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Future Directions for Intrathecal Pain Management: A Review and Update From the Interdisciplinary Polyanalgesic Consensus Conference 2007

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ABSTRACT

Background. Expert panels of physicians and nonphysicians, all expert in intrathecal (IT) therapies, convened in the years 2000 and 2003 to make recommendations for the rational use of IT analgesics, based on the preclinical and clinical literature known up to those times, presentations of the expert panels, discussions on current practice and standards, and the result of surveys of physicians using IT agents. An expert panel of physicians and nonphysicians has convened in 2007 to update information known regarding IT therapies and to update information on new and novel opioid and nonopioid analgesic compounds that might show promise for IT use. **Methods.** A review of preclinical and clinical published relevant studies from 2000 to 2006 was undertaken and disseminated to a convened expert panel of physicians and nonphysicians to discuss new and novel analgesic agents for IT use. **Results.** The panelists identified several agents that were worthy of future studies for the clinical and rational use of IT agents that are presented in this article. **Conclusions.** A list of nonopioid IT analgesics, including *gabapentin*, *adenosine*, *octreotide*, the χ-conopeptide, *Xen2174*, the conopeptide, neurotensis 1 agonist, *CGX-1160*, the ω-conotoxin, *AM-336*, and *physostigmine*, were identified as worthy of future research by the panelists.

KEY WORDS: *Intrathecal, expert panel, polyanalgesic, IT agents.*

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Introduction

Three Polyanalgesic Consensus Conferences have convened since 2000 for the purpose of formulating an algorithm for drug selection in intrathecal (IT) polyanalgesia based on "best evidence" and expert opinion. Reports generated by these expert panelists in 2000, 2003, and 2007 include guidelines for utilizing an IT drug selection algorithm (1–3); the results of surveys given to clinicians in the field (4,5); and directives for future studies (6). This article is an update on future research of experimental analgesic agents as potential IT therapeutic drugs.

Recent discoveries of multiple nonnociceptive mechanisms involved in chronic pain syndromes have expedited the search for novel analgesic drug candidates. Mechanisms of action identified in several new and experimental agents with potential analgesic effects include peripheral changes in sodium and potassium channels and increased central N-methyl-D-aspartate (NMDA) and N-type calcium channel activity (7). Other novel compounds produce analgesia by increasing neurotransmitter release from intact neurons, or alternatively, inducing changes in opioid, norepinephrine, and serotonin systems (7).

Conotoxins, derived from the venom of *Conus* snails, are peptides containing only 10–40 residues, making them smaller than most known protein toxins (8). The *Conus* genus is composed of an estimated 500 species. Conotoxins are derived from a wide range of species in this genus and fall into several classes. ω-Conotoxin peptides block voltage-sensitive Ca^{2+} channels to suppress neurotransmitter release (8). Other groups of *Conus*-based protein toxins include σ-conotoxins that act on the serotonin 5-hydroxytryptamine-3 (5HT-3) receptor, κ-conotoxins that block voltage-sensitive K^+ channels, and γ-conotoxins that target voltage-sensitive nonspecific cation channels (8).

Ziconotide (Prialt®, Elan Pharmaceuticals Inc., San Diego, CA, USA), a nonopioid, non-NSAID, nonlocal anesthetic analgesic, derived from the cone snail *Conus magus*, is the synthetic form of the cone snail peptide ω-conotoxin, M-VII-A, an N-type calcium channel blocker. Ziconotide received approval from the Food and Drug Administration in 2004 for the treatment of chronic intractable pain. While ziconotide is associated with potentially serious adverse effects in some patients, it is nonaddictive and 1000 times stronger than morphine as an analgesic (9). Ziconotide is approved for use only as an IT therapeutic agent, but its use in current clinical practice has paved the way for significant breakthroughs in the discovery of other medications. The unique structure–function relationships of conotoxins make them especially promising, not only as analgesics, but also possibly as therapies for the treatment of epilepsy, Parkinson's disease, and schizophrenia (8).

Investigations into promising new IT, nonopioid analgesic agents have advanced over the past two decades, but there remain critical issues that can be addressed only through placebo-controlled, blinded clinical studies that meet the rigorous standards of evidence-based medicine. The consensus opinion of the 2007 expert panelists is that future research on experimental drugs of interest to the polyanalgesic medical community should focus first on preclinical models that yield data on spinal toxicity and efficacy in animals. In an effort to move the field forward, the key compounds recently identified by the 2007 consensus panelists that merit future study are presented in this report. These compounds have been placed on "Line 6" of the 2007 Polyanalgesic Consensus algorithm, and designated as experimental drugs that are not yet supported by published data for routine clinical use in treating uncontrollable, chronic pain (3). Rather, as experimental agents, these compounds may be considered for occasional clinical use only under special circumstances, such as at end of life when all else fails and at the discretion of physicians knowledgeable in the treatment of intractable chronic pain, including malignant pain. The panel, as a note of caution, also feels that for a compound to be considered for use in humans that has bypassed preclinical toxicity testing, the compound needs a spinal toxicology profile.

