

Ziconotide for treatment of severe chronic pain



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Pharmacological management of severe chronic pain is difficult to achieve with currently available analgesic drugs, and remains a large unmet therapeutic need. The synthetic peptide ziconotide has been approved by the US Food and Drug Administration and the European Medicines Agency for intrathecal treatment of patients with severe chronic pain that is refractory to other treatment modalities. Ziconotide is the first member in the new drug class of selective N-type voltage-sensitive calcium-channel blockers. The ziconotide-induced blockade of N-type calcium channels in the spinal cord inhibits release of pain-relevant neurotransmitters from central terminals of primary afferent neurons. By this mechanism, ziconotide can effectively reduce pain. However, ziconotide has a narrow therapeutic window because of substantial CNS side-effects, and thus treatment with ziconotide is appropriate for only a small subset of patients with severe chronic pain. We provide an overview of the benefits and limitations of intrathecal ziconotide treatment and review potential future developments in this new drug class.

Introduction

Chronic or persistent pain affects more than 15% of the population and is a major therapeutic challenge. For many patients, pain produces severe distress, dominating and disrupting their quality of life.^{1–3} Management of chronic pain is complex and includes pharmacological, interventional (eg, surgery), and psychophysical treatments. The first-line drug treatment option is oral administration of analgesics, such as non-steroidal anti-inflammatory drugs (NSAIDs), opioids, or, for neuropathic pain, specific antidepressants or anticonvulsants.^{4,5} However, in 10–30% of patients, oral drug administration fails to achieve adequate and sustained pain relief,⁶ as do other systemic (eg, transdermal or parenteral) routes of drug administration. Moreover, serious adverse events can restrict use of systemic analgesics.

When pain relief is insufficient or side-effects are intolerable from systemically administered analgesics, increasingly invasive strategies can be used. These advanced interventional approaches include nerve blocks, surgical interventions, or spinal or intrathecal injection of drugs such as morphine, hydromorphone, fentanyl, clonidine, or local anaesthetics, given alone or in combination.⁷ A novel approach for intrathecal pain management is the administration of ziconotide—a synthetic conopeptide. This drug is the first member of a new class of analgesics that selectively target N-type voltage-sensitive calcium channels. Ziconotide was approved by the US Food and Drug Administration (FDA) in December, 2004, for intrathecal treatment of severe chronic pain in patients for whom such therapy is warranted and who are intolerant of or refractory to other treatments, such as systemic analgesics, adjunctive therapies, or intrathecal morphine. In February, 2005, ziconotide was approved by the European Medicines Agency (EMA) for severe chronic pain in patients needing intrathecal analgesia. An expert panel⁸ recommended ziconotide, beside morphine and hydromorphone, as a first-line drug for intrathecal polyanalgesic therapies. We summarise the clinical pharmacology, efficacy, and toxicity of ziconotide and

discuss possible future developments associated with this new drug class.

Pharmacology of ziconotide

Conopeptides (also called conotoxins) are a class of more than 70 000 compounds derived from about 700 species of marine predatory cone snails (genus *Conus*).^{9,10} Every *Conus* species contains 100–200 small venom peptides, which are synthesised in and secreted from a venom duct (figure 1). During past decades, study of conopeptides has identified a great diversity of pharmacological functions and uses. Pharmacological targets of conopeptides include several different families of ion channels (eg, calcium, potassium, and sodium), receptors (eg, nicotinic, α -adrenergic, and serotonin), and transporters (eg, norepinephrine), providing a rich source for drug development.^{10,13}

Ziconotide (previously called SNX-111) is the synthetic form of the hydrophilic conopeptide ω -MVIIA from the venom of the Pacific fish-hunting snail, *C magus* (figure 1).^{14,15} Its pharmacological activity was identified in mice that received an intracranial drug injection and were observed for unusual symptoms. In these mice, a purified fraction of the *C magus* venom containing ω -MVIIA elicited a characteristic persistent tremor that developed a few minutes after injection, showing that the conopeptide is neuroactive in mammals.¹¹ Later, researchers^{16,17} established that ω -MVIIA binds reversibly and with high affinity to a subset of voltage-sensitive calcium channels (N-type channels), whereas other types of voltage-sensitive calcium channels are not affected by ω -MVIIA. Generally,

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Search strategy and selection criteria

We searched the PubMed database and the Cochrane Library with the terms “ziconotide”, “SNX-111”, “MVIIA”, “intrathecal pain therapy”, or “N-type calcium channel and pain”, and included all reports published until Nov 30, 2009.

Publications from the past 5 years were preferentially selected. We also searched the reference lists of articles we identified and selected those we judged relevant.

