Spinal Opioid and Non-Opioid Drugs

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A systematic review of the pain literature spanning the 1980s and 1990s (1) revealed that a 1984 review of intrathecal and epidural administration of opioids (2) was the fifth most highly cited article of over 100,000 publications evaluated. A recent comparison of this review with the other ten most highly cited articles now places it as the third most frequently cited publication. This confirms that the spinal route of analgesia has consolidated its place as a major modality in the treatment of acute, chronic and cancer pain. This is a relatively rapid evolution, given that the first application of spinal opioids occurred little more than 20 yr ago. Also, the initial applications were all of relatively short duration, whereas the spinal route of analgesia is now increasingly used in nonhospitalized patients for long-term treatment of chronic and cancer pain.

The initial concept of "selective" blockade of pain by spinal opioids proved difficult to achieve with existing agents (3). Particularly by the epidural route, systemic absorption frequently resulted in substantial effects on brain and spinal cord, with the end result showing very little difference from that of systemic administration of opioids. However, with refinement of technique, and particularly with the administration of opioid and non-opioid drugs in combination, truly selective analgesia has now been achieved in many settings (3).

This course will focus predominantly on the intrathecal and epidural administration of opioid and non-opioid drugs for the treatment of chronic and cancer pain. Wherever possible there will be an emphasis on examining the best available evidence for the efficacy of individual agents and combinations of agents.

Current Status of Spinal Opioid Mono-Therapy

Unfortunately the spinal administration of opioids is not exempt from the major problems that have beset the long-term administration of opioids via the systemic route. Thus dose escalation because of tolerance, various opioid side effects, loss of efficacy, and relative ineffectiveness for severe mechanical pain are seen for spinal administration as they are for systemic administration. In addition, some specific problems have been identified for the spinal route of administration and these include a higher potential for the development of generalized hyperalgesia in association with high spinal opioid dose (3), encapsulation of epidural catheters (4), and formation of a fibrous tissue mass at the tip of intrathecal catheters (5) (possibly partly attributable to a tissue irritation effect of highly concentrated opioid solutions), occasional cases of severe central nervous system syndromes, and all of the potential technical complications (including epidural abscess, epidural hematoma, and meningitis). With meticulous attention to sterility and well-developed protocols, many of these problems can be minimized. The major problem, however, remains the relentless requirement for increased opioid dose and eventual loss of efficacy.

Single-agent intrathecal drug therapy for chronic pain has recently been reviewed by Dougherty and Staats (6). Also, the basic and clinical science and practical techniques associated with this topic have been thoroughly reviewed by Carr and Cousins (3). The reader is referred to these sources for single agent therapy. This review will concentrate on a discussion of the role of combinations of opioid and non-opioid drugs for spinal analgesia.

Combination Spinal Opioid and Non-Opioid Analgesia

The basic science of combination spinal analgesia has advanced very rapidly and now provides a solid framework that points to the spinal cord as a key target for inhibition of the neuroplasticity changes that are associated with persistent pain states (7) (Fig. 1). Indeed, this new knowledge poses the real potential for what we propose is "spinal analgesic chemotherapy," which would target the underlying pathophysiology rather than attempt to palliate the symptom of pain. The importance of this subtle change of approach would be the real potential for long-term reversal of conditions such as complex regional pain