Potential IT Analgesic Agents

Gabapentin

Gabapentin, a γ-aminobutyric acid (GABA) analog, was brought to the pharmaceutical market in 2000 under the name Neurontin® for the treatment of epilepsy (7,10). The proposed mechanism of action of this drug for neuropathic pain is blockade of calcium ion channels at the postsynaptic dorsal horns to suppress neuropathic pain sensation in neurons using GABA, a key inhibitory neurotransmitter (9,11). Gabapentin acts supraspinally on mechanical hypersensitivity by activating spinal α2-adrenergic receptors. In preclinical studies, IT gabapentin, 25–200 μg, dose-dependently reduces tactile allodynia via both Ca^{2+}-activated and ATP-sensitive K^+ channels in neuropathic rat models (10). The drug decreases the formalin-induced release of glutamate and aspartate in spinal cord dorsal horns, and decreases the elevation in the noxious stimulus-induced spinal liberation of glutamate reported in neuropathic rats (10). Mechanical and cold hypersensitivity are reduced in response to gabapentin administered as either an IT pretreatment or posttreatment. In a rat model of postherpetic neuralgia, intrathecally administered gabapentin, 10–30 μg, affects the mechanical withdrawal threshold in resiniferotoxin-treated rats (12).

Intrathecal gabapentin combined with low-dose morphine decreases the incidence of pain-related behaviors, such as hind limb extension, restoring them to surgical baseline levels. It is thought that IT gabapentin lowers morphine tolerance by suppressing the excitatory amino acid concentration in spinal cerebrospinal fluid dialysate (13).

Other studies show that spinal gabapentin does not affect acute nociception, although it produces full antinociception in injury-induced hyperalgesia (14). It is noteworthy that IT gabapentin reinforces the effects of clonidine and neostigmine in the formalin test when combined with either agent. This suggests that the therapeutic benefit of gabapentin may be associated with its use as a cotherapy or adjuvant in an admixture. The potential synergistic action of gabapentin on dizocilpine [MK801, a noncompetitive antagonist of the NMDA receptor that binds inside the ion channel of the receptor and thus prevents the flow of ions, such as calcium (Ca^{2+}) through the channel] and NBQX (2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione, an AMPA receptor antagonist), two agents shown to have antinociceptive effects, was revealed in an isobolographic analysis of the phase II flinching response (15).

The 2007 consensus opinion of the expert panelists is that gabapentin exhibits minimal effects on the spinal cord, possibly in the periphery, but its primary site of action appears to be in the brain following oral administration. While there is concern over the utility of delivering gabapentin intrathecally, spinal mechanisms involving gabapentin as described above indicate that this drug warrants ongoing and further investigation. As in the case of all of experimental agents, gabapentin can be considered a viable new drug only if toxicology studies clearly demonstrate its safety.

Adenosine

Adenosine has recently drawn attention as a potential analgesic, because both systemic and IT delivery of this compound induce antinociception in animal models (16). Adenosine is an endogenous ligand that plays a role in modulating nociceptive transmission at the spinal level via four types of spinal adenosine receptors (14,17,18). Opioid medications increase the spinal release of adenosine in animal models (19). However, IT adenosine does not produce analgesia in response to acute noxious stimuli (20). Studies on various effects of adenosine receptor antagonists suggest that adenosine receptors exert their effects via several mechanisms of actions involved in the mediation of pain. For example, A1 adenosine receptor activation reduces hypersensitivity associated with chronic pain (19), while adenosine A3 receptors are implicated in the regulation of the late phase response to formalin (14,16). Low doses of adenosine show a more consistent effect on reducing allodynia/hyperalgesia than on decreasing spontaneous pain (21).

