

Original Article

Gabapentin as an Adjuvant to Opioid Analgesia for Neuropathic Cancer Pain

Augusto Caraceni, MD, Ernesto Zecca, MD, Cinzia Martini, MD, and Franco De Conno, MD

Pain Therapy and Palliative Care Division, National Cancer Institute of Milan, Milan, Italy

Abstract

Gabapentin was administered as an "add on" therapy to 22 patients with neuropathic cancer pain only partially responsive to opioid therapy. Global pain, burning pain, shooting pain episodes, and allodynia were assessed separately. Gabapentin was given for at least a week and efficacy was assessed after 7 to 14 days of therapy. Global pain score decreased from a mean (\pm SD) of 6.4 (\pm 1.5) to 3.2 (\pm 1.3) (95% confidence interval of the baseline minus final score differences [95% CI] = 1.0–2.4). Burning pain intensity decreased from a mean (\pm SD) of 5.1 (\pm 3.6) to 2.0 (\pm 2.3) (95% CI = 1.5–3.8), and episodes of shooting pain decreased in frequency from 7.2 (\pm 3.7) to 2.2 (\pm 2.2) daily episodes (95% CI = 1.8–4.3). Allodynia was found in 9 patients and disappeared in 7 during gabapentin administration. Twenty patients judged the new drug efficacious in relieving their symptoms. The potential role of gabapentin as an adjuvant to opioid analgesia in cancer pain is discussed. J Pain Symptom Manage 1999;17:441–445. © U.S. Cancer Pain Relief Committee, 1999.

Key Words

Cancer pain, gabapentin, opioid analgesia, adjuvant, neuropathic pain

Introduction

Opioid drugs are the first-line analgesic treatment for moderate to severe cancer pain.^{1,2} Adjuvant drugs have specific indications, such as neuropathic pain, and are often used together with opioids with the purpose of enhancing analgesia, without increasing, if possible, opioid-related side effects.³

Initial clinical reports suggest the usefulness of gabapentin as analgesic in the treatment of several neuropathic pain syndromes.^{4–9} No re-

port is available at the moment about the use of this drug as an adjuvant analgesic in cancer pain. For this reason, we performed a preliminary unblinded systematic evaluation of the analgesic effect of gabapentin in cancer pain with a neuropathic component.

Methods

Consecutive patients with neuropathic cancer pain that was not completely controlled with opioid analgesics were included in the study. Neuropathic pain was defined as pain that was due to a peripheral neurologic lesion caused by cancer and was described by at least one of the following: burning pain, paroxysmal episodes of shooting pain, or pain with light touch. If the pain was not completely controlled by opioids, or the opioid dose was lim-

Address reprint requests to: Augusto Caraceni, MD, Neurology Unit, Pain Therapy and Palliative Care Division, National Cancer Institute of Milan, Via Venezian 1, 20133 Milan, Italy.

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ited by side effects, oral informed consent was obtained and gabapentin was started.

Global pain intensity and burning pain intensity were assessed on 0–10 numerical scales, paroxysmal pain episodes were quantified as approximate number per day (when the number was higher than 10, a score of 10 was used in the statistical analysis), and allodynia was rated as present or absent when gently brushing the skin with cotton or after lightly stimulating the skin with a finger. All symptom assessments, except for allodynia, refer to the previous 24-hour time period.

A dose titration period of 3 to 7 days was allowed, using 300 mg or 400 mg gabapentin capsules to optimize analgesia while keeping the opioid dose stable. Pain and side effect assessments were performed before starting gabapentin (T0) and at a stabilized gabapentin dose (at least 3 days without dose change). The latter assessment took place after 7 to 14 days of therapy (T1). Opioid “rescue” doses were available as needed and patients could always

increase their opioid dose if pain relief was felt unsatisfactory. The type and dose of other analgesics or adjuvants that were already being administered were kept unchanged (nonsteroidal anti-inflammatory drugs, 10 patients; dexamethasone, 9; amitriptyline, 4; clonazepam, 2; carbamazepine, 1). No new drug was started during this period.

Statistical analysis was performed by calculating the basal (T0) score minus final (T1) score differences and the corresponding 95% confidence intervals (95% CI). The Student's *t* test for paired samples was used to show eventual differences, while Fisher's exact test was used for allodynia, which was scored only as present or absent. Mean scores and standard deviations are also given as descriptive statistics.