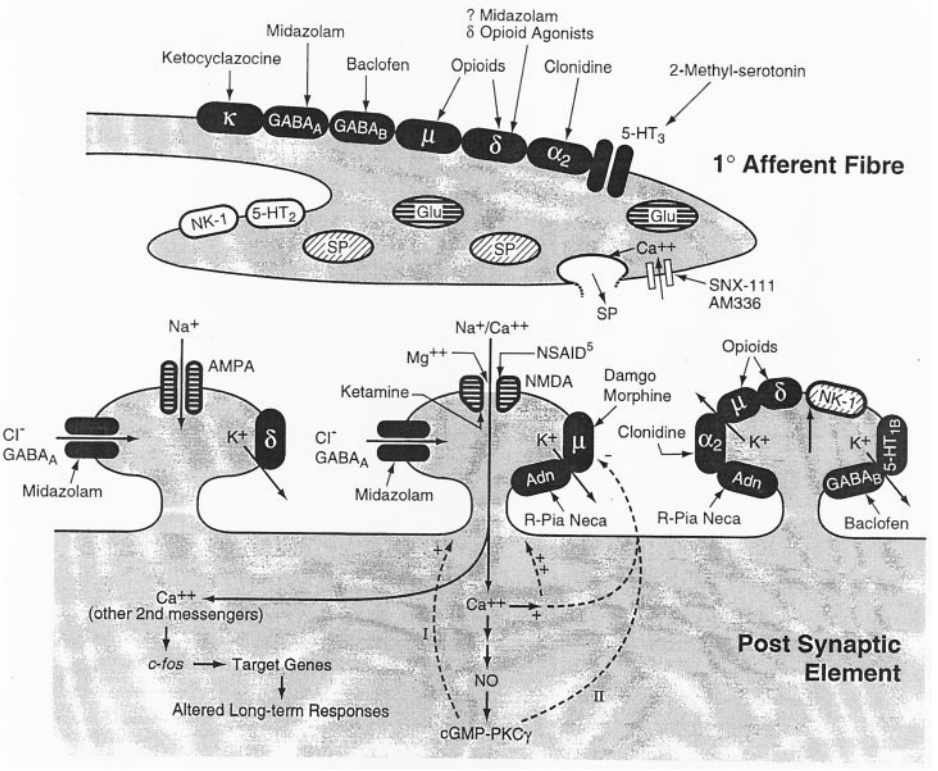

Figure 1. Possible arrangement of pre- and postsynaptic receptors on structures in the dorsal horn of the spinal cord, and potential sites of action of opioid and non-opioid spinal analgesic agents. Presynaptic release of the neurotransmitter glutamate (Glu) results in activation of the postsynaptic AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor, which controls a rapid response sodium (Na^+) channel. Substance P (SP) interacts with the neurokinin (NK-1) receptor and results in activation of second messengers. With prolonged activation, the NMDA (N-methyl-d-aspartate) receptor is primed, glutamate activates the receptor, the magnesium (Mg^{++}) plug is removed, and the ion channel allows entry of sodium and calcium (Ca^{2+}) ions. The increase in intracellular calcium then triggers a number of second messenger cascades. Production of nitric oxide (NO) increases via the calcium/calmodulin dependent enzyme nitric oxide synthase. Nitric oxide may diffuse out of the neuron to have a retrograde action on primary afferents, and also activates guanylyl cyclase leading to increases in intracellular cGMP and activation of cGMP-dependent protein kinases. Activation of the calcium-dependent PKCγ (protein kinase C γ isoform) leads to phosphorylation of the NMDA receptor, which reduces the magnesium block (dotted line II) relating to the development of opioid tolerance. The increase in intracellular calcium also results in induction of protooncogenes such as c-fos with a presumed action on target genes to alter long-term responses of the cell to further stimuli. κ, μ, δ = opioid receptors; GABA = γ-amino butyric acid; α_2 = α-2 adrenoceptor; 5-HT = serotonin; NK-1 = neurokinin-1; SP = substance P; Glu = glutamate; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA = N-methyl-d-aspartate. Details of the potential analgesics are outlined in the text. NSAIDs = nonsteroidal antiinflammatory drugs; SNX-111 and AM336 = omega conopeptides that block neuronal calcium channels.

syndrome, post-spinal cord injury pain and other severe neuropathic pain states that are often amenable only to symptomatic treatment.

The approach of using multiple drugs that target different spinal receptors and thus act on different aspects of the nociceptive/neuropathic process is quite similar to that frequently used in the treatment of cancer, and thus the term "combination spinal analgesic chemotherapy" is appropriate for a deliberate attack on the reorganization and central sensitization that occurs at a spinal cord level in association with persistent pain.