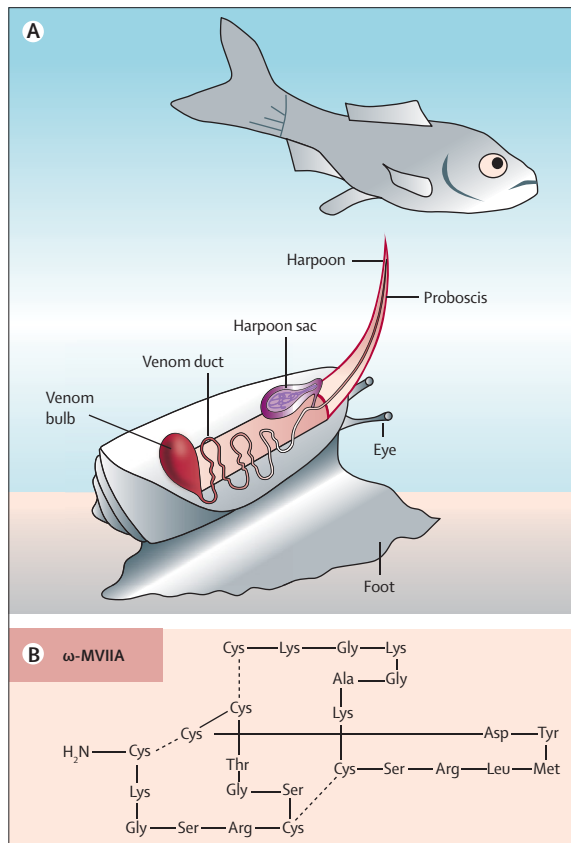


Figure 1: *Conus magus*

(A) Fish-hunting snail *Conus magus* produces venom to subdue its prey. Venom is synthesised in a long tubular duct from which it is squeezed by muscular bulb and injected into prey through a hollow radular tooth. These disposable teeth are like barbed needles, and thus are difficult for prey to dislodge. (B) Amino acid sequence and disulfide bridging pattern (shown as dotted lines) of ω -MVIIA, a component of the *C magus* venom, are depicted. Synthetic peptide ziconotide corresponds to structure of conopeptide ω -MVIIA from *C magus*.^{11,12}

voltage-sensitive calcium channels are divided into L, N, P/Q, R, and T types on the basis of their electrophysiological and pharmacological properties (figure 2).

Different types of calcium channels have different cellular and subcellular distributions, and are associated with distinct functions. For example, L-type channels, targets of the classical cardiovascular drugs verapamil, diltiazem, and nifedipine, serve as the main calcium source for contraction of cardiac and smooth muscle cells. By contrast, N-type channels are localised at presynaptic terminals of neurons, and calcium entry through these channels is needed for neurotransmitter release. Notably, N-type calcium channels are expressed at high density on the central (ie, presynaptic) terminals of primary afferent neurons that terminate in the dorsal horn of the spinal cord.²⁰ This area is important for processing pain (figure 3). On nociceptor activation in the periphery, excitatory transmitters such as glutamate and neuropeptides are released in the dorsal horn, and, in turn, neurons in the spinal cord are stimulated, modulating the nociceptive transmission

in a complex way and conveying the information to supraspinal brain areas. Thus the dorsal horn of the spinal cord acts as a filter at which millions of peripheral signals arrive and are modulated before being sent to supraspinal sites that establish the final pain response, and add an affective and emotional context to nociception (figure 3).^{21,23}

After binding of ziconotide on N-type calcium channels in the dorsal horn, calcium influx into the nerve terminals is blocked, thereby reducing release of pain-relevant neurotransmitters, such as glutamate and neuropeptides, from the primary afferent nerve terminals into the synaptic cleft (figure 3). On the basis of this inhibiting effect of ziconotide at the first synapse in the nociceptive system, ziconotide might effectively reduce pain by interruption of spinal transmission of pain information. Notably, findings from animal studies show that expression of N-type calcium channels is upregulated in the dorsal horn after peripheral tissue inflammation or nerve injury.^{24,25} This finding suggests that N-type calcium channels have an especially important role in nociceptive processing under pathological conditions. These events might contribute to the analgesic action of ziconotide in chronic pain.¹⁸ However, we should take into account the wide distribution of N-type calcium channels throughout the CNS.^{15,20} For example, these channels are associated with hippocampus-dependent learning and memory and some forms of long-term potentiation.²⁶ Thus supraspinal neurological side-effects, such as dizziness, confusion, ataxia, abnormal gait, memory impairment, nystagmus, or hallucinations, can develop after ziconotide is given intrathecally if sufficient amounts move rostrally up the neuraxis and reach the brain (figure 4).

Notably, findings show that gabapentin and pregabalin, which have proven clinical efficacy in the treatment of neuropathic pain,⁴ also act through modulation of calcium channels. Both drugs bind at calcium-channel $\alpha 2\delta$ subunits,²⁷ which have an auxiliary function for several calcium-channel types, (figure 2) and are upregulated in the dorsal horn after peripheral nerve injury.²⁸ After binding of gabapentin and pregabalin, release of neurotransmitters is reduced. In studies with [³H]gabapentin autoradiography, mainly $\alpha 2\delta$ subunits of both N-type and P/Q-type calcium channels in the spinal dorsal horn and in the forebrain are affected.^{19,29} Hence, voltage-gated calcium channels are novel therapeutic targets for pain control, and are inhibited by gabapentin or pregabalin and ziconotide, although modulation of channel subunits differs between both drug classes.

