

Aspirin, the Miracle Drug: Spinally, Too?

Aspirin and morphine have been used in crude form for centuries, and in pure form for decades, for the treatment of pain. Morphine's powerful analgesic actions after spinal injection, rediscovered by Yaksh and Reddy¹ and others in animal experiments 12 yr ago, sparked clinical interest and widespread use of intraspinal opioid analgesia. Their focus now turns to aspirin-like drugs.² The striking differences in approaches used and clinical implications between the current study and those of 12 yr ago highlight our advances in knowledge, and the current study may spark a new advance in clinical care.

Receptors Versus Enzymes

Aspirin belongs to a class of drugs, termed nonsteroidal antiinflammatory drugs (NSAIDs), that produce their pharmacologic effects by inhibition of prostaglandin synthesis. On the surface, this mechanism of action (enzyme inhibition) appears to be quite different from that of morphine binding to specific intramembrane receptors, which causes altered transmembrane permeability to ions. Herein lies the first distinction between these classes of drugs. Therapeutic and adverse effects of opioids increase with dose, as more receptors that cause these effects are occupied. Such simple relationships with dose need not occur with NSAIDs, because they affect synthesis of a variety of products that may have opposing actions. A classic example is the use of aspirin for patients with atherosclerotic vascular disease. Low doses produce the desired effect (thromboxane synthesis decreased more than prostacyclin synthesis), and greater doses are less therapeutic (thromboxane and prostacyclin synthesis decreased similarly).³

Twelve years ago, Yaksh and Reddy¹ showed that spinal morphine caused dose-dependent analgesia. In the current study,² spinal injection of the NSAID ketorolac resulted in a maximal effect only two-thirds as great as morphine. This reflects clinical experience with sys-

temic administration, in which large systemic doses of potent NSAIDs (*e.g.*, ketorolac) alone are often completely effective for moderate pain, but usually require supplementation with opioids for treatment of severe pain.⁴ Reduced efficacy of NSAIDs may relate to the fact that not all prostaglandins are pain-causing. Some prostaglandins may diminish pain sensitivity.⁵ Thus, this difference in maximum efficacy between NSAIDs and opioids may be caused by complete inhibition of synthesis of all prostaglandin species—both “painful” and “analgesic” prostaglandins—at high NSAID doses. Examination of the relative role of each prostaglandin species in sensory transmission, and the effects of different NSAIDs on local prostaglandin concentrations, could help to define optimal NSAID doses and lead to new drug development.

Spinal Cord Plasticity

Unlike the acute-pain model employed in the original spinal morphine studies,¹ the current study² also examined a delayed onset, long-lasting behavior after injection of formalin in the rat paw. Electrophysiology studies indicate that this delayed-onset behavior occurs despite reduced activity in the sensory afferents. A “windup” phenomenon occurs in the spinal cord, in which neurons in the dorsal horn become hyperexcitable (*i.e.*, they respond to normal afferent activity in an exaggerated manner, as if a painful stimulus were occurring).⁶ A similar phenomenon is thought to underlie the hyperesthesia and pain in postoperative patients.⁷ Blockade of this spinal cord windup phenomenon may prevent postoperative hyperesthesia and reduce the need for analgesics and their attendant side effects.

The pharmacology of this spinal cord windup phenomenon differs markedly from that involved in transmission of acute pain (fig. 1), as exemplified by the current study. For example, opioid, α_2 -adrenergic, purinergic, and serotonergic agonists are among those most powerful in the inhibition of acute pain behaviors. In contrast, antagonists of excitatory amino acids and nitric oxide synthesis are most important in selective

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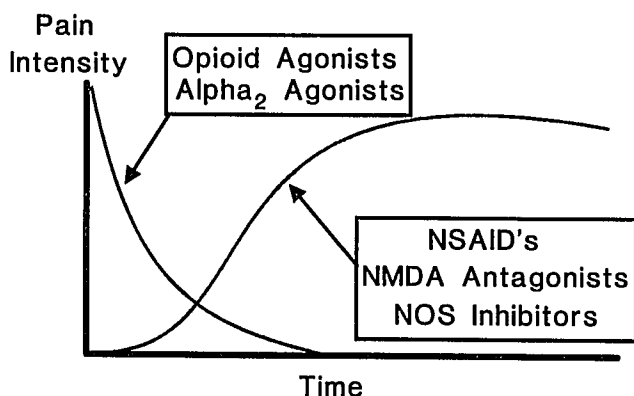


Fig. 1. The two phases of pain following acute injury. Initially, pain is perceived from stimulation of peripheral afferents. This pain is amenable to treatment with intraspinally administered opioids or α_2 -adrenergic agonists. Later, a hypersensitivity response develops, caused, in part, by increased responsiveness of spinal cord dorsal horn neurons. The development of this delayed-onset pain and hypersensitivity is reduced by intraspinally administered NSAIDs, n-methyl-d-aspartate (NMDA) antagonists, and inhibitors of nitric oxide synthase (NOS).

blockade of the hypersensitivity windup phenomenon. Of course, blocking the acute pain stimulus in the first place, either by peripheral nerve block or spinal analgesic drug injection, should diminish the magnitude of delayed hypersensitivity. Presumably, this is how the opioid, α_2 -adrenergic, and purinergic agonists reduce the delayed response in the current study.

