

Original Article

Clinical Guidelines for Intraspinal Infusion: Report of an Expert Panel

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Abstract

Consensus guidelines developed by an expert panel are helpful to clinicians when there is variation in practice and lack of a firm evidence base for an intervention, such as intraspinal therapy for pain. An internet-based survey of practitioners revealed remarkable variation in practice patterns surrounding intraspinal therapy. This prompted an interdisciplinary panel with extensive clinical experience in intraspinal infusion therapy to evaluate the results of the survey, the systematic reviews of the literature pertaining to this approach, and their own clinical experience with long-term spinal infusions. The panel proposed a scheme for the selection of drugs and doses for intraspinal therapy, and suggested guidelines for administration that would increase the likelihood of a successful outcome. These expert panel guidelines were designed to provide an initial structure for clinical decision making that is based on the best available evidence and the perspectives of experienced clinicians. J Pain Symptom Manage 2000;20:S37-S43. © U.S. Cancer Pain Relief Committee, 2000.

Key Words

Intraspinal therapy, intrathecal, guidelines, clinical practice, decision making

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Introduction

Consensus guidelines developed by an expert panel may be helpful to clinicians when there is variation in practice and lack of a firm evidence base for an intervention. Intraspinal

therapy is such an intervention. Uncertainty in the decision-making process surrounding intraspinal therapy for pain was strongly suggested by an internet-based survey of practitioners, which revealed remarkable variation in practice patterns (see accompanying paper, page S4). Although this variation will most likely diminish as research establishes the safety and efficacy of specific intraspinal therapies, the evidence is currently scant (see systematic reviews, page S12), and guidelines for practice must rely on the best available data and clinical experience.

An interdisciplinary panel (see Preface) with extensive clinical experience in intraspinal infusion therapy evaluated the results of the internet survey, the systematic reviews of the literature pertaining to this approach, and their own clinical experience with long-term spinal infusions. They met in small working groups and a plenary session to develop treatment guidelines. There were two primary objectives: 1) to propose a scheme for the selection of drugs and doses for intraspinal therapy, and 2) to suggest guidelines for administration that would increase the likelihood of a successful outcome.

Drug Selection for Intraspinal Therapy

The panel's review suggested that the overall approach to intraspinal infusion could be considered a hierarchy of therapeutic strategies (see Fig. 1). The first-line approach gains clear support from the available data and an extensive clinical experience. Second-line approaches have limited supporting data, but a large clinical experience supports the use of these therapies and they are now commonly applied. The third-line and fourth-line strategies have clinical promise, but both the scientific data and clinical experience are extremely limited. It may be appropriate for experienced clinicians to consider these approaches in highly selected cases. The evidence in support of fourth-line strategies is so meager, however, that only the most extreme clinical situation would justify treatment. Over and above these four levels, the consensus panel listed a final group of drugs which should not be used in clinical practice based on concerns about safety.

First-Line Approach

The mainstay drug for long-term intrathecal infusion has been morphine and the expert panel agreed that morphine, as a single entity, should be considered the first-line strategy for most patients. Although randomized trials are lacking, the use of this drug is supported by a relatively large published literature and a long history of use.

The expert panel noted that the daily morphine doses reported by the physicians responding to the internet-based survey were 1.0–23.5 mg/day. This experience is consistent with the panel's opinion that the usual appropriate dose range for intrathecal morphine should be 0.2 mg/day to 20 mg/day, with an average starting dose of 0.53 mg/day and an average maximum long-term infusion dose of 21.1 mg/day. These conclusions are derived largely from practical considerations. The lower limit reflects concerns about daily drug doses that are so low that they are homeopathic and the upper limit is determined by the desire to maintain a minimum time (perhaps 2 to 4 weeks) between pump refills. Because the volume of most pumps is 18 to 20 mL and the usual maximum compounded concentration of morphine is 50 mg/mL, the maximum dose that can be delivered between refills is 1000 mg. If refills are usually administered after 16 to 17 mL have been infused, the minimum time between each visit is 42 days if the daily dose rate is 20 mg/day. As the interval between refills becomes shorter, the frequency of office visits for refills and risk of infection increase.