Results

Twenty-two patients entered the study. Table 1 reports demographics, tumor, pain syndrome diagnosis, opioid dose and gabapentin

Table 1
Patient Demographics, Diagnosis, Pain Syndrome, Gabapentin, and Opioid Dose

Patient	Sex	Age	Tumor	Pain syndrome	Gabapentin dose at T1 (mg/day)	Opioid dose ^a at T0/T1 (mg/day)
1	F	48	Breast	Brachial plexopathy	1200	60
2	F	16	Carcinoid	Sacral radiculopathy and bone metastases	900	80
3	F	17	Sarcoma	Sciatic neuropathy	1200	90
4	F	30	Breast	Polyradiculopathy due to meningeal carcinomatosis	800	270
5	F	26	Sarcoma	Sciatic neuropathy	1200	300
6	F	35	Sarcoma	Femoral neuropathy	600	40
7	F	73	Breast	Brachial plexopathy	1200	60
8	F	49	Mouth	Trigeminal and cervical nerve infiltration	1200	60
9	M	70	MM	Brachial plexopathy	1800	120
10	F	58	Breast	Trigeminal neuropathy due to meningeal carcinomatosis	900	30
11	F	65	Breast	Brachial plexopathy	900	20
12	F	60	Colon	Lumbosacral plexopathy	900	30
13	F	49	Sarcoma	Sciatic neuropathy	1200	90
14	M	65	Rectum	Rectal tenesmus due to local infiltration	800	60
15	F	34	Breast	Spinal cord compression; lancinating leg pain	800	60
16	F	60	Cervix	Sacral plexopathy	800	40
17	M	18	Sarcoma	Thoracic radiculopathy and vertebral lesion (T12)	1200	726
18	M	49	Lung	Brachial plexopathy	800	120
19	F	55	Rectum	Lumbosacral plexopathy	800	900
20	F	63	Breast	Brachial plexopathy	800	30
21	F	77	Breast	Brachial plexopathy	900	30
22	F	69	Breast	Brachial plexopathy	1200	30

^aDaily morphine equivalent. Opioid dose did not change at T1.

dose used for each patient. Mean age was 49.3 years (range 16–77), and mean time since cancer diagnosis was 48.1 months (range 6–204). Mean daily dose of gabapentin at T1 was 1004 mg (SD 262, range 600–1800). Opioid mean daily dose was 147 mg oral morphine equivalents (SD 228, range = 20–900 mg). Individual doses are reported in Table 1. All patients kept their opioid dose stable during the study period.

In 8 patients, opioid dose had been titrated to a maximum pain relief. There was only partial relief and treatment-limiting side effects included sedation, confusion, vomiting, and myoclonus. In the remaining cases, only partial relief was obtained with opioids before starting gabapentin, but patients were unwilling to increase their opioid dose further due to disturbing side effects such as constipation and light-headedness. In all cases, the presence of neuropathic pain, according to the operational definition adopted, suggested the potential usefulness of an adjuvant analgesic.

Figure 1 and Table 2 summarize some of the results. Global pain score decreased from a mean of 6.4 (± 1.5 , SD) to 3.2 (± 1.3 , SD), with a 95% CI of the pain score differences = 1.0–2.4. Burning pain intensity decreased from a mean of 5.1 (± 3.6 , SD) to 2.0 (± 2.3 , SD), 95% CI = 1.5–3.8. Episodes of shooting pain decreased in frequency from 7.2 (± 3.7) to 2.2 (± 2.2) daily episodes, 95% CI = 1.8–4.3. Allodynia was found in 9 patients and disappeared in 7 after gabapentin administration ($P < 0.01$, Fisher's exact test).

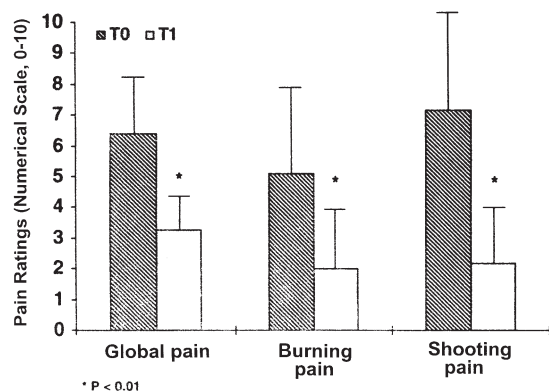


Fig. 1. Mean and standard deviations of the pain scores at T0 (basal assessment) and T2 (1–2 weeks of gabapentin administration). *Student's *t* test.

Twenty patients judged the new drug efficacious in reducing their symptoms. Of the remaining 2 patients, one had invasion of the brachial plexus by rapidly progressing malignant melanoma and high psychological distress. Pain control was partial and burning pain was still significant when taking gabapentin. The patient underwent subsequently percutaneous cordotomy. The other patient had complete control of lancinating pain episodes but no change of the constant pain component.

Follow-up duration after the study observation period varied. Fifteen patients had an observation period longer than 14 days. These patients used gabapentin for a mean of 144.6 days (range 37–380). For the remaining 7 patients, treatment duration was limited to the study duration due to progression of disease or to geographical unavailability of patients for follow-up.

Side effects attributed to treatment at T0 and at T1 are reported in Table 3. No change in side effects was seen, with the exception of one case of increased sedation with gabapentin, and one case of new-onset dizziness. Opioid-induced myoclonus decreased in one case.