Suggestive evidence that adenosine may not cause neurotoxicity of the spinal cord comes from preclinical findings showing that IT delivery of adenosine in mannitol (as well as IT mannitol alone) increases spinal cord blood flow in rats. Conclusive data are not yet available from phase I/II clinical studies. Intrathecal adenosine reportedly decreases neuropathic pain in humans (13), but does not mitigate postoperative pain when delivered 30 min before anesthesia (22). In phase I studies for safety, Eisenach et al. (23) studied 65 volunteers in two separate trials: an open-label, dose-escalating trial with IT adenosine doses of 0.25–2.0 mg (25 subjects) and a double-blind, placebo-controlled trial of adenosine, 2 mg (40 subjects). Blood pressure, heart rate, end-tidal carbon dioxide, and sensory, motor, and reflex neurologic functions were systematically examined for 24 hours after injection, and volunteers were contacted by telephone at times up to six months after injection. The authors found that adenosine did not affect blood pressure, heart rate, end-tidal carbon dioxide, or neurologic function. Headache was reported by 10 and back pain was reported by 8 of 30 subjects exposed to adenosine in the second double-blind trial, whereas none of these symptoms was reported by the 10 saline-treated subjects. The authors concluded that their data support further investigation of IT adenosine for analgesia in humans and suggested that this agent does not produce a high incidence of severe side-effects. Belfrage et al. (24) performed an open-label study of IT adenosine (500 µg [$N = 9$] or 1000 µg [$N = 5$]) administration studied for the evaluation of efficacy and side-effects in 14 patients. All patients had chronic neuropathic pain with tactile hyperalgesia and/or allodynia primarily of traumatic origin. Spontaneous and evoked pain (visual analog scale scores 0–100) and tactile pain thresholds were assessed before and 60 min after injection. The injection caused transient pain (< 60 min) in the lumbar region in five patients. There were no other side-effects. Spontaneous and evoked pain was reduced (median score from 65 to 24 [$p < 0.01$] and from 71 to 12 [$p < 0.01$], respectively) in parallel with increased tactile pain thresholds in allodynic areas. Areas of tactile hyperalgesia/allodynia were reduced (median reduction 90%; $p < 0.001$). Twelve patients experienced pain relief (median 24 hours). The authors concluded that IT adenosine transiently causes lumbar pain in a subgroup of patients and may reduce various aspects of chronic neuropathic pain. However, in a study ($N = 90$) in females undergoing elective abdominal hysterectomy, IT adenosine, 1000 µg, was not effective in relieving postoperative pain when administered 30 min before delivery of anesthesia (21).

The consensus opinion of the 2007 Polyanalgesic Consensus Conference expert panelists is that there are presently insufficient data on the safety, stability, and analgesic efficacy of prolonged infusions of adenosine for the treatment of spontaneous pain to recommend its clinical use.

Octreotide

Somatostatin, the growth hormone located in the substantia gelatinosa, produces inhibitory action on nociception, but has a short half-life. Octreotide, a synthetic octapeptide

derivative of somatostatin, is a more stable compound with a longer half-life than somatostatin (25). There is evidence that IT octreotide (sandostatin) is analgesic. Ocreotide, at doses of 20, 40, and 80 μg, produces a dose-dependent reduction in evoked spinal c-fos expression (a model resembling mechanical allodynia). In addition, IT octreotide reduces behavioral effects of thermal hyperalgesia in rats with chronic constriction injury (CCI) of the sciatic nerve (26). No neurodegenerative complications are induced by IT octreotide infusions of 40 μg/hour in a dog model (Deer et al., 2005) (24). Su et al. found that the antinociceptive effects of octreotide in visceral pain were central and not peripheral by comparing the effects of either intrathecally administered octreotide or intravenously administered octreotide in a rat model of colorectal distention (27). In their behavioral study, pressor and electromyographic responses to colorectal distension were evaluated before and after intravenous or IT administration of octreotide. In pelvic nerve afferent fiber recordings, responses of mechanosensitive fibers innervating the colon to noxious colorectal distension (80 mmHg, 30 s) were tested before and after octreotide. The authors found that octreotide was ineffective in attenuating responses to colorectal distension in either normal or acetic acid inflamed colon when administered intravenously, but attenuated responses when given intrathecally. The authors concluded that, in the rat, octreotide has no peripheral (pelvic nerve) modulatory action in visceral nociception. The antinociceptive effect of octreotide in this model of visceral nociception is mediated by an action at central sites. Chronic IT octreotide administered over a five-year period in two patients resulted in pain reduction without adverse side-effects in patients with cancer pain (28). No neurotoxicity or adverse side-effects were reported in patients receiving IT octreotide at doses as high as 20 μg/hour in a prospective, double-blind study (24). Although no neurologic complaints were observed in this published study, the 2007 expert panelists raised concerns over the risk of development of tolerance to IT octreotide due to the need for frequent pump refills of this medication. Future work is needed on concentrating the compound and determining the dose–response curve.

Xen2174

Xen2174 is a χ-conopeptide isolated from the venom of *Conus marmoreus,* the marine cone snail. It is a structural analog of Mr1A, also a χ-conopeptide, isolated from *Conus marmoreus*, but has higher chemical stability than Mr1A. χ-Conopeptides are potent, noncompetitive selective inhibitors of the norepinephrine transporter, a subgroup of monoamine transporters (29,30). Preclinical research suggests that IT Xen2174 may be a novel therapeutic agent for treatment of chronic neuropathic pain. A study compared the effects of Xen2174 with those of tricyclic antidepressants and clonidine, an α2-adrenoreceptor agonist, on mechanical allodynia in rats with either a CCI of the sciatic nerve or an L5/L6 spinal-nerve injury (31). Both of the latter drugs have been shown to mitigate neuropathic pain. Xen2174 administered via IT bolus doses results in dose-dependent antiallodynia in two rat models of neuropathic pain, while producing mild side-effect profiles. The findings suggest that the wider antiallodynic, antihyperalgesic, and antinociceptive responses elicited by IT Xen2174a and Mr1A may contribute to up-regulation of descending noradrenergic inhibitory inputs to the ipsilateral spinal dorsal horn (27). The panel feels that before undertaking human studies, preclinical animal toxicity data are needed on this agent.