Although consideration of higher-dose morphine may be justified in some situations, concerns about the need for frequent refills, combined with the risk of a drug-related hyperalgesia syndrome at higher doses,¹ suggest that patients should be considered for an alternative therapeutic strategy when the required morphine dose approaches 20 mg/day. Most patients require more modest doses, and morphine concentrations less than 50 mg/mL (e.g., 10–25 mg/mL) are appropriate for these patients. The expert panel emphasized that the selection of a concentration should consider several factors, including pump program capabilities and the most desirable interval between refills. Given the important opportunity for monitoring provided by a refill visit, the panel suggested that the concentration be ad-

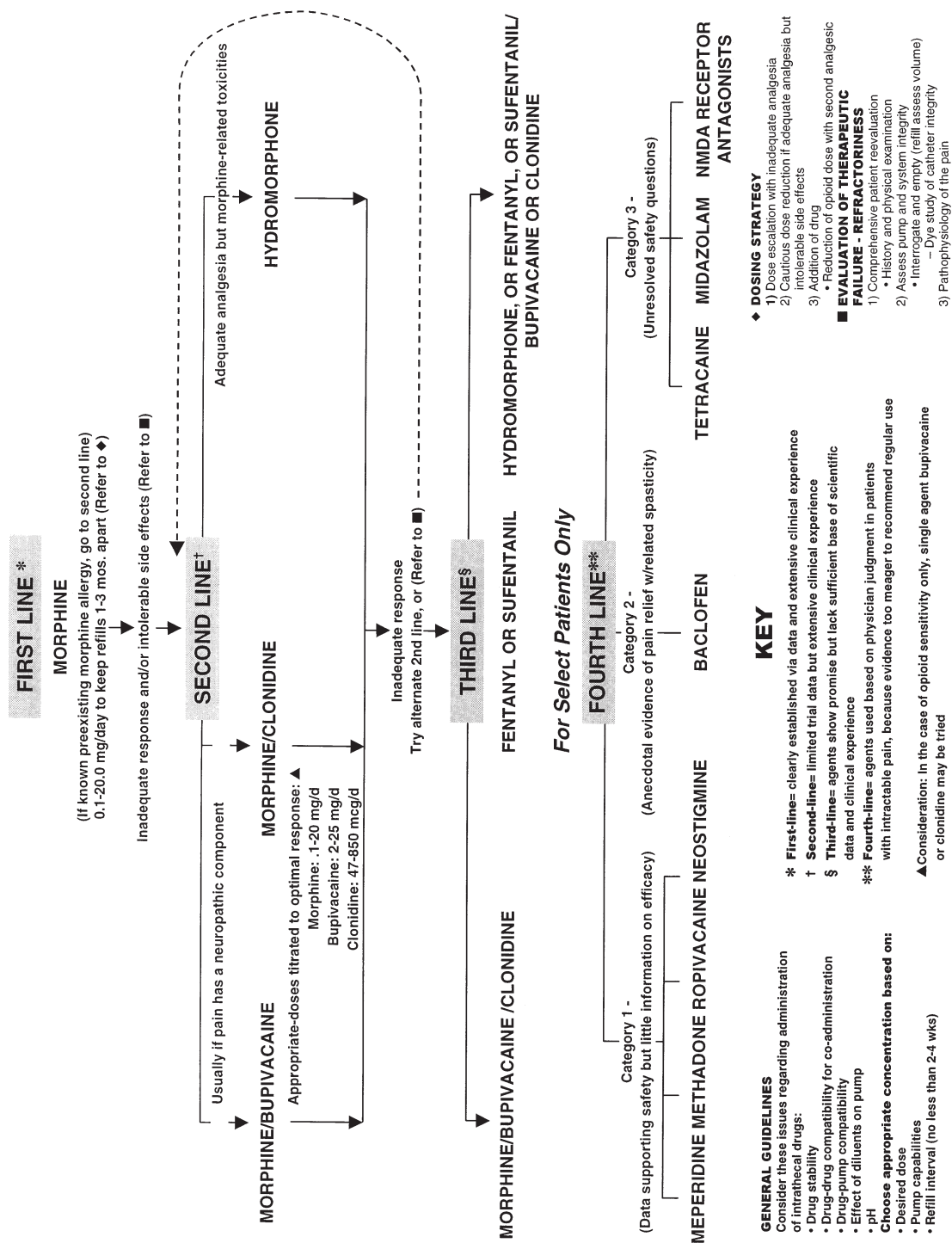


Fig. 1. Clinical guidelines for the use of intraspinal drug infusion in pain management.