Analgesic efficacy of ziconotide

In a broad array of animal models of pain, intrathecal ziconotide produced strong antinociceptive effects, and was at least ten times more potent than was intrathecal morphine.^{14,30,31} However, so far the analgesic efficacy data for ziconotide in human beings are mainly based on

three randomised, double-blind, placebo-controlled trials in patients who had severe chronic pain refractory to conventional treatments (table). Two trials^{6,32} used a fast titration schedule with ziconotide and one trial a slow one.³³ At the fast-dose titration rates, ziconotide had a highly significant analgesic efficacy compared with placebo ($p < 0.001$). In one study,⁶ ziconotide treatment decreased the Visual Analogue Scale of Pain Intensity scores by 53.1% (35.0% placebo-adjusted) in patients with cancer (breast, lung, colorectal, prostate, myelogenous or lymphatic, skin, or other cancer) or AIDS, who had severe pain despite a regimen of systemic or intrathecal analgesics. In the other,³² with fast-dose titration, visual analogue pain scores were reduced in the ziconotide group by 30.7% (24.8% placebo-adjusted) in patients with chronic non-malignant pain of neuropathic or non-neuropathic origin and unsatisfactory responses to systemic opioid therapy. However, in both studies, many patients developed serious cognitive and neuropsychiatric adverse events which were persistent, necessitated admission to hospital, and could not be excluded as being causally related to three deaths.³⁴

The study³² with a slow rate of dose titration was in patients with severe chronic pain of any cause (neuropathic pain was the most common disorder and failed back surgery was the most common cause) that was inadequately controlled by systemic or intrathecal analgesics, or both. Occurrence and severity of adverse events were greatly reduced compared with the fast rate of titration (table), but the average pain relief obtained with ziconotide was only moderate (14.7%, 7.5% placebo-adjusted, $p = 0.036$).³³ Notably, in a small subset of these otherwise treatment-refractory patients with severe chronic pain, slowly titrated ziconotide produced complete pain relief and improved quality of life.³⁴ Therefore substantial benefits can arise at the individual level.

Because of the serious adverse events in clinical trials with fast titration of ziconotide, only the regimen of slow titration was approved by the FDA and EMEA. Initial doses should be low and not exceed 2.4 μg per day (0.1 $\mu\text{g}/\text{h}$). The optimum dose should be slowly uptitrated on an individual basis at intervals of no more than two to three times times per week. The recommended maximum dose (by day 21) is 19.2 μg per day in the USA and 21.6 μg per day in Europe.³⁵ These recommendations correspond to the actual and the maximum dose as per protocol, respectively, used in the clinical trial with the slow-titration regimen. However, in trials,³⁶⁻³⁸ some patients who tolerated the recommended maximum dose after slow titration during 3-4 weeks also tolerated high doses of intrathecal ziconotide. The reasons for this result are unknown.

During intrathecal ziconotide treatment, clinicians need to be aware of the lag for the onset and offset of analgesia and adverse events. This lag probably results from the fact that the peptide ziconotide is a large molecule compared with non-peptidergic drugs, and is

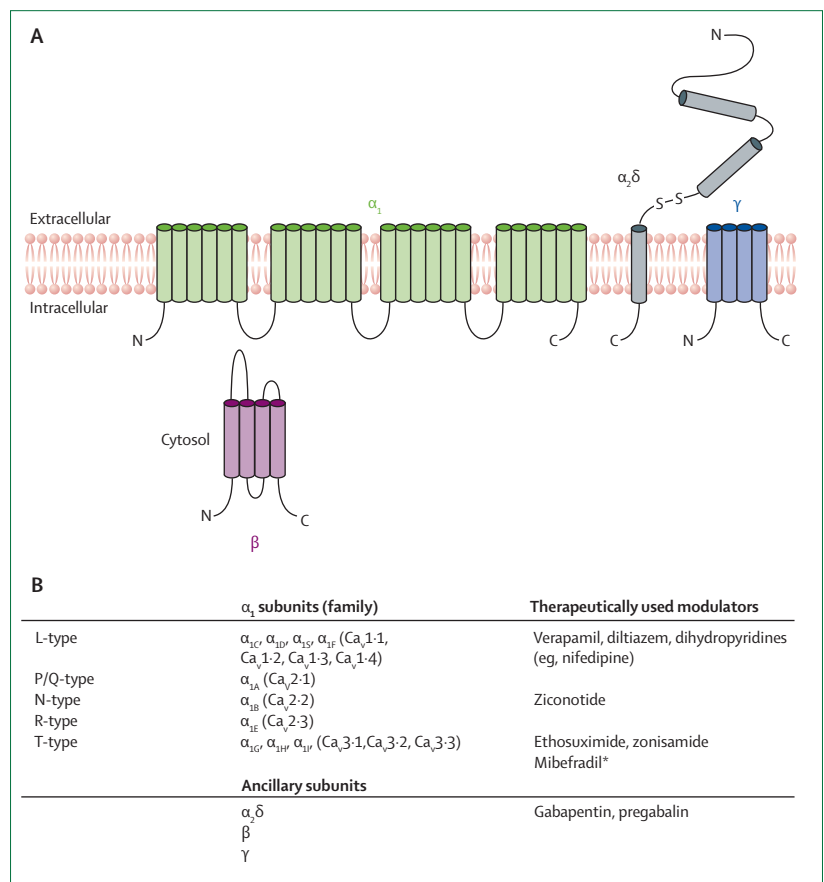


Figure 2: Voltage-sensitive calcium channels and pharmacologically relevant ligands by channel class

