Observational Study

Ziconotide Adverse Events in Patients with Cancer Pain: A Multicenter Observational Study of a Slow Titration, Multidrug Protocol

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Background: Ziconotide is a new analgesic agent administered intrathecally. It is challenging to use and can induce several and sometimes serious adverse events. A low initial dosage followed by slow titration may reduce serious adverse events.

Objective: To determine whether a low starting dosage of ziconotide, followed by slow titration, decreases the incidence of major adverse events associated with ziconotide when used for intractable cancer pain.

Study Design: Observational cohort study.

Setting: Three French cancer centers.

Methods: Patients with incurable cancer causing chronic pain rated above 6/10 on a numerical scale while receiving high-dose opioid therapy (more than 200 mg/d of oral morphine equivalent) and/or exhibiting severe opioid-related adverse events received intrathecal infusions of ziconotide combined with morphine, ropivacaine, and clonidine.

Results: Seventy-seven patients were included. Adverse events were recorded in 57% of them; moderate adverse events occurred in 51%. Adverse events required treatment discontinuation in 7 (9%) including 5 (6%) for whom a causal role for ziconotide was highly likely; among them 4 (5%) were serious. All patients experienced a significant and lasting decrease in pain intensity (by 48%) in response to intrathecal analgesic therapy that included ziconotide.

Limitations: Limitations include the nonrandomized, observational nature of the study. Determining the relative contributions of each drug to adverse events was difficult, and some of the adverse events manifested as clinical symptoms of a subjective nature.

Conclusions: The rates of minor and moderate adverse events were consistent with previous reports. However, the rate of serious adverse events was substantially lower. Our study confirms the efficacy of intrathecal analgesia with ziconotide for relieving refractory cancer pain. These results indicate that multimodal intrathecal analgesia in patients with cancer pain should include ziconotide from the outset in order to provide time for subsequent slow titration.

Key words: Ziconotide, adverse events, intrathecal therapy, cancer pain, morphine, ropivacaine, clonidine.

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The annual incidence of newly diagnosed cancer in France has been estimated at 320,000 cases (1); 30% of cancer patients report pain at the time of diagnosis (2). Analgesics prescribed according to the World Health Organization ladder (3) are effective at relieving cancer pain in over 80% of cases (4). However, in 15% to 20% of patients, conventional analgesic therapy either fails to relieve pain or induces unacceptable adverse events (5). Miguel (6) therefore suggested that the ladder should have a fourth step, consisting of interventional analgesic techniques such as radiotherapy, interventional radiology, surgery, and epidural as well as intrathecal analgesia.

Intrathecal administration of analgesic agents is one of the treatment options for persistent pain that is refractory to conventional analgesia. Intrathecal analgesia underwent considerable development in the 1990s thanks to the introduction of fully implantable pumps that were compatible with everyday activities and therefore became one of the standard treatment options available in pain clinics. Several studies have established the efficacy of this method for relieving cancer pain (7-9). When used by experienced physicians, intrathecal analgesia decreases morphine requirements by about 300% (10) compared to oral analgesia and has a far better safety profile, thus improving quality of life, which is a crucial objective in patients receiving long-term treatment.

In addition to morphine therapy, combinations of analgesic agents have been shown to improve the efficacy of intrathecal analgesia. Van Dongen et al (11) established that the local anesthetic drug bupivacaine acted synergistically with morphine when the 2 agents were given intrathecally. Other drugs that have been proven effective include the alpha-adrenoceptor agonist clonidine (12-13) and the N-methyl-D-aspartate receptor antagonist ketamine (14-15).

Ziconotide is a new analgesic agent that selectively blocks N-type voltage-gated calcium channels (16). Several studies have established that intrathecal ziconotide is effective for relieving pain (17-18). The advantages of ziconotide include its morphine-independent mechanism of action, the absence of respiratory depression, and the low dosages needed to achieve clinical effects. As a result, at the last consensus conferences on analgesia held in the US (19-20), ziconotide was recommended as the first-line drug for intrathecal analgesia. However, ziconotide is challenging to use, as adverse events are numerous (18,21-22) and sometimes serious. Slow dosage titration may diminish the adverse event rate (17)

and the concomitant administration of other analgesics may result in greater efficacy and safety (23-25).

