecological	1	3	4	1	
Sarcoma	2	0	0	0	
Gastrointestinal	2	3	3	2	
Neck	0	2	1	0	
Prostate	2	0	0	2	
Pancreas	2	4	1	3	
Karnofsky performance status score	60 (50–70)	60 (50–70)	65 (55–80)	60 (50–65)	0.935
Daily opioid dose[a] at T0/T1 (mg/day)	45 (30–60)	55 (45–60)	55 (30–60)	35 (22.5–120)	0.578
Opioid medication (n)					0.969
Oxycodone SR	7	7	6	7	
Fentanyl patch	7	7	6	5	
Pain descriptors (n)					
Sharp	8	12	12	10	
Shooting	14	14	11	12	
Burning	5	5	5	6	
Classification of pain syndrome (n)					
Peripheral nerve syndrome due to retroperitoneal mass	2	6	1	3	
Radiculopathy due to vertebral lesion	8	4	2	5	
Brachial plexopathy	1	2	2	0	
Lumbosacral plexopathy	1	1	3	4	
Sacral plexopathy	2	1	4	0	

Values are median (interquartile range) or number

[a] Orally administered morphine equivalent

For this reason, we performed an evaluation of the analgesic effect of low-dose gabapentin–antidepressant combination in cancer pain with a neuropathic component.

Methods

Cancer patients diagnosed as having neuropathic pain that was not completely controlled with opioids analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) were enrolled in this study. Neuropathic pain was defined as pain associated with nerve compression or direct neoplastic invasion of the peripheral nerves or spinal cord. Patients with both sharp pain and burning or shooting pain (electric-shock-like) with or without allodynia were regarded as having neuropathic pain [8]. Approval from the local ethics committee was obtained, and if the pain was not completely controlled by opioids and NSAIDs, or the opioid dose was limited by side effects, oral informed consent was obtained and then gabapentin or/and imipramine were started after the first referral visit to our clinic.

In this randomized, controlled trial, cancer patients were allocated to one of four groups using computer-generated random numbers:

1. G400-I group: gabapentin 200 mg and imipramine 10 mg every 12 h orally.
2. G400 group: gabapentin 200 mg every 12 h orally.
3. G800 group: gabapentin 400 mg every 12 h orally.
4. I group: imipramine 10 mg every 12 h orally.

Previous 24-h average intensity of total pain was assessed on 0–10 numerical scales, and previous 24-h paroxysmal pain (shooting or lancinating pain) episodes were recorded [11]. Pain assessments were performed at the first visit (T0) and 7 days after the start of the medication (T1, the second visit). Opioid "rescue" doses were available as needed.

Table 2 Total pain score, daily paroxysmal pain episodes, previous 24-h opioid rescue dose, and adverse events

	G400-I ($n = 14$)	G400 ($n = 14$)	G800 ($n = 12$)	I ($n = 12$)	p value
Total pain score					
T0	7 (5–8)	7 (5–8)	6.5 (6–7)	7 (5–8)	0.970
T1	2 (2–3)	4.5 (3–6)*	4 (3–5)	5 (3–6.5)*	0.005
Pain episodes					
T0	4.5 (3–6)	4 (4–5)	5 (4–5)	4 (4–6)	0.749
T1	1 (0–2)†	3 (3–4)	3.5 (2.5–4.5)	4 (3–6)	<0.001
Opioid rescue dose at T1 (mg/day)	8 (0–25)	30 (25–30)*	25 (20–40)	25 (15–42.5)	0.008
Adverse events (n)					
Mild drowsiness	5	5	7	4	0.559
Mild dizziness	0	0	4	1	0.014
Severe dizziness	0	0	3	0	0.015
Nausea	1	1	1	1	0.999

Values are median (interquartile range) or number

* Different from the G400-I group ($p < 0.05$)

† Different from the other groups ($p < 0.05$)

[a] Oral morphine equivalent

NSAIDs already administered remained unchanged. No new drug was started during this period.