(A) Voltage-sensitive calcium channels permit calcium entry into cells under conditions of membrane depolarisation. They contain large monomeric α_1 -subunit of four domains joining together to form the channel pore. α_1 -subunits further establish channel permeation properties and contain binding sites for many pharmacologically relevant ligands. Most voltage-gated calcium channels contain ancillary $\alpha_2\delta$, β , and γ subunits, modulating the membrane insertion of the α_1 -subunit and voltage-dependence and kinetic properties of channel gating. (B) Ten different genes encoding α_1 -subunits of voltage-gated calcium channels have been identified so far. On basis of sequence homology, channel proteins cluster into three families, Cav1, Cav2, and Cav3, which are further divided into types L, N, P/Q, R, and T. For every gene product, many splice variants exist, sometimes displaying tissue-specific localisation.^{18,39} *Withdrawn from the market because of serious drug interactions.

highly hydrophilic, meaning that it moves only slowly from the cerebrospinal fluid through the parenchyma to its target site in the dorsal horn of the spinal cord.³⁹ Findings from microdialysis studies⁴⁰ in rat brains with radioiodinated ziconotide confirmed its slow penetration into tissues, because detectable ziconotide diffused only up to 1 mm from the dialysis probe into tissue during 2 h of perfusion. Thus onset of pain relief after intrathecal ziconotide can be delayed 2-4 h, maximum effects might develop after 8-12 h, and analgesic effects can last up to 48 h after discontinuation.^{34,41}

Toxicity of ziconotide

Adverse events with approved dose

Corresponding to the wide distribution of N-type calcium channels in brain tissues, the most often reported side-effect of ziconotide affects the CNS (table). In the placebo-controlled trial³³ with FDA-approved and

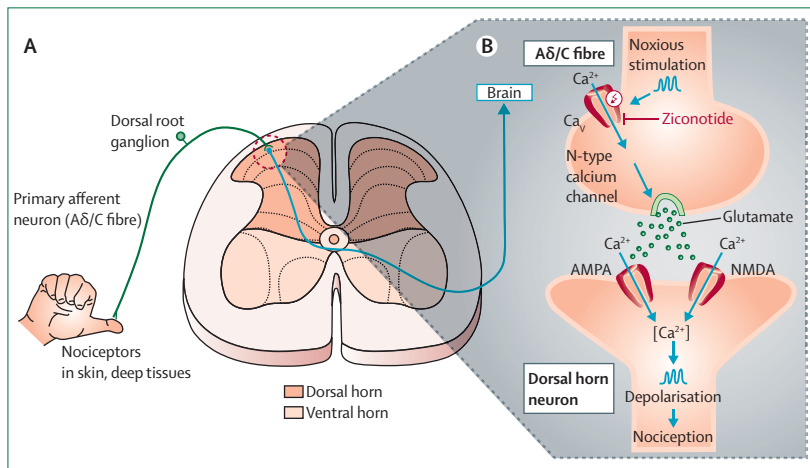


Figure 3: Mechanism of action of ziconotide

(A) Spinal cord dorsal horn is first synaptic processing station for pain. Stimulation of nociceptors activates A δ and C fibres, which transmit action potentials to their terminals in superficial dorsal horn of spinal cord where first synaptic transmission arises leading to activation of spinal cord neurons and forwarding of excitation in contralateral spinothalamic tract to brain, where it is received as pain.²⁷ (B) Release of neurotransmitters from A δ and C fibres in superficial dorsal horn of spinal cord is predominantly (not exclusively) controlled by N-type calcium channels.²⁷ These channels allow calcium to enter presynaptic terminals when membrane is depolarised, thereby triggering release of neurotransmitters, such as glutamate, into synaptic cleft. Binding of ziconotide on N-type calcium channels blocks calcium permeability, disrupting calcium influx into presynaptic terminals and release of neurotransmitters. By this mechanism, intrathecally administered ziconotide is able to effectively inhibit pain transmission in spinal cord. AMPA= α -amino-3-hydroxy-5-methyl-4-isoxazole-propionate receptor. NMDA=N-methyl-D-aspartic acid receptor.

EMA-approved low starting doses and slow-titration schedules, patients assigned to ziconotide had a greatly increased risk of dizziness (47.3% vs 13.0% with placebo), confusion (17.9% vs 4.6%), ataxia (16.1% vs 1.9%), abnormal gait (15.2% vs 1.9%), memory impairment (11.6% vs 0.9%), nystagmus (8.0% vs 0%), hallucinations (7.1% vs 0%), and vertigo (7.1% vs 0.0%). Nausea (41.1% vs 30.6%) and vomiting (15.2% vs 13.0%) also arose frequently, but did not substantially differ from placebo. Most adverse events were mild to moderate in severity, and only a few patients (2.4%) discontinued treatment. Adverse events mostly developed with the lag of onset and offset, probably resulting from the slow diffusion of ziconotide in neural tissue. The median time to onset for these adverse events ranged from 3.0 to 9.5 days, whereas the time to resolution was mostly up to 2 weeks after ziconotide discontinuation.³³

Toxic effects of high doses

Adverse events that occurred in the two placebo-controlled trials with high starting doses and fast titration (which has not been approved by the FDA and EMA) are shown in the table. Serious adverse events were reported in 38.1% of all patients, although many of these were associated with comorbid disease. Those events regarded as treatment-related developed in 14% of all patients, with confusion (3.5%) and dizziness (1.1%) being the most frequent.³⁵ Other serious side-effects reported in trials and documented in case reports included prolonged delirium and agitation, unresponsiveness, nystagmus, ataxia, bradycardia, orthostatic hypotension, periods of

apnoea, and urinary retention.³⁴ Such events are usually manageable, but can take weeks to months to resolve, and in some instances needed prolonged stays in hospital and intensive care monitoring.^{14,34,42} Moreover, ziconotide can cause or worsen depression, increasing risk of suicide in susceptible patients.^{12,40} Therefore patients with pre-existing psychiatric disorders should not be treated with ziconotide.