Ziconotide has been used since 2008 for the treatment of chronic cancer pain in our center. Given the data in the literature (17,26-28), we developed a ziconotide therapy protocol that involves slow titration and the concomitant administration of other analgesic drugs. We instituted a follow-up program for monitoring pain intensity and potential ziconotide-related adverse events; 2 other comprehensive cancer centers adopted this protocol. Here, we report the results obtained in these 3 centers and discuss the role of ziconotide for the treatment of refractory chronic cancer pain.

Methods

This observational follow-up cohort study was conducted from December 2008 through August 2010 in 3 comprehensive cancer centers in France: the Institut de Cancerologie de l'Ouest-Paul Papin in Angers, the Oscar Lambret center in Lille, and Institut Bergonié in Bordeaux. The primary objective was to measure the incidence of ziconotide-related adverse events seen with a low starting dosage and slow titration in a multidrug protocol. We determined whether the rates of major adverse events in our study were lower than reported in earlier studies. The secondary objective was to evaluate whether slow dosage titration affected the degree of pain relief. The local institutional review board approved the study.

Patient Selection

Patients were selected using the algorithm for intrathecal analgesia developed at the 2007 consensus conference (19). Eligible patients had incurable cancer responsible for chronic intractable pain rated above 6/10 on a numerical analog scale while on high-dose opioid therapy (more than 200 mg/d oral morphine equivalent) Doses of opioid pain medications were summarized as the oral morphine equivalent dose-and/or experiencing severe morphine-related adverse events. Patients were on different opioids and their intake were expressed as equivalent morphine.

Exclusion criteria relating to the pump implantation technique consisted of intracranial hypertension, systemic infection or injection site infection, spinal cord lesions, and coagulation disorders. Exclusion criteria relating to ziconotide were psychiatric disorders such as a history of psychosis, a depressive syndrome, or suicidal behavior. We did not include pregnant women or patients with known hypersensitivity to ziconotide or any

of its components. All patients gave informed written consent prior to implantation.

A multidisciplinary meeting was held to select eligible patients. In this meeting, records of patients with refractory cancer pain were reviewed and all available interventional techniques like neurolytic blocks, radiofrequency, cementoplasty, and neurosurgery were considered. Selected patients attended an information visit. The baseline study visit included a thorough physical examination and an assessment of pain intensity on a 0-10 numerical scale (0, no pain; 10, worst pain imaginable). Adverse events of currently used analgesic agents were listed, and the Eastern Cooperative Oncology Group (ECOG) Performance Status was determined (29). Blood was drawn for the following tests: creatine phosphokinase (CPK), activated partial thromboplastin time, prothrombin time, blood cell counts, and platelet count. An electrocardiogram was obtained and blood pressure was measured after a 10-minute rest.

Before implantation of the intrathecal catheter, a computed tomography (CT) brain scan was carried out to determine that no intracranial hypertension was present. In addition, a spine CT scan was carried out to look for obstacles to cerebrospinal fluid (CSF) flow, to identify sites suitable for puncture, and to measure the distance between the skin and the CSF. A few days before pump implantation, the efficacy of intrathecal analgesia was tested using an external intrathecal catheter.

Selection of the Infusion Technique

When life expectancy was estimated at less than 3 months, intrathecal analgesia was administered via a simple catheter connected to a subcutaneous reservoir. The infusion was given using an external pump.