justed to allow refill visits at least every 4 to 6 weeks, and no more than every 2–3 months apart. Thus, total drug dose (mg/L) is defined by analgesia and side effect while the desired refill interval serves to define drug infusion concentration.

Drug-pump compatibility and the effects on the pump from the drug diluents and pH are important considerations for all intraspinal drugs. Morphine has never been associated with problems related to these factors, and an extensive clinical experience suggests that solutions up to 50 mg/mL are tolerated by the pump and are acceptable for long-term clinical use. Nonetheless, the panel noted the lack of empirical data concerning these factors as a clear gap in the literature pertaining to intraspinal therapy, including therapy with morphine. Although it is generally accepted that a pH of 4–5 is compatible with pumps, more information should be acquired for each of the drugs discussed herein.

Second-Line Approaches

If infusion of morphine alone provides unacceptable analgesia, a second-line strategy is needed. On the basis of the available literature and a large clinical experience, the expert panel concluded that several options should be considered at this stage. These include 1) the combination of morphine and the local anesthetic bupivacaine; 2) the combination of morphine and the α -2 adrenergic agonist clonidine; and 3) the use of an alternative opioid, specifically hydromorphone. Although other local anesthetic drugs and opioids can be used intrathecally, the expert panel concluded that only bupivacaine and clonidine can be justified as second-line approaches for combination with morphine given the published literature and the accumulated clinical experience.

The empirical data supporting each of these approaches are very limited (see accompanying paper) and there is no systematic information that would support the use of one approach over another. The expert panel noted that bupivacaine and clonidine usually are considered appropriate add-ons when the pain syndrome has a neuropathic component. This strategy has widespread support among clinicians (see accompanying survey). In the event of adequate analgesia but intolerable opioid-related side effects (e.g., nausea or pedal edema), an attempt with an alternative opioid might be considered the prefer-

able next step before proceeding to a combination of drugs. This strategy, however, reflects only anecdotal experience.

The expert panel acknowledged that the recommendation for a morphine combination with bupivacaine or clonidine as a second-line strategy for intraspinal infusion could be used to justify the use of bupivacaine or clonidine as single-entity drugs. In the absence of an empirical literature concerning these approaches, however, the panel concluded that the single-agent infusion of bupivacaine or clonidine should be considered only when there is a clear indication (e.g., demonstrated extreme sensitivity to opioid-related toxicities).

The optimal dose for morphine when administered in combination with bupivacaine or clonidine remains unclear. The panel supported a starting dose of 0.5 mg/day for morphine when combined with either drug. In most situations, the dose will be titrated during a trial prior to implantation, and subsequently during the course of therapy. The range employed when morphine is administered as a single entity should guide this titration. In a similar fashion, the doses of bupivacaine and clonidine usually require titration, both during the pre-implantation trial and after long-term therapy is initiated. The panel noted that the typical starting dose of bupivacaine is in the range of 2–3 mg/day and the typical maximum dose is 25 mg/day; the dose range of clonidine in this setting is around 50–800 μ g/day.

As a single-entity opioid, hydromorphone may be administered like morphine. Based on the known relative potency ratio of hydromorphone and morphine, the usual starting dose for single-agent hydromorphone is 0.3 mg/day and the maximum dose for long-term infusion is approximately 12 mg/day. The solubility problem that complicates the use of higher-dose morphine does not apply to the same extent to hydromorphone, and higher concentrations of this drug are used. As with morphine, hyperalgesia syndrome with hydromorphone can occur, however, and it is prudent to consider a switch to an alternative strategy when relatively high doses are required.

Third-Line Approaches

When second-line intraspinal therapy does not provide adequate pain relief, the clinician might consider a switch to an alternative second-line approach or consider a new set of strategies.