Rises in creatinine kinase

Some patients treated with ziconotide had non-progressive rises in serum concentrations of creatine kinase muscle isoenzyme (CK-MM). CK concentrations three times or more the upper limit of normal were reported in 11% of patients during (mostly open-label) clinical studies.³⁴ Although this change was harmless in most patients, one case of symptomatic myopathy and two cases of acute renal failure associated with rhabdomyolysis were reported. Other disease processes or concomitant drugs probably caused the increased creatinine kinase concentrations. However, attribution to ziconotide therapy cannot be excluded and thus serum creatinine kinase should be monitored during ziconotide treatment.¹⁴ Moreover, other drugs that increase creatinine kinase concentrations (eg, statins) might interact with ziconotide.

Intrathecal catheter-associated complications

Intrathecal delivery is one of the last choices, according to guidelines for pharmacological pain management,⁴¹ and is associated with its own risks of device-associated infection and complications. Accordingly, a few cases of meningitis developed after ziconotide was given intrathecally. However, the occurrence of meningitis was similar to that reported with other intrathecal analgesics, and was more often noted when an external infusion system was used than with an internal subcutaneously implanted pump,⁴³ suggesting that ziconotide itself does not increase risk of meningitis. Because of the general risks associated with intrathecal delivery, ziconotide is contraindicated in cases of concomitant treatment or medical disorders that would render intrathecal delivery hazardous (eg, uncontrolled bleeding diathesis, infection at the microinfusion injection site, or spinal canal obstruction).

Intrathecal delivery is further contraindicated in combination with intrathecal chemotherapy, because of increased risks of infections after repeated instrumentation of the subarachnoid space, and co-administration of chemotherapy with an indwelling intrathecal catheter possibly alters the dynamics of flow of cerebrospinal fluid, rendering the pharmacokinetics of ziconotide in cerebrospinal fluid unpredictable.^{34,35} Despite these general obstacles associated with this type of treatment, the benefits of intrathecal drug-delivery systems for treatment of chronic pain are obvious. An equianalgesic effect might be reached at doses about 100 times lower than with systemic administration, greatly decreasing dose-related side-effects. Continuous drug delivery further

eliminates fluctuations in drug concentrations, which are inevitable with oral or parenteral dosing, and also reduces risk of abuse or mishandling of analgesics. Additionally, chemical neuromodulation is testable, adjustable, and reversible, and usually not associated with longlasting consequences after discontinuation.

Immunological reactions

Risk of immunological reactions to intrathecal ziconotide in patients seems to be low. No raised concentrations of ziconotide-specific IgE or IgG were reported³⁵ in 58 patients after an intravenous dose of ziconotide for 72 h, who were sampled 3 months later, or in 41 patients who received intrathecal doses for at least 3 months, most of whom had an off-dose period before further challenge. Accordingly, so far no evidence of hypersensitivity or anaphylaxis in response to intrathecal ziconotide was noted in another clinical trial³⁷ in which patients were permitted to temporarily discontinue ziconotide therapy and later restart it. However, infrequent immunological reactions cannot be excluded on the basis of these data.

Typical opioid-induced adverse events

No substantial systemic endocrine, haematological, hepatic, renal, or metabolic side-effects have been reported for ziconotide so far. Typical adverse events reported with opioids (ie, respiratory depression, tolerance, and dependence), or spinal catheter-tip granulomas that might arise during intrathecal morphine or hydromorphone treatment have not yet been recorded for ziconotide. Moreover, by continuous intrathecal infusion, ziconotide seems to maintain its analgesic efficacy for months and permanent adverse sequelae are apparently not caused.⁴³ This safety profile has been confirmed in an open-label trial in 644 patients with severe chronic pain treated with intrathecal ziconotide for up to 1215 days (≥ 360 days in 119 patients), giving a total exposure time of 351 patient-years.³⁷ However, data about the safety of ziconotide remain scarce and further investigation is needed to assess the long-term risks and benefits. Notably, in the few published studies with small patient numbers, rare adverse events might be undetected because study populations were too small.

Management of intolerable adverse events

Ziconotide toxicity seems to be related to rate of infusion, and is reversible after discontinuation.⁴⁴ Hence, most side-effects can be managed through dose reduction or symptomatic treatment. If an intolerable adverse event develops, ziconotide can be immediately discontinued without withdrawal effects.³³ However, because of slow tissue-diffusion and resultant lag for the offset of drug effects, ziconotide-induced adverse effects generally resolve only slowly and in some instances can persist for several weeks. Notably, so far, there is no known pharmacological antagonist for the toxic effects of