Patients who were expected to live for more than 3 months had a pump implanted. The catheter was inserted using the same technique but was connected to a Synchromed II subcutaneous pump (Medtronic, Minneapolis, MN). This pump can be programmed transcutaneously and can deliver variable flow rates from a 20 mL or 40 mL reservoir. The pump was implanted in the operating room under general anesthesia. Intraoperative fluoroscopy was used to check the intraspinal position of the catheter. The catheter was tunneled subcutaneously from the lumbar incision to the abdomen, and the pump was then implanted subcutaneously in the abdominal wall. The patient was monitored in the hospital over one week for complications inherent in pump implantation and intrathecal analgesia initiation.

Ziconotide Titration

The US Food and Drug Administration recommends starting ziconotide at a dosage no higher than 2.4 µg/d and increasing the dosage in steps no larger than 2.4 µg, spaced at least 48 hours apart (30). In our study, the target starting dosage was 1 µg/day. The optimal dosage was determined by slow titration, with pump refills never more than every 7 days and increments of 0.25 to 0.5 µg/d. The minimum interval between increments was 48 hours. The daily dosage was increased until effective analgesia was obtained. We did not define a maximum daily dosage. We informed the patients about potential adverse events. Ziconotide therapy was stopped in the event of serious adverse events or upon patient request. With this titration modality, effective analgesia cannot be obtained rapidly and other analgesics must therefore be used concomitantly, as cancer patients require prompt pain relief.

Concomitant Analgesic Agents

Three drugs were given concomitantly with ziconotide.

Morphine hydrochloride (50 mg/mL) is a hydrophilic agent without adjuvants that diffuses rapidly in the CSF (31). Because lipid solubility is low, the effect is long-lasting, and morphine hydrochloride is consequently the drug of choice for intrathecal analgesia (32). Morphine concentration in final mixtures never exceeded 20 mg/mL as recommended by 2007 polyanalgesic conference consensus (19) to lessen the chances of developing catheter tip granuloma. The high daily doses were obtained by increasing the pump's flow rate.

Clonidine (150 µg/mL) inhibits nociceptive impulses by activating presynaptic and postsynaptic $\alpha2$ adrenoreceptors in the dorsal horn of the spinal cord and possibly by inhibiting substance P release (13,33). The role of clonidine is particularly prominent in neuropathic pain (34).

Ropivacaine (10 mg/mL) is a local anesthetic. Local anesthetics are usually second-line drugs for intrathecal analgesia but can be used as first-line drugs in association with morphine for cancer pain (35-36). Bupivacaine is generally chosen based on its long duration of action, but in France, bupivacaine is not available in the high concentrations required for intrathecal administration. We therefore chose to use ropivacaine.

The intrathecal dosage was calculated using dosage calculation software built on a Microsoft Access 97 database (Microsoft Corporation, Redmond, WA).also

used for collecting all others data. The prescribed drug combination was prepared under a laminar flow hood at the centralized cytostatic agent reconstitution unit in the pharmacy of the relevant study center and was then packaged and taken to the operating room .The pumps were filled in the postoperative monitoring room under strict aseptic conditions, by nurses who had received specific training in this procedure. This stringent protocol was used to minimize errors in prescription, preparation, and dosage. In addition, all manipulations, from the preparation to the administration of the drug combination, were performed under controlled aseptic conditions. An on-call physician was always available for the management of any complications.

Evaluations

We visited the patient at each pump refill. The same numerical pain scale as used at baseline was used to assess pain intensity based on the most severe pain experienced within the last 24 hours. The long-term safety of ziconotide was assessed by listing all adverse events at each visit. Special attention was directed to major adverse events (defined as requiring treatment discontinuation). In addition, the known adverse effects of ziconotide were checked routinely (30): mood disorders, confusion, memory alterations, visual disturbances, vertigo, speech disorders, hypotension, diaphoresis, nausea, acute urinary retention, muscle cramps, and CPK elevation. We routinely recorded the complications related to the intrathecal route of administra-

tion such as meningitis, shift in pump orientation, and catheter migration. To assess quality of life, we determined the ECOG Performance Status (29) at each visit.