The expert panel considered the following as third-line approaches: 1) the combination of morphine, bupivacaine, and clonidine; 2) a switch to an alternative opioid, specifically fentanyl or sufentanil; 3) a combination of an alternative opioid, usually hydromorphone but possibly fentanyl or sufentanil (if previously tried), and one of the non-opioid second-line drugs, specifically bupivacaine or clonidine.

The empirical data supporting these approaches are limited. The expert panel nonetheless felt that sufficient experience exists to believe that these are reasonable approaches and can sometimes improve outcome for patients who have not responded to more traditional therapies. The use of a combination of morphine, bupivacaine, and clonidine is used widely (see accompanying paper) and there are published data concerning the stability of this combination. This strategy often is tried first for refractory neuropathic pains. In contrast, an alternative opioid usually is considered when opioid-related side effects undermine an otherwise effective therapy.

The doses of the more lipophilic drugs fentanyl and sufentanil that may be used in intraspinal infusion vary widely. Like hydromorphone, the solubility of these drugs allows for high doses to be administered without the need for frequent pump changes. Hyperalgesia has not been reported, but the likelihood of systemic opioid toxicity is relatively greater given the systemic redistribution associated with relatively lipophilic drugs. At this point, experience is too limited to suggest a usual daily dose range for intrathecal infusion.

Fourth-Line Approaches

If a third-line therapy yields a poor outcome, a change to an alternative third-line approach should be considered. In very uncommon circumstances, an experienced clinician may decide on an approach for which the evidence of long-term safety and efficacy is very limited and outcomes related to pump-drug compatibility, drug stability, diluents, and pH are unresolved. The decision to pursue such a therapy, which is supported solely by preclinical data and limited anecdotal human data, requires a thoughtful reevaluation of the clinical situation and a discussion of the risks and benefits with the patient.

The fourth-line approaches for intraspinal therapy are best considered in several categories. The first comprises drugs that are in use,

have some limited data supporting safety, but little information about efficacy. These include 1) meperidine, 2) methadone, 3) ropivacaine, and 4) neostigmine. Given a very small but favorable anecdotal experience, droperidol might be added to this category. The expert panel noted that the data supporting the safety and efficacy of these drugs is sufficiently limited that clinicians should consider an approved institutional protocol before offering these approaches on a routine basis.

The second category includes baclofen. This drug is approved for intrathecal use and is effective for spasticity. There is anecdotal evidence that it can help when pain is specifically related to spasticity, but evidence that it has a broader analgesic effect is lacking.

The third category includes drugs with unresolved questions concerning safety, specifically 1) tetracaine, 2) midazolam, and 3) the N-methyl-D-aspartate (NMDA) receptor antagonists such as dextropropofol, dextromethorphan, memantine, and possibly ketamine. There have been reports associating tetracaine and midazolam with spinal cord toxicity. Although midazolam has been used in a large number of patients for epidural and brief intrathecal infusions, the preclinical data are not uniformly reassuring. Similarly, recent animal studies suggest that the NMDA receptor antagonists can cause spinal cord injury. The use of these drugs should be limited to extreme circumstances or research protocols.

Future Therapies

The review of the expert panel highlighted the likelihood that other drugs will be considered for intraspinal delivery in the near future. Although some of these drugs could be compounded for spinal use now, the published preclinical and clinical literature and clinical experience are too limited to endorse their use. These drugs include gabapentin, tizanidine, octreotide, adenosine, aspirin, and ziconotide (SNX-111). Of these drugs, adenosine, octreotide, and ziconotide have animal safety data, but effects in humans are unclear.

Factors Affecting Medical Decision-Making

Noting the great variation in clinical practice demonstrated in the internet-based survey of

practitioners, the expert panel focused on several key aspects of intraspinal therapy and suggested guidelines intended to optimize drug administration. These recommendations reflect the experience of the panelists, informed by the systematic review of literature.

Evaluation of Therapeutic Failure

A change from one strategy to another is predicated on the assessment of therapeutic failure. An intraspinal therapy may fail if intolerable side effects develop, whether or not analgesia is occurring, or doses of a specific treatment are required that exceed those conventionally used. When this occurs, a comprehensive re-evaluation of the patient, including a history and physical examination, is an essential step in clarifying the nature of the inadequate response, and then determining the appropriate therapeutic response.