Drug Interactions

Twelve years ago, Yaksh and Reddy¹ showed that minimally effective spinal doses of an opioid and an α_2 -adrenergic agonist produced a large effect when combined, indicating that these classes of drugs enhance each other. Subsequently, the isobolographic method, as used in the present study, has become the gold standard for rigorously defining how drugs interact.⁸ This method is simple, statistically valid, and makes no assumption regarding mechanism of action or shapes of dose-response functions.⁹ The method is efficient, because it requires the construction of only three dose-response curves to assess drug interactions for a fixed-ratio combination (fig. 2).

Using isobolographic analysis, the current study² demonstrates a synergistic rather than mere additive interaction between spinal morphine and ketorolac. This is pharmacologically important, because it implies

different mechanisms of action for these two drugs, and clinically important, because large reductions in dose of each may be employed in combination. A study of similar design demonstrated synergy between spinal morphine and lidocaine,¹⁰ supporting the common clinical use of opioid-local anesthetic mixtures for intraspinal analgesia. In this case, combination use makes good clinical sense, because these drug classes have different side effects (*i.e.*, motor and sympathetic blockade with local anesthetics, and pruritus and respiratory depression with opioids), and their combination does not enhance their individual side effects. Whether the same is true with spinal opioid-NSAID combinations is unclear, and should be tested. It is conceivable that there could also be a synergistic interaction between these drugs in the production of side effects, such as the enhanced ulcerogenic action of NSAIDs when combined with opioids.

Implications

Antinociceptive efficacy of spinally administered drugs varies widely with the experimental model employed (*e.g.*, powerful effect of purinergic or kappa opioid agonists in one model of acute pain, but not another), and these studies should be repeated with other experimental models. Several lines of evidence indicate that spinal opioids produce analgesia *via* an adenosine intermediary;¹¹ however, these studies are

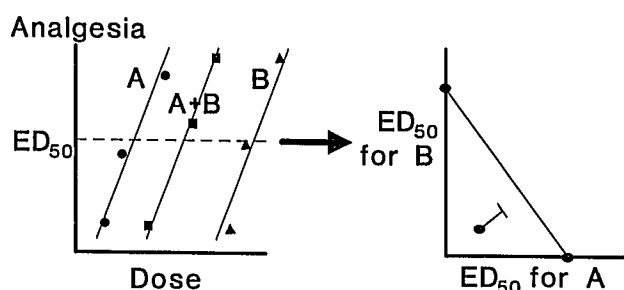


Fig. 2. Isobolographic design to determine additive *versus* synergistic drug interactions. Dose responses are initially determined for drug A and drug B alone, and a fixed ratio combination of drug A + drug B. From these curves, the effective dose to produce a 50% maximal effect, the ED_{50} , is determined. An isobologram is then constructed, with dose of drug A on one axis and dose of drug B on the other. The ED_{50} values for each drug alone are charted, and the line connecting them is constructed. This is the line of additivity (*e.g.*, combinations that show additive effects should fall within the confidence limits of this line). The ED_{50} for the drug combination obtained is charted, and if it falls significantly to the left of the line of additivity, synergism is demonstrated.

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in direct conflict with the current study. To determine why this is so, the roles of individual prostaglandin species and prostaglandin synthesis inhibitors in spinal modulation of sensory transmission should be examined.

The current study² treats spinal analgesia as a black box, injecting drugs near the spinal cord and monitoring a behavior response, paw licking. These studies are useful in that they generate hypotheses that can be tested. More precise questions, and understanding of how these drugs act and interact, will require more precise methods, such as the use of microdialysis and electrophysiologic recording in unanesthetized animals and the use of molecular biologic probes. Such methods are now being applied by anesthesiologists and other neuroscientists to pain research,¹²⁻¹⁴ and the results of studies using these methods will probably appear in future issues of *ANESTHESIOLOGY*.

A variety of clinical questions are raised by this study. A myriad of recent clinical trials have examined the efficacy of systemic ketorolac, alone or with morphine, for postoperative analgesia; however, a simple isobolographic study asking how these drugs interact has not been performed. Similarly, systemic NSAIDs have been reported to improve postoperative analgesia from intraspinal morphine,¹⁵ but their formal interaction has not been explored. There is good experimental evidence that opioids and