Table 2
Results on the Four Pain Scales for Each Patient^a

Patient	Global pain		Burning pain		Shooting pain episodes		Allodynia	
	T0	T1	T0	T1	T0	T1	T0	T1
1	5	2	7	0	8	0	no	no
2	6	5	8	4	10	2	yes	no
3	7	3	6	3	10	5	no	no
4	8	3	0	0	10	3	no	no
5	8	3	8	0	>10	0	no	no
6	7	3	10	3	>10	3	no	no
7	10	6	10	6	6	4	yes	yes
8	5	1	5	3	>10	3	no	no
9	9	3	9	5	>10	2	yes	yes
10	6	4	0	0	0	0	no	no
11	6	3	7	5	>10	5	yes	no
12	5	4	7	5	0	0	no	no
13	6	3	7	4	>10	4	yes	no
14	5	3	0	0	6	0	no	no
15	7	4	0	0	3	0	yes	no
16	8	1	5	0	6	3	yes	no
17	5	2	8	0	4	0	yes	no
18	6	2	0	0	6	3	no	no
19	6	6	0	0	10	0	yes	no
20	6	4	8	6	0	0	no	no
21	6	4	3	0	>10	6	no	no
22	4	2	4	1	>10	6	no	no

^aAt T0 only opioids were given; at T1 (1–2 wk) gabapentin was added to the same opioid dose.

Table 3
Presence of Side Effects at T0 and T1

Side effect	T0	T1
Constipation	13	13
Sedation	4	5
Nausea	1	1
Vomiting	1	1
Confusion	1	1
Myoclonus	1	0
Dizziness	0	1

Discussion

Cancer pain pathophysiology is complex and almost always involves multiple mechanisms.^{10,11} Some patients have pain syndromes that are relatively resistant to opioids; that is, treatment yields an unfavorable balance between analgesia and side effects.¹² In particular, the presence of a neuropathic pathophysiology has been associated with a less favorable outcome of opioid pharmacotherapy.^{13,14} This observation suggests the need for nonopioid analgesics to be used in combination with morphine and other opioids. Anticonvulsants and tricyclic antidepressants are the most commonly used adjuvant analgesics in pain syndromes due to cancer when a neuropathic pathophysiology is inferred from clinical findings.^{3,15,16}

Experimental data suggest that gabapentin is antihyperalgesic in animals^{17,18} and that it potentiates morphine analgesia when the two drugs are coadministered at subanalgesic doses.¹⁹ In particular, gabapentin seems to be effective in animal models of hyperalgesia and allodynia.^{20,21} The mechanism of gabapentin analgesic effects in animals has been recently linked to an interaction with the N-methyl-D-aspartate receptor system.^{22,23} This raises the possibility that gabapentin can interfere with some of the mechanisms of opioid resistance often considered associated with the clinical phenomena of neuropathic pain and tolerance.²³

In a double-blind, placebo-controlled study, pain from multiple sclerosis significantly improved with gabapentin (daily dose 1600 mg).²⁴ Other controlled studies show that gabapentin is analgesic in painful diabetic neuropathy and in postherpetic neuralgia (doses up to 3600 mg/day).^{8,9} Other uncontrolled clinical observations suggest that gabapentin is useful in several other neuropathic pain conditions, including Guillain-Barré syndrome,⁶ multiple sclerosis,⁷

postherpetic neuralgia,^{5,25} trigeminal neuralgia,²⁶ and reflex sympathetic dystrophy.⁴ In these experiences, gabapentin doses ranged from 900 to 2400 mg/day, most often in the range between 900 and 1600 mg/day.

Our preliminary clinical observation shows that adding gabapentin to an opioid analgesic is safe and, at the doses employed, does not worsen opioid side effects in most cases. Under unblinded conditions, gabapentin improved analgesia in most cases of neuropathic cancer pain and was judged effective by 20 of 22 patients.

In some of these patients analgesia might have been improved by increasing their opioid doses, whereas in others (i.e., patients 4, 5, 7, 9, 16, 17, 18, 19), doses had already been increased to maximum analgesia without satisfactory relief. However, the aim of this experience was to document that gabapentin may improve analgesia without excessive side effects when coadministered with opioids. The improvement of analgesia eventually obtained with gabapentin, therefore, could be due to an opioid-sparing effect in many of our patients. While this is true for all adjuvant analgesics or coanalgesics,²⁷ it would be important for those patients experiencing dose-limiting side effects with opioids to know if adding gabapentin or another adjuvant to their analgesic regimen can improve analgesia without increasing the burden of side effects.²⁷

Other anticonvulsants and antidepressants used as adjuvant analgesics in cancer pain have central side effects and can interact via pharmacokinetic or pharmacodynamic mechanisms with opioids.²⁸ Gabapentin has no major drug interactions and does not induce hepatic enzyme activity. It might therefore be an attractive adjuvant drug in advanced cancer patients who already are on multiple medications and have altered metabolic functions. Side effects, at the doses used in our experience, were mild and this profile is confirmed by other experiences, when doses below 1800 mg are used; somnolence and dizziness can be reported by about 23% of patients when the dose is titrated to 3600 mg/day.⁹

At the moment, both experimental and clinical observations suggest a potential role for gabapentin as an adjuvant analgesic in neuropathic cancer pain partially responsive to opioid drugs. Controlled clinical trials are needed to confirm whether gabapentin is indicated for specific cancer pain syndromes, to show dose-

effect relationships, and to compare it with other available adjuvants as to side effects and efficacy.

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