Statistical Analysis

Statistical tests were performed using winSTAT 7.0 (R. Fitch Software, Chicago, IL). Survival rates were determined by the Kaplan-Meier method. Pain intensities before and after the treatment were compared using the Mann-Whitney-Wilcoxon test at the 5% significance level. Normality of data was assessed with the Kolmogorv-Smirnov test. The means ± standard deviations are described.

Results

Seventy-seven patients were recruited: 39 males and 38 females. Their mean age was 59 (± 13.4) years (median, 60 years; range, 16-88 years). Metastatic cancer was the diagnosis in 74 patients and sarcoma in 3 patients (Table 1). Fifteen (19.5%) patients had pancreatic cancer. A simple intrathecal catheter was used for 19 (25%) patients.

Safety

Adverse events were recorded for 44 patients (57%) (Table 2). Nausea was the single most common complication (23 patients [30%]). Neurological complications accounted for most of the recorded adverse events. Adverse events that required treatment discontinuation or those who requested treatment dis-

Table 1. *Types of malignancies for cancer patients treated with ziconotide.*

Cancer Type	n	%
Pancreas	15	19.5
Colorectal	11	14.3
Uterus	10	13
Prostate	9	11.7
Breast	8	10.4
Chest	6	7.8
Kidney	4	5.2
Urinary Bladder	4	5.2
Sarcoma	3	3.9
Hepatocarcinoma	2	2.6
Head and Neck	2	2.6
Unknown Primary	1	1.3
Stomach	1	1.3
Ovary	1	1.3

Table 2. *Main adverse events for cancer patients treated with ziconotide.*

	n	%
All Types of Adverse Events	44	57
Memory Alterations	20	26
Mood Disorders	19	24
Confusion	12	16
Visual Disorders	7	9
Vertigo	7	9
Speech Disorders	6	8
CPK Elevation	2	3
Nausea	23	30
Diaphoresis	6	8
Urinary Retention	13	17
Hypotension	9	12

continuation occurred in 7 patients (9%) (Table 3). Among them, 4 (5%) were serious adverse events. Of these 4 patients, one received a very high dosage (Adverse Event 6, Table 3) and 2 received large increments (Adverse Events 4 and 5); one received a low dose and a small increment.

A causal relationship with ziconotide was highly likely for 5 of the 7 patients who experienced adverse events, including all 4 who had serious adverse events (depressive syndrome, confusion), and one (Patient 2) who asked to stop ziconotide due to a visual disorder (ziconotide level 1µg/d). All adverse events disappeared 2 days after treatment discontinuation.

For the 2 other patients (1 and 3), the adverse event was a moderate mood disorder which manifested after they received information on their disease's evolution. A relationship with ziconotide is not clear. In 2 patients, the treatment was successfully resumed.

Efficacy

The pain intensity score on the numerical scale was significantly decreased versus baseline at 15, 30, 60, and 90 days after the initiation of intrathecal analgesia (Fig. 1). The maximum pain intensity dropped from 8.07 ± 1.27 at baseline to 4.14 ± 1.37 after 30 days (P < 0.01). The mean pain intensity decrease was 48% after one month. A similar mean decrease was noted after 2 months, 4.29 ± 2.30, and after 3 months, 4.12 ± 2.07 (P < 0.01). Mean survival time was 36 (±27) days for patients implanted with a simple catheter. The 58 (75%) remaining patients with a pump implanted survived for a mean of 138 (±124) days (Fig. 2). The mean duration of intrathecal analgesia per patient was 113.4 (±117.4) days and the total number of treatment days for all patients was 6,021 days.

Dosages used

In our study of patients with uncontrolled cancer pain, the mean daily morphine dosage at baseline was 625 ± 709 mg/d. The 77 patients' pumps were refilled a total of 681 times. The mean ziconotide starting dosage was 0.93 ± 0.43 µg/d (range 0.25-2.4 µg/d) and the mean maximum dosage was 4.2 ± 3.4 µg/d (range 0.5-19 µg/d). The mean ziconotide increment size was 0.07 ± 0.02 µg/d and the mean interval between increments was 10 days. The mean ziconotide dosage in the overall patient population was 3.5 ± 2.8 µg/d. The dosages of each of the medications used are listed in Table 4.