A pilot study of 20 cancer patients showed the mean [standard deviation (SD)] of the total pain score at T1 to be 2.3 (1.5), 4.2 (1.7), 4.0 (1.2), and 4.8 (1.0) in the G400-I, G400, G800, and I groups, respectively. We assumed that low-dose gabapentin–imipramine combination would improve the total pain score by at least 2° compared with gabapentin alone or imipramine alone. Thus, sample size of 9–14 was needed to show a difference of 2.0 (SD 1.2–1.5) in the total pain score at T1, with a significant level of 0.05 ($\alpha = 0.05$) and a power of 80% ($\beta = 0.20$). Data are presented as median (interquartile range). As Kolmogorov–Smirnov test was failed, data of patients' characteristics, daily opioid dose (oral morphine equivalent [12]), pain score, paroxysmal pain episodes, and previous 24-h opioid rescue dose at T1 (oral morphine equivalent [12]) were analyzed using the Kruskal–Wallis test followed by Dunn's method for multiple comparisons. Sex, opioid medication, and adverse event distributions were analyzed by the chi-squared test. A p value <0.05 was regarded as significant.

Results

Fifty-two patients with neuropathic pain were randomized into the G400-I ($n = 14$), G400 ($n = 14$), G800 ($n = 12$), and I ($n = 12$) groups, respectively. The four groups were comparable with respect to patient characteristics, daily opioid dose (oral morphine equivalents), and opioid medication (Table 1).

The four groups were comparable with respect to total pain score and daily paroxysmal pain episodes at T0 (Table 2). Low-dose gabapentin–imipramine combination significantly decreased total pain score and daily paroxysmal pain episodes (Table 2). Also, the combination significantly decreased the previous 24-h opioid rescue dose. Several patients developed mild adverse symptoms in the four groups, and three patients in the G800 group discontinued treatment due to adverse events (Table 2). As pain control was not sufficient in the G400, G800, and I groups, imipramine or gabapentin was prescribed at the second visit in order for the patients to take gabapentin 200 or 400 mg, and imipramine 10 mg every 12 h orally. At 7 days after the second visit, the median (interquartile range) of the total pain score and paroxysmal pain episodes was 2 (1–3) and 1 (0–1), respectively.

Discussion

Some cancer pain syndromes are less responsive to opioid analgesics than others [4–6, 13]. The pathophysiology involves multiple mechanisms. In particular, the presence of a neuropathic pathophysiology is associated with a less favourable outcome of opioid use [5, 8, 11, 13]. This observation indicates the need for nonopioid analgesics to be used in combination with opioids. Anticonvulsants and antidepressants are the most commonly used adjuvant analgesics in pain syndromes of cancer patients when a neuropathic pathophysiology is inferred from clinical findings [8, 11]. Thus, we planned to prescribe gabapentin

or/and imipramine instead of increasing the opioid dose at the first visit in patients in this study.

Presently, gabapentin is widely used to relieve pain, especially neuropathic pain. Several studies have shown that it is more effective than placebo in treating neuropathic pain caused by nonmalignant and malignant etiology [1, 7–10, 14–17]. In the experiences of nonmalignant etiology, gabapentin doses ranged from 600 to 3,600 mg/day. In the experiences of malignant etiology, doses ranged from 300 to 1,800 mg (median 1,200–1,800 mg). Also, gabapentin combined with morphine achieved better analgesia at lower doses of each drug than each drug alone [18]. However, we experienced many cancer patients reporting moderate to severe side effects in our daily clinical practice when doses >800 mg/day are used, leading to a discontinuation of gabapentin. Several experiments support the potential of combination pharmacotherapy for neuropathic pain [10, 19]. That is, combination pharmacotherapy could provide greater efficacy with lower doses and fewer adverse effects. A limitation of the methodology in this study was the failure to use placebo. However, the combination of low-dose gabapentin and imipramine more effectively alleviated cancer pain than gabapentin or imipramine alone. Furthermore, gabapentin 200 mg and imipramine 10 mg every 12 h were more effective than gabapentin 400 mg every 12 h. We thus believe that our results show the synergistic effectiveness of gabapentin–antidepressant combination pharmacotherapy in treating cancer-related neuropathic pain, without severe adverse effects.

In conclusion, low-dose gabapentin–antidepressant combination with opioids was effective in managing neuropathic cancer pain without severe adverse effects.

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