Potential Advantages of Combination Spinal Analgesic Chemotherapy

The following advantages could accrue from this approach.

- Improvement in analgesic efficacy.
- Reduction in side effects.
- Reduction in the development of opioid tolerance.

Evidence for Efficacy of Combination Analgesic Therapy

Unfortunately, there has been an empirical growth in the use of agents via the spinal route. Of most concern is the use of agents without the availability of preclinical data that clearly demonstrate efficacy and side effect profiles, and even more importantly, lack of neurotoxicity. Even more practical issues remain to be addressed and these include the long-term systemic effects of spinal administration of combination therapies, the stability of various drugs in differing concentrations when mixed in implanted infusion devices,

and the effects of combination of drugs on components of implanted pump systems.

In assessing the current literature, the key question is "do analgesics available for spinal administration provide a better therapeutic ratio if combined than if either component is administered singly?" In this age of "evidence-based medicine," it is desirable to select randomized controlled trials. In assessing spinal combination therapies the optimal study should include treatment groups of a combination and of either components of that combination. Most desirable of all are studies that employ the isobolographic method of analysis.

Another important criterion for assessing the efficacy of combination spinal therapy is the method of documenting outcome. We are in an era where governments and other payers wish to see evidence of improved function and, unfortunately, very few studies of spinal analgesia document measures other than pain relief.

Opioids and Opioids

New evidence of some differences in "downstream effects" of different opioids has led to the combination of different μ-opioid analgesics. There is clinical evidence that switching patients from oral morphine to hydromorphone, at a stage of tolerance to morphine may improve analgesia. To date, no rigorous studies have addressed this issue at a spinal level and none have reported on a combination of two different μ-agonist opioids in chronic pain treatment. On the other hand, there is animal and clinical evidence that combining a δ-opioid agonist with a μ-opioid agonist has a dose-sparing effect (8,9). At this stage the evidence for this strategy is weak. The combination of a single injection of morphine and sufentanil has been documented to combine the short onset time of sufentanil and the long duration analgesia attributable to morphine (10). However, this strategy would have only secondary relevance to the management of persistent pain, except in the situation of the use of a patient administered regimen with intermittent dosing, or for breakthrough pain.

Opioids and Local Anesthetics

In animal studies, a synergistic, anti-nociceptive effect has been demonstrated with co-administration of morphine and lidocaine by intrathecal and by epidural routes (11,12). Unfortunately, it does not appear that co-administration of lidocaine with morphine has any effect on the development of tolerance associated with intrathecal morphine infusion (11,12). Nevertheless, the presence of lidocaine helps to maintain the morphine dose at a lower level (11,12). Thus, there may be an indirect effect on the development of dose escalation because less tolerance develops with lower doses of morphine. A single clinical study has reported a reduction in escalation of opioid dose with intrathecal administration of morphine and bupivacaine over a 10- to 30-day period of treatment (13).

Most of the evidence relating to the long-term use of morphine and bupivacaine comes from case series of patients with cancer pain (14–17). For example, in 51 patients with cancer pain, 17 were treated with a mixture of morphine and bupivacaine, with subsequent improvement in pain relief in 10 of these patients, whereas 4 patients had only moderate improvement and 11 patients continued to require oral morphine supplementation (17). In patients with chronic noncancer pain, there are seven studies that compare intrathecal opioid with intrathecal opioid plus bupivacaine. Satisfactory pain relief was achieved in 88% of those with opioid alone compared with 93% in those with opioid + bupivacaine (18). Unfortunately, the studies are marred by lack of randomization, variable inclusion criteria (particularly type of pain), and variable definitions of satisfactory pain relief. Nevertheless, there are two prospective studies that have shown improvement in analgesia with bupivacaine and morphine compared with opioid alone (19,20). Both studies are marred by problems in randomization or blinding and, in both studies, patients were only included when pain was refractory to other treatments, with the inevitable result that the level of preexisting pain varied among patients. A major problem with all of these studies is the lack of documentation of changes in mood and function. Nevertheless, there are some valuable data about dose relationships with important side effects. Bladder and bowel dysfunction and motor weakness have not been reported at intrathecal bupivacaine doses below 30 mg/day (17), while motor weakness has been reported to occur with intrathecal doses of bupivacaine $>$45 mg/day (16).