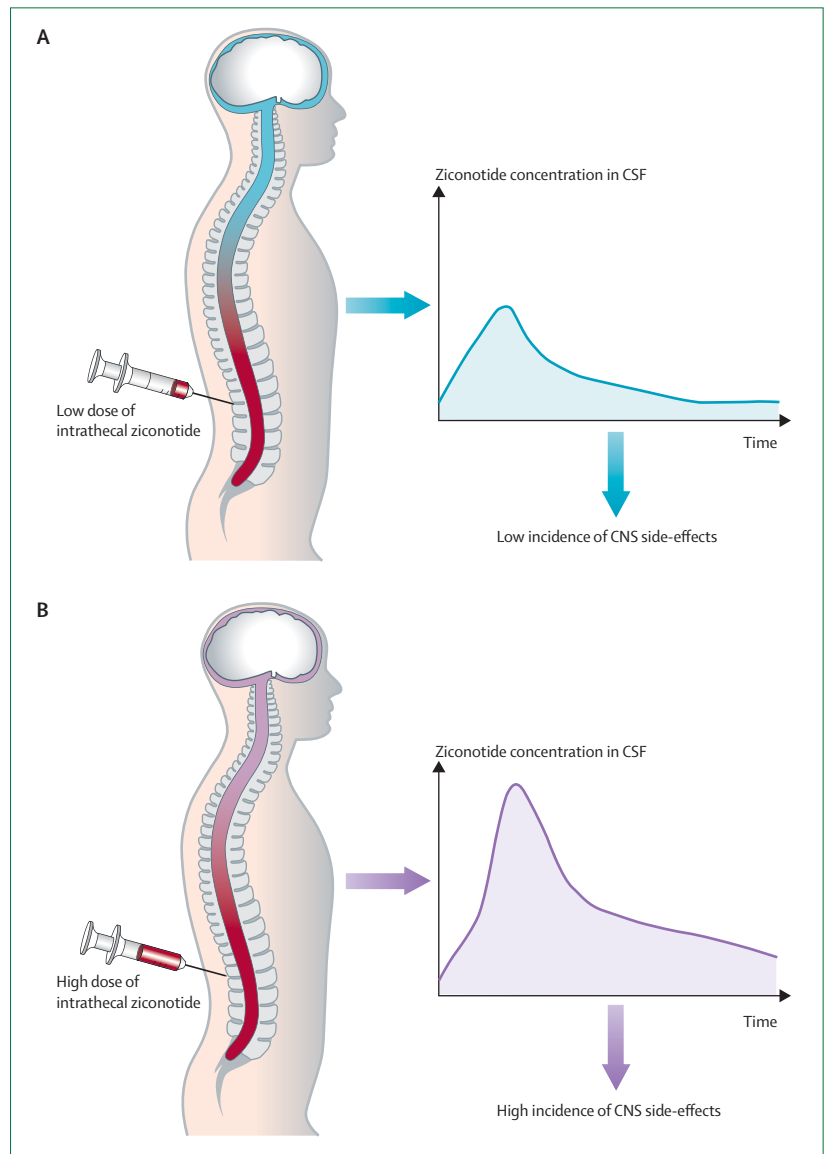


Figure 4: Incidence of CNS side-effects during intrathecal ziconotide treatment

After administration of low doses of ziconotide, occurrence of CNS side-effects is low (A), whereas it is high after administration of high doses (B). Co-administered drugs interacting with clearance of ziconotide from cerebrospinal fluid might shift situation (A) to (B), or vice versa. CSF=cerebrospinal fluid.

ziconotide. Although overdose with classical cardiovascular calcium-channel blockers can be treated with intravenous calcium or glucagon, we do not know whether these substances would be useful in treatment of unwanted CNS side-effects of ziconotide, even if an intracellular calcium deficit arose within the CNS.

Switch from intrathecal opioids to intrathecal ziconotide

Ziconotide is approved as intrathecal monotherapy, but some challenges might arise when patients pretreated with intrathecal opioids are converted to ziconotide alone. Maintenance of adequate analgesia and management of opioid withdrawal could be difficult. Intrathecal opioid

| | Staats et al (2004) ⁶ | Wallace et al (2006) ³² | Rauck et al (2006) ³³ |
|--|--|---|--|
| Titration schedule | Fast* | Fast* | Slow† |
| Treatment duration | 10–11 days | 6–11 days | 21 days |
| Population | Patients with pain (VASPI score \geq 50 mm) associated with cancer or AIDS | Patients with severe chronic pain (VASPI score \geq 50 mm) of non-malignant cause | Patients with severe chronic pain (VASPI score \geq 50 mm) of any cause |
| Number of patients given Z/P | 71/40 | 169/86 | 112/108 |
| Pain reported | | | |
| Neuropathic (Z/P) | NR | 75.7%/76.7% | 75.9%/71.3% |
| Non-neuropathic (Z/P) | NR | 13.0%/12.8% | 35.7%/32.4% |
| Mean baseline VASPI score for Z/P group (mm) | 74/78 | 80/77 | 81/81 |
| Mean decrease in VASPI scores after Z/P | 51.4%/18.1% (p<0.001) | 31.2%/6.0% (p<0.001) | 14.7%/7.2% (p=0.036) |
| Adverse events | | | |
| Nervous system‡ | Dizziness (50.0%)§; nystagmus (45.8%); somnolence (23.6%)§; confusion (20.8%)§; abnormal gait (12.5%)§ | Dizziness (53.5%)§; nystagmus (40.0%)§; abnormal gait (27.1%)§; somnolence (12.4%)§; confusion (11.8%)§; amblyopia (10.6%)§ | Dizziness (47.3%)§; somnolence (22.3%)§; confusion (17.9%)§; ataxia (16.1%)§; abnormal gait (15.2%)§; memory impairment (11.6%)§ |
| Digestive system‡ | Nausea (29.2%)§; vomiting (18.1%)§; constipation (12.5%)§ | Nausea (48.8%)§; constipation (18.2%)§; vomiting (14.1%)§ | Nausea (41.1%); diarrhoea (18.8%); vomiting (15.2%) |
| Other systems‡ | Fever (25.0%)§; postural hypotension (23.6%)§; urinary retention (18.1%)§; headache (15.3%)§ | Pain (16.5%)§; headache (16.5%)§; urinary retention (15.3%)§; postural hypotension (11.8%)§ | Asthenia (22.3%); headache (15.2%); pain (10.7%) |