The first step in clarifying the nature of refractoriness involves assessment of the pump and other aspects of the infusion system. Computerized telemetry can ensure that the programmer can communicate with the pump and the pump is programmed accurately and performing as intended. The pump should be emptied and refilled, and the volume removed should be compared to the expected value determined from telemetry. If needed, the pump should be evaluated radiographically. Injection of contrast or radionuclide through the pump sideport can determine whether there is partial occlusion of the catheter or a leak at a connection.

If the pump is working appropriately, the poor therapeutic response presumably involves one or more factors related to the pain syndrome itself, or to other patient characteristics. In most cases, the clinical assessment may allow inferences about these processes, but these will not lead to any specific recommendations for therapy. The hierarchy of therapeutic strategies can help narrow the clinical choices, but there have been no comparative clinical trials that would help the clinician decide on the next step for treatment. As noted previously, however, therapeutic decisions often are influenced by inferences concerning the pathophysiology of the pain (e.g., the early use of bupivacaine or clonidine if the pain is determined to be neuropathic) and the type of response observed with prior therapy (e.g., a switch to an alternative opioid if the analgesic

response is good but opioid side effects compromise therapy). The experience of the clinician, the extent of pharmacy support, reimbursement considerations, and other factors also may influence decision-making.

Occasionally, the evaluation suggests that refractoriness may be related to the positioning of the catheter tip at a site too remote from the segmental level for processing of the nociceptive input. If this is suspected, the clinician might consider continuing with a relatively hydrophilic drug, which will have greater spread through the neuraxis than a lipophilic drug. For example, clonidine and bupivacaine have different lipophilicity values and this observation may influence the selection of a second-line strategy.

Dosing

The expert panel noted large practice variations in virtually all aspects of intraspinal dosing. To some extent, this variation occurs as a result of limited experience and insufficient data from well-conducted surveys and randomized trials. As an example, the panel noted that the internet-based survey revealed remarkable differences in how physicians would handle further therapy changes in patients with good analgesia but uncomfortable side effects during intraspinal therapy. Similarly, there were remarkable differences between physicians in the clinical management of patients with inadequate analgesia and no/limited side effects. The panel emphasized the need for better surveys of outcomes associated with specific interventions and recommended that clinicians who undertake intraspinal infusion become familiar with conventional dosing guidelines for systemic opioid therapy.²⁻⁴ These guidelines may lead to more informed decision making during intraspinal therapy. Adaptation of the latter guidelines to intraspinal therapy suggests, for example, that patients who report continued pain should be considered for dose escalation unless side effects are intolerable or doses exceed some conventional safe level. Patients with good analgesia but intolerable side effects should have the side effect treated and the dose cautiously lowered. Should pain then recur, the need for an alternative treatment strategy is confirmed.

As a second example of the need for specific information to assist dosing decisions, the

panel noted the lack of consensus concerning the approach to opioid dosing when a second drug, specifically bupivacaine or clonidine, is added. Some clinicians always reduce the opioid dose, some reduce it only when clonidine is added, and some do not reduce it. The panel endorsed the safest approach, which recommends a reduction in the opioid dose whenever a second analgesic is added.

Conclusion

Advances in pain research and therapy have combined with the development of sophisticated technologies to reveal the extraordinary potential of long-term intrathecal therapy as an approach to the problem of chronic pain. Unfortunately, clinical capabilities have proceeded quickly and far exceed the scientific underpinning of these approaches. There is little information about long-term efficacy and safety of the numerous drugs that have been used intraspinally. Important information about pump-drug compatibility, drug-drug stability, and the effects of the pH and diluents on various outcomes is lacking.

The guidelines proposed by an expert panel

can generate controversy in a field with so little consensus. If this controversy encourages caution and drives a critical evaluation of outcomes, it will be a favorable result. At minimum, the expert panel hopes that these guidelines provide an initial structure for clinical decision making, which is based on the best available evidence and the perspectives of experienced clinicians.

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