Opioids and Clonidine

There is substantial evidence in the basic research literature confirming the anti-nociceptive properties of α_2 adrenergic agonists when administered spinally (21,22). In volunteer studies, reduction of pain intensity after epidural clonidine administration correlates with CSF concentrations rather than serum concentrations (22). Of significant importance to systemic side effect generation, much lower bolus doses of clonidine are required via the intrathecal route to produce potent and long-lasting analgesia (23). Interesting evidence points to the release of endogenous norepinephrine as the mechanism of spinal analgesia of clonidine (24) Also, animal data indicate that clonidine produces at least an additive, and in some cases a synergistic effect when co-administered with opioids at a spinal level (21,23).

Although a total of 15 randomized controlled trials has investigated the analgesic effects of combinations of various opioids and clonidine, compared with the effects produced by opioids or clonidine alone, only two of these trials addressed the management of chronic pain. Eisenach et al. (25) compared analgesic efficacy of epidural combination of morphine 0.05 mg/kg plus clonidine 3 μg/kg with that of epidural morphine 0.05 mg/kg plus saline in a group of 85 patients with intractable cancer pain who had failed to obtain analgesia with large doses of opioids. Success was defined as a reduction in pain intensity (using a 0–10 visual analog scale) or reduction of morphine use. Using this definition of success, patients receiving clonidine had significantly better pain relief than those receiving placebo. This difference appeared to be more pronounced in those patients who were judged to have neuropathic pain. Unfortunately, quality of life indices at baseline and at the end of the study did not differ between the two groups.

Inpatients with chronic non-cancer pain due to spinal cord injury, Siddall et al. (26) conducted a randomized prospective controlled "within patient" study of morphine 0.2–1 mg, clonidine 50–100 μg and the combination of clonidine and morphine. In stage I of this study, each patient received saline, clonidine, and morphine in a random sequence, and the dose of each drug was titrated over a period of 3 days toward a positive response, defined as >50% reduction in baseline pain score or occurrence of side effects. Starting doses of intrathecal morphine and clonidine were calculated based on previous use of these drugs. Titration of clonidine and morphine was determined as follows: if there was no pain relief or adverse side effects (sedation or respiratory depression), patients received an increased dose of the same drug (initial + 50% of the initial dose) on the second day, and 2 × initial dose on the third day. In the second phase of the study each patient received a combination consisting of 50% of the final dose of morphine combined with 50% of the final dose of clonidine. The combination of morphine and clonidine was significantly superior to either morphine or clonidine alone, which were no different from saline. Interestingly in this study of spinal cord injured patients, some patients had an exacerbation of their pain with administration of morphine alone (26) (Fig. 2 and Fig. 3).

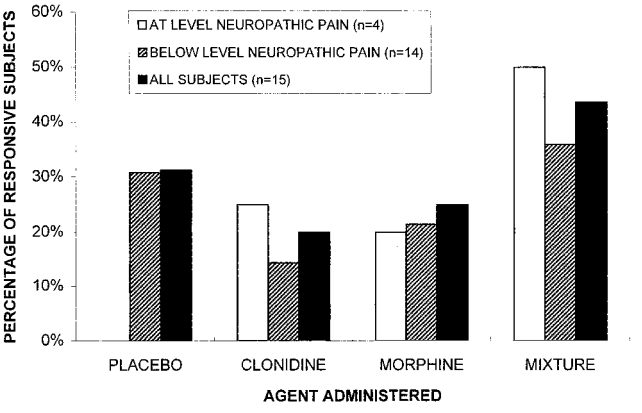

Figure 2. Percentage of people in each group (at level neuropathic pain, below level neuropathic pain) who obtained 50% or greater pain relief following administration of intrathecal saline (placebo), morphine, clonidine, or a mixture of morphine and clonidine (26).