Z=ziconotide, P=placebo, NR=not reported. *Fast titration: initial dose 9–6 µg per day, a dose increase 7–14 times per week, maximum dose per protocol 57.6 µg per day, time to maximum dose 5–6 days. †Slow titration: initial dose 2.4 µg per day, a dose increase 2–3 times per week, maximum dose per protocol 21.6 µg per day, time to maximum dose 21 days. ‡Adverse events reported in >10% of patients treated with ziconotide. §Occurred with significantly greater frequency with ziconotide than with placebo (p<0.05).

Table: Overview of randomised placebo-controlled clinical studies with ziconotide

infusion should be gradually tapered off over a few weeks and replaced with oral opioids in an attempt to mitigate withdrawal symptoms.⁴² However, despite use of oral opioids, some patients become emotionally distressed and develop psychological symptoms during the conversion process, express misgivings about ziconotide, and wish to discontinue treatment with ziconotide. A therapeutic option can be education about opioid withdrawal, psychological interventions such as cognitive-behavioural coping strategies or relaxation techniques, and adjunct drugs to reduce anxiety and depression. A multimodal approach for these patients, with close contact with the treating physicians and good psychological support, is strongly recommended. Notably, in two studies,^{38,45} additive analgesic effects were observed when intrathecal ziconotide was combined with intrathecal morphine, confirming previous studies in animals.^{15,46} This combination, however, has not yet been approved by the FDA or EMEA.

Distribution, metabolism, elimination, and drug interactions

Ziconotide needs to be administered intrathecally via continuous infusion (panel). After administration, ziconotide's mean cerebrospinal fluid volume of distribution is close to the total human volume of cerebrospinal fluid (about 140 mL), suggesting that intrathecal ziconotide is nearly exclusively distributed in the cerebrospinal fluid.^{34,43,47} Data for the pharmacokinetics of ziconotide in cerebrospinal fluid after intrathecal administration are scarce, because of the need to both

infuse the drug and sample cerebrospinal fluid through the same catheter, because insertion of two catheters might disturb kinetics, and for ethical reasons one catheter is used to keep the risk of dural puncture to a minimum. Ziconotide seems to not be metabolised in the cerebrospinal fluid and to be 100% bioavailable after intrathecal administration, and it shows linear pharmacokinetics in the cerebrospinal fluid. After one 1-h intrathecal infusion of 1–10 µg ziconotide, C_{max} concentrations in the cerebrospinal fluid ranged from 16 to 132 ng/mL, as assessed 2 h after the start of infusion.^{44,47}

The main mechanism for ziconotide's clearance from the cerebrospinal fluid (terminal half-life 4.6 h) is transport into the systemic circulation, where the drug is rapidly degraded by peptidases and proteases at many sites of the peptide. After several days of continuous infusion, only low concentrations of ziconotide, if any, have been detected in plasma.^{34,48} However, the proteolytic pathway of ziconotide in human beings is not known, and biological activity of the degradation products has not been assessed. Thus, theoretically, we have to keep in mind that unknown degradation products of ziconotide might be antigenic in some patients.

Unfortunately, pharmacokinetic drug–drug interaction studies have not yet been done. However, in some circumstances, intrathecal concentrations of ziconotide could possibly increase when ziconotide is combined with other drugs, resulting in increased toxicity (figure 4). Because diuretics can decrease the turnover of ziconotide, the risk of side-effects might be increased during concomitant use of ziconotide and diuretics,

although evidence for this interaction is not consistent.³¹ Because of the low plasma concentrations after intrathecal administration, low plasma-protein binding (about 50%), and the absence of biotransformation by cytochrome P450 enzymes and other phase I biotransformation processes, ziconotide is not expected to interact in plasma pharmacokinetically with other drugs. Thus dose reduction is probably not needed in response to renal or hepatic failure, unless a specific organ insufficiency affects cerebrospinal fluid clearance of ziconotide.^{14,43,47}

Data about pharmacodynamic drug interactions are also scarce. Because N-type calcium channels are widely distributed in the CNS, pharmacodynamically based interactions with drugs that affect transcellular calcium movement or N-type calcium channels could theoretically exist.⁴¹ Concomitant use of CNS depressants, such as sedatives, antiepileptics, and neuroleptics, increase risk of CNS adverse events.³⁴