Table 3. *Characteristics of the 7 patients who experienced adverse events requiring treatment discontinuation.*

Adverse Event	Dosage at Discontinuation (µg/d)	Increments (µg/d)	Resumption	Severity	Causality
1	3.5	0.16	Yes	Moderate	Weak
2	1	0.1	No	Moderate	Strong
3	1	0.1	No	Moderate	Weak
4	6	0.3	Yes	Severe	Strong
5	6	0.51	No	Severe	Strong
6	19	0.1	No	Severe	Strong
7	2.6	0.13	No	Severe	Strong

Table 4. *Distribution and mean dosages of intrathecal analgesic agents.*

	Ziconotide µg/d	Morphine mg/d	Ropivacaine mg/d	Clonidine µg/d
Number of Refills	681	681	680	672
Mean Dosage (±SD)	3.5 ± 2.8	19.3 ± 18	18.3 ± 11.5	9.3 ± 11
Lowest Dosage	0.25	0.3	0.94	2
Highest Dosage	19	89	57	58
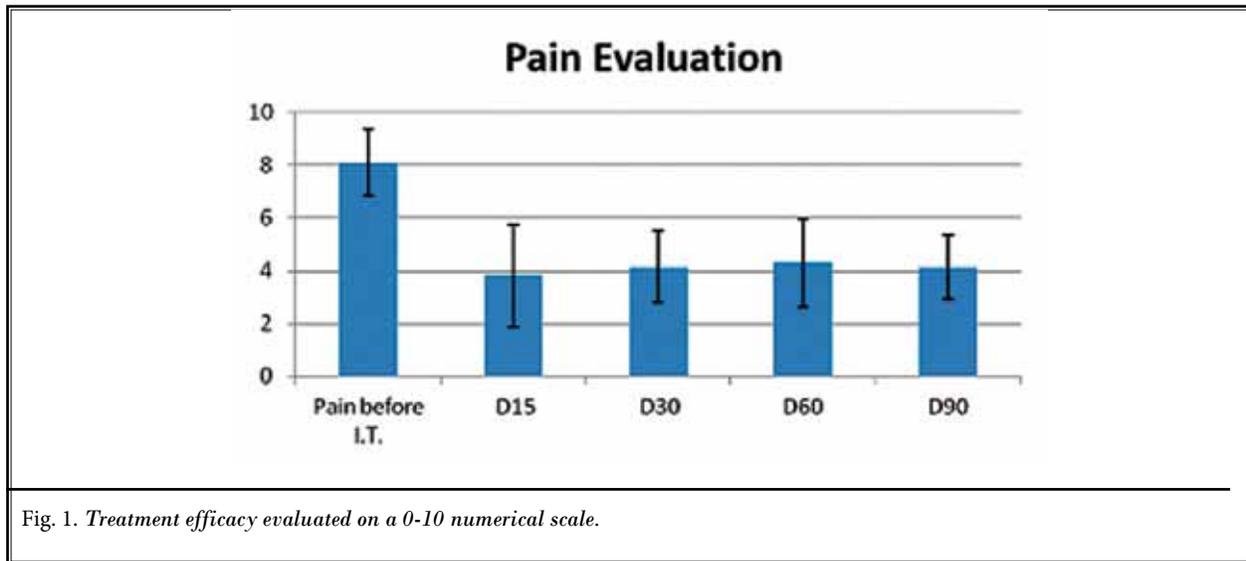
Fig. 1. *Treatment efficacy evaluated on a 0-10 numerical scale.*
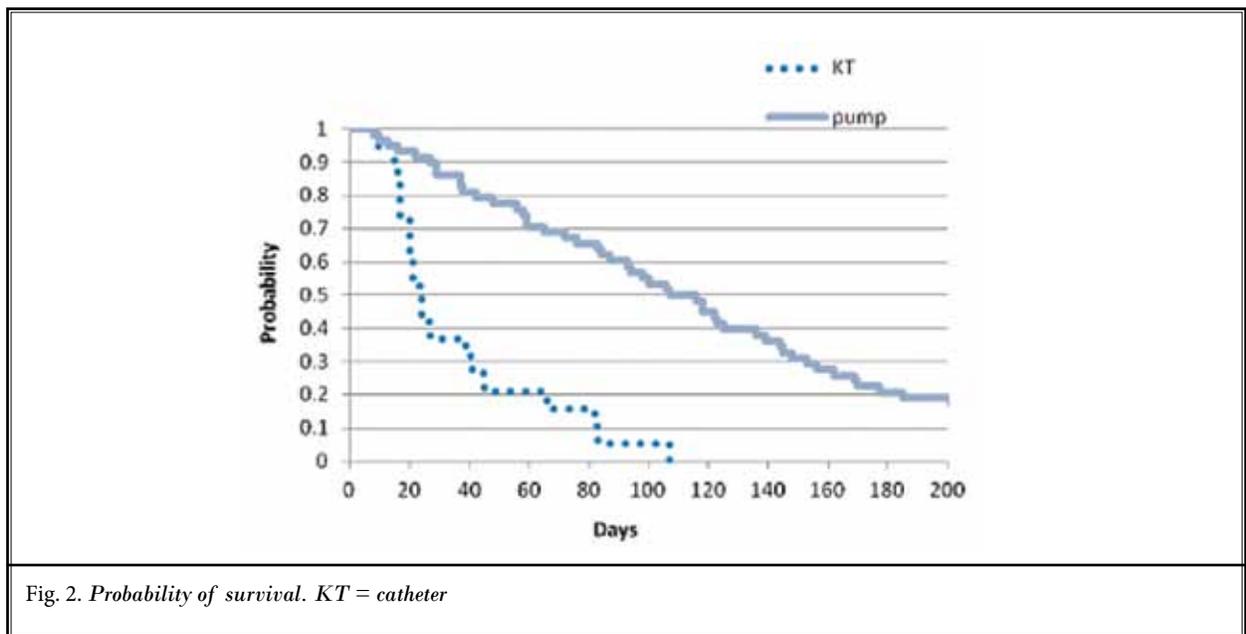
Fig. 2. *Probability of survival. KT = catheter*