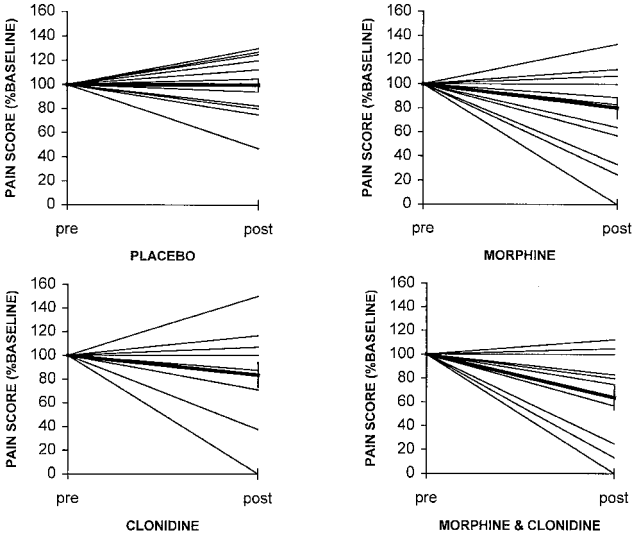

Figure 3. Pain relief (expressed as a percentage of the pretest baseline numerical pain rating score) after administration of saline (placebo), morphine, clonidine, and a mixture of morphine and clonidine in the group of subjects with spinal cord injury. Lines represent the change in individual subjects and the heavy lines represent the means for the group with the vertical line indicating SEM (26).

Opioids and NMDA Antagonists

Significant animal data document potentiation of opioid analgesia by NMDA receptor antagonists (27,28). In patients, administration of ketamine via the spinal route has a number of problems. First, there are no clear data that establish the safety of long-term administration of ketamine via the spinal route. Also spinal administration of ketamine has dose-limiting side effects. The ability of combination therapy to reduce the incidence of side effects seems variable in the available studies. There are two randomized prospective controlled trials in postoperative patients that reported a reduction in PCEA opioid consumption by the use of the combination of ketamine and opioid but side effect levels were reduced in only one study (29,30). Only one study has examined the use of epidural ketamine in terminal cancer pain. A daily bolus of epidural ketamine 0.2 mg/kg was added to a regime of twice daily epidural morphine administration with improved analgesia reported compared with a control group who received an additional bolus dose of morphine 2 mg instead of the ketamine (31). Only one

well-designed study has investigated analgesic efficacy of intrathecal ketamine, in a cross-over design of intrathecal morphine with or without ketamine. Addition of ketamine resulted in more rapid titration to a lower effective dose of morphine and there was a reduced requirement for breakthrough analgesia. However, statistical analysis was only conducted by comparison of pre- and posttreatment scores rather than a comparison of scores in both groups (32).

Neostigmine in Combination Therapy

Neostigmine, an acetyl cholinesterase inhibitor, produces dose-related analgesia via a muscarinic action when administered spinally. When administered intrathecally as a sole agent in volunteers, it produces a large number of limiting side effects such as nausea, vomiting and leg weakness in doses of over 50 μg, and blood pressure and heart rate increases are noted at doses $>$200 μg (33). Thus, the main potential for intrathecal neostigmine lies in combination therapy. To date, studies have been carried out only in patients with acute pain. There have been minor improvements in analgesic efficacy by combining neostigmine with local anesthetic or clonidine, but these have frequently been accompanied by increased side effects. Neostigmine also allows a reduction in the dose of co-administered opioid but there has not been an associated reduction in side effects. Although combination of neostigmine with clonidine or local anesthetic theoretically could antagonize hypotensive effects (34) there is insufficient data to confirm this potential.