CGX-1160 (*contulakin-G*)

CGX-1160 (*contulakin-G*), a nonopioid compound with a novel mechanism of action, is currently in clinical development by Cognetix Inc., Salt Lake City, UT, USA, a biotechnology company, for the treatment of chronic intractable pain. This conopeptide-based drug acts on the neurotensin, NTR1 receptor to induce analgesia. It has a stronger activation of the NTR1 receptor when compared to neurotensin; thus, giving CGX-1160 a uniquely high level of efficacy for the relief of pain. To assess nociceptive activity of *contulakin-G*, Allen et al. (32) delivered *contulakin-G* as a bolus intrathecally (0.03, 0.1, 0.3, and 3 nmol) or epidurally (10, 30, and 89 nmol) in rats. Intrathecal *contulakin-G* significantly decreased Phase II and, to a lesser degree, Phase I paw flinching produced by intradermal formalin. The ED_{50}s of IT and epidural doses of were 0.07 nmol and 45 nmol, respectively, giving an epidural/IT ED_{50} ratio of 647. In dogs, IT *contulakin-G* (50–500 nmol) produced a dose-dependent increase in the thermally evoked skin twitch latency by 30 min after administration as did morphine (150 and 450 nmol). Epidural morphine (750 and 7500 nmol), but not epidural *contulakin-G* (1000 nmol), also significantly decreased skin twitch in dogs. No changes in motor function were seen in any rats or dogs receiving these doses of *contulakin-G*. In dogs, no physiologically significant dose-dependent changes in motor function, heart rate, arterial blood pressure, or body temperature were found. The authors concluded that *contulakin-G* is a potent antinociceptive drug when delivered intrathecally with no observable negative side-effects in rats or dogs and may provide an alternative to opioid spinal analgesics.

In 2005, CGX-1160 received an orphan drug designation for IT therapy for neuropathic pain associated with spinal cord injury. A phase 1b clinical trial of CGX-1160 for the treatment of chronic intractable pain was completed at Brigham and Womens Hospital in Boston (33,34). The trial was conducted in a small population of spinal cord injured patients. The results supported the company's

opinion that CGX-1160 will be a safe and effective drug for the treatment of chronic intractable pain.

Am336

AM336 (CVID) is a synthetic analog of the ω-conotoxin first isolated from the venom of *Conus catus*, a cone snail inhabiting Australia's Great Barrier Reef. The compound is a novel peptidic, N-type, calcium channel blocker. Intrathecal bolus dosing of AM336 produces dose-dependent antinociception with adjuvant-induced chronic inflammatory pain of the right hindpaw in rats (35). N-type calcium channels regulate the release of important pronociceptive neurotransmitters, including substance P and glutamate. Both AM336 and MVIIA (an ω-conotoxin originally isolated from the venom of the fish-hunting cone snail, *C. magus*, is a blocker of voltage-sensitve Ca^{2+} channels in neurons) showed antinociceptive effects via inhibition of the release of substance *p* from rat spinal cord slices in a concentration-dependent manner (EC_{50} values = 21.1 and 62.9 nM, respectively). Acute dosing of IT AM336 induces dose-dependent antinociception (ED_{50} approximately 0.110 nmol). Of note is the fact that motor side-effects (serpentine tail movements and intermittent mild body shakes) developed at doses of one order of magnitude larger than the doses that result in nociception.

Conclusions

The potential IT use of agents or agents to reverse the toxic effects of IT administered analgesics or antispasmodics discussed in this report are not recommended for routine clinical use in patients with chronic intractable pain. However, some of these agents may benefit patients with end-of-life, cancer-related pain who have exhausted all other treatment options (3). It must be emphasized, however, that the recognition that some of these experimental agents may mitigate extreme pain in a subset of patients is not an endorsement of their use in clinical practice (3). Furthermore, it is the consensus opinion of the 2007 Polyanalgesic Consensus Conference expert panelists that any of these agents should be delivered to patients only by qualified medical personnel experienced in both the skill and art of IT drug delivery. This caveat is also true for the two medications (morphine and ziconotide) that already have been approved by the Food and Drug Administration, for compounds administered intraspinally as off-label drugs, and especially for experimental agents that may offer improvement in quality of life in certain terminally ill patients.

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