Discussion

This study confirms that the high rate of serious adverse events observed in earlier studies (21,26) may be controlled using a very low starting dosage and a slow increment protocol. However, 7 (9%) of our 77 patients experienced adverse events requiring treatment discontinuation. In addition, a detailed analysis of these 7 patients indicated that the adverse events in 2 patients were not clearly related to ziconotide. Among these 7 patients, only 4 (5%) had serious (all neuropsychological) adverse events, which were ascribable to the dosage schedule in 3 of them. One patient (Adverse Event #6) received a high level of ziconotide (19 μg/d) and the other 2 patients (Adverse Events #4 and #5) received large increments.

Although the recommended starting dosage is 2.4

μg/d, one of our patients experienced a ziconotide-related adverse event when receiving the far smaller dosage of 1 μg/d. Therefore, starting ziconotide in a low dosage is mandatory, and dosage escalation must proceed in small increments of 0.25 to 0.5 μg once or twice a week. These results are consistent with the finding of the recent Italian registry (37). With a low initial daily dose and a similar slow titration protocol, no serious adverse events were observed in this study, but a higher rate of discontinuation due to adverse events (18%) was highlighted.

Definitive conclusions about mild and moderate adverse events are difficult to draw in cancer patients. Most of our patients were receiving not only other intrathecal analgesics, but also cytostatic agents, and determining the relative contributions of each drug to adverse events was extraordinarily difficult. In addition, some of the adverse events manifested as clinical symptoms of a subjective nature. Staats et al (18) reported that the rate of moderate adverse events was 97% with ziconotide and 72% with a placebo. Furthermore, determining the ziconotide dosage to be administered in mixtures by pump infusion may require complex computations that can only be performed accurately using dosage calculation software and compounding in a hospital pharmacy. These considerations may, in part, explain the higher adverse events rates in earlier work compared to our study,

Evidence-based data for using ziconotide in combination with other medications are limited (23). In our study, combining drugs did not induce previously unknown adverse events nor exacerbate previously described adverse events. Two cohort studies of intrathecal analgesia, one by Wallace et al (38) and a recent one by Alicino et al(39) suggest that ziconotide may have a morphine-sparing effect. Our study design did not permit an assessment of such an effect. Although the data from our prospective follow-up study do not constitute proof that ziconotide exerts analgesic effects, the levels of analgesia were comparable to those in earlier reports (7-8). However, a complementary study would be of interest to demonstrate a morphine-sparing effect.

The stability of ziconotide in drug mixtures is unknown, particularly during long-term clinical use (when the drug is at 37.0°C and combined with variable concentrations of other analgesics). The rate of spontaneous ziconotide degradation varies with the ziconotide concentration and with the nature and concentration of the concomitant drugs. Ziconotide stability is 90% after 60 days in the presence of clonidine but falls by

30% after 20 days in the presence of morphine (40). Stability is satisfactory in the presence of bupivacaine, with ziconotide levels greater than 90% of baseline after 45 days (40). There are no data about stability with ropivacaine. In our study the intervals between pump refills were short and the ziconotide flow rates administered were therefore probably very close to the prescribed flow rates.

Our prospective follow-up data showed a rapid, significant, and long-lasting decrease in pain intensity (48% decrease) despite the presence of progressive cancer. The efficacy of intrathecal analgesia in our study was similar to that reported in the international literature (7-8,25,41). The analgesic effect was attributable not only to ziconotide, but also to the morphine, ropivacaine, and clonidine used concomitantly.

The treatment strategy consists in using multiple intrathecal drugs that target different pain mechanisms in order to obtain additive or even synergistic effects. However, experience in patients with sufficiently long life expectancies suggests that, after a few weeks, ziconotide probably decreases the dosage requirements for the other intrathecal drugs. Ziconotide is thus emerging as a useful additional tool for the management of intrathecal analgesia. Studies in rats showed the morphine-sparing (42) and clonidine-sparing (43) effects of ziconotide, which were later replicated in human patients (25).

Ziconotide is not appropriate for emergency analgesia in cancer pain. When using ziconotide as part of a multimodal intrathecal analgesia strategy for cancer patients, stepping up the pace of the morphine or local anesthetic titration is the preferred first-line treatment. However, a suitable strategy may consist of early ziconotide initiation, in a low dosage, with the goal of improving the quality of the analgesia later on. There is a sound rationale (23) for adding ziconotide to support the effects of intrathecal morphine, as part of a multimodal intrathecal analgesia protocol (24). The risk of major adverse events is small with a low starting dosage followed by slow titration.

Conclusion

In this first clinical observational study of ziconotide conducted in France, the serious adverse event rate was lower than in earlier studies. Moderate adverse events occurred at rates similar to those reported previously. Ziconotide used in combination with other intrathecal drugs further improves the management of analgesia in patients with cancer pain that fail to respond to con-

ventional treatments. To improve the safety profile, ziconotide should be started in a low dosage (0.5 to 1 μg/d) then titrated slowly in increments of 0.5 μg/d once or twice a week. With this strategy, major adverse events are uncommon (5%). A faster pace of titration carries a risk of marked adverse events. There is a paucity of data on the use of ziconotide as recommended by panels of experts in combination with other drugs. Thus, further studies are needed, most notably to assess the stability of ziconotide in clinical practice and to evaluate the potential morphine-sparing effect.

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