Midazolam in Combination Therapy

Basic research provides clear evidence of analgesic efficacy of $GABA_A$ agonists and also suggests an analgesic interaction between $GABA_A$ agonists and morphine following intrathecal co-administration (35–38).

Unfortunately, the intrathecal administration of midazolam has been hampered by a lack of controlled clinical data and conflicting animal studies of neurotoxicity. An early clinical study reported prolonged postoperative analgesia after intrathecal administration of midazolam in a small number of patients (39). A pilot study in chronic low back pain reported that a single dose of intrathecal midazolam provided prolonged analgesia (40). A randomized placebo controlled trial reported only in abstract form found no analgesic efficacy and no difference from placebo when intrathecal midazolam was administered to patients with chronic mechanical low back pain (41). Intrathecal infusion of midazolam and clonidine has been reported in four patients with chronic non-cancer pain (42) and in isolated case reports of patients with cancer pain (43,44). In all of these reports, there is anecdotal evidence of improved analgesia when midazolam was added to existing regimens. However, currently, there is no clinically approved preparation of midazolam and there are substantial problems with currently available midazolam preparations in terms of presence of additives and rather low concentration of midazolam for practical use in implanted pumps. Available neurotoxicity data are currently conflicting (45). Our own experience is of intrathecal midazolam administered to a small number of patients when all other options have failed. For example, in a patient with severe mechanical back pain resulting from gross destruction of a lumbar disk, midazolam reinstated analgesia that had failed with maximal doses of opioid and other non-opioid drugs. In a patient with severe neuropathic cancer pain unresponsive to opioids, clonidine, and local anesthetic, midazolam restored analgesia in a rather dramatic manner. All of these data point to a possible usefulness for midazolam in combination analgesic therapy; however, definitive data remain to be obtained.

Opioids and Voltage Gated Calcium Channel Antagonists

There is substantial animal data to confirm the efficacy of intrathecal voltage gated calcium channels (VGCCs) (46,47) but clinical data are very sparse. In one clinical study of postoperative pain, intrathecal SNX 111 provided analgesia but with substantial side effects (48). Therefore combination analgesic therapy would seem to be the best potential application. In an animal model, acute intrathecal administration of SNX111 and morphine produced additive analgesic effects, with analgesia being sustained during chronic intrathecal infusion. However, co-administration of SNX111 with morphine did not prevent or reverse opioid tolerance (49). A small number of patients with cancer pain have received SNX111 and there are anecdotal reports of analgesic efficacy, but again, with serious side effects. A new VGCC agent, AM336 appears to have an advantage over SNX111 because of a lower side effect potential; however, this remains to be confirmed in clinical studies.

Further Developments

There will undoubtedly be further developments in combination analgesic chemotherapy. These could include:

- Potential spinal manipulation of growth factors such as the following:
  Nerve growth factor (NGF),
  Brain derived neurotrophic factor (BDNF),
  Neurotrophin 3 (NT3),
  Glial derived neurotrophic factor (GDNF)

- Evidence from basic studies to date confirms that manipulation of such growth factors may attenuate important markers of pathophysiology associated with persistent pain, such as nerve injury-induced sprouting and allodynia (50), ectopic discharges, and hyperalgesia (51).
- Spinal administration of "chimeric" agents acting on more than one population of receptors.
- Spinal encapsulated xenografts that produce more than one endogenous ligand.

Summary

In summary, there is now substantial basic and clinical evidence to support the use of combination analgesic chemotherapy in the treatment of chronic non-cancer pain and cancer pain. Future developments of this promising analgesic tool will depend upon enhanced knowledge of underlying mechanisms of persistent pain, well-designed clinical studies as indicated above, much needed neurotoxicity data, and practical examination of drug formulations and their stability in the settings in which they will be used.

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