Future developments

Intrathecal ziconotide can reduce pain and improve quality of life in patients with severe chronic pain. However, its efficacy is not predictable, the responder rates for pain relief vary greatly, and side-effects develop at a high interindividual and intraindividual variability. A valid selection process for subgroups of patients who might benefit most from intrathecal ziconotide is needed, but available data are insufficient. Because chronic pain has many causes, to elucidate which types of pain respond to ziconotide therapy best will be important. Findings from a meta-analysis^{34,35} of the efficacy data from three placebo-controlled trials show that ziconotide has a therapeutic effect in both neuropathic and non-neuropathic pain subgroups, with possibly a better response in neuropathic pain (placebo-adjusted mean percentage change in VASPI scores from baseline 16.8% and 7.9%, respectively). Efficacy of ziconotide in patients with neuropathic pain was also reported in a recent meta-analysis⁴⁹ of five preclinical and 23 clinical studies. Additionally, data from case reports suggest ziconotide might effectively provide pain relief for complex regional pain syndrome,^{50,51} and perhaps some intractable visceral pain states.⁵² In view of the concomitant diseases of patients with pain, ziconotide might be suited for those who are not ideal candidates for opioid therapy, including patients with active substance-abuse issues, obstructive sleep apnoea, and substantial lung disease or reduced pulmonary reserve.⁵² Further investigation is needed to identify subgroups of patients who might benefit from intrathecal ziconotide and to assess this drug's true place in therapy.

So far, ziconotide's dose-limiting adverse events and route of administration restrict the use of ziconotide to a small subpopulation of patients with chronic pain.²⁷ Hence a substantial improvement might be the development of orally available, small molecule N-type calcium channel blockers. When administered intravenously, ziconotide has poor penetration across the

Panel: Administration of ziconotide

For intrathecal administration, a programmable implanted variable-rate microinfusion device or external microinfusion device and catheter needs to be used. Ziconotide is available in vials of 25 µg/mL or 100 µg/mL. Dilution, if needed, should be done aseptically with preservative-free sodium chloride (0.9%) solution. Concentration of solution in infusion pump should be not lower than 5 µg/mL in external pump and 25 µg/mL in internal pump. Ziconotide's concentration in naive pump might be reduced because of adsorption onto surfaces of the device, or dilution by residual space of the device, or both. After first use, reservoir should therefore be emptied and refilled after 14 days. Subsequently, pump should be emptied and refilled every 60 days.

blood-brain barrier and produces profound sympatholytic effects that result in orthostatic hypotension. Additionally, dizziness, sinus bradycardia, rhinitis, and nausea have been described⁵³ after intravenous administration of ziconotide. We hypothesise that these adverse events and those observed during intrathecal ziconotide treatment could also develop if small molecules with similar pharmacological properties to those of ziconotide were administered orally. Thus orally available N-type calcium blockers might cause even more side-effects than does intrathecal ziconotide. However, findings from several studies are encouraging in this respect. Notably, different subtypes of N-type calcium channels might exert different functions in nociception.⁵⁴ There are alternatively spliced messenger RNAs yielding N-type calcium channels with distinct neuronal localisations and, perhaps, functional properties.¹³ An especially interesting splice variant (encoded by exon 37a) is expressed only in sensory neurons and is abundant in nociceptive neurons. This fact raises the possibility that targeting this splice variant with a specific drug might selectively inhibit N-type-channel-mediated transmission of pain signals.^{18,54,55}

Moreover, voltage-sensitive ion channels exist in several discrete biophysical states (eg, open, closed or resting, and inactivated) that presumably show distinct time-dependent and voltage-dependent conformations. The block induced by ziconotide develops in all three states and little evidence of frequency or voltage dependence was identified. Hence novel state-dependent N-type channel blockers might potentially improve the therapeutic index above that of ziconotide.^{31,56} Another aspect that remains to be elucidated comes from the characterisation of three different strains of knockout mice that have an absence of N-type channel activity. These mice had reduced pain behaviour in models of inflammatory and neuropathic pain, but few adverse physiological consequences although N-type channels are widely distributed in the CNS. By contrast, the intrathecal injection of ziconotide is associated with

many CNS adverse events. Therefore ziconotide might possibly interact with other targets, in addition to N-type calcium channels, that have not been identified yet.³¹ If this assumption is true, further selective N-type channel blockers would have an improved risk–benefit profile.

However, there is no doubt that ziconotide serves as model compound for a new class of drugs. Several novel small molecule blockers of N-type calcium channels are being developed.⁵⁷ Some have antinociceptive activity in animal models of pain after oral administration and seem to have pharmacological properties that are partly distinct from those of ziconotide, which might be because of splice variant or biophysical channel-state selectivity.^{15,58–65} Their development might offer new perspectives in the management of pain.

Conclusions

Intrathecal administration of ziconotide is a novel and promising option for treatment of severe chronic pain when other pharmacological and non-pharmacological therapies have been exhausted. Advantages of this new drug include its efficacy for various pain disorders, absence of tolerance developing for the drug, and the potentially synergistic analgesic effects when combined with other analgesics. However, use of ziconotide is restricted by several obstacles including the need for intrathecal administration, the narrow therapeutic index attributable to important CNS adverse events, the lag for the onset and offset of analgesia and side-effects, the low response rates, and the absence of a validated selection process to identify subgroups of patients who have a high benefit-to-risk ratio. Although the treatment decision is associated with several challenges, ziconotide is successful and effective in a small subpopulation of patients with pain. The molecular diversity of N-type calcium channels offers the possibility that new drugs might overcome these difficulties. Hence development of orally bioavailable small-molecule blockers of N-type calcium channels has begun, with ziconotide paving the way for a new generation of effective analgesics.

Contributors

AS undertook the literature search, selected relevant reports, designed the figures, and wrote the first draft of the report; GG initiated the project, designed figures, and edited the report and the figures. JL and RF contributed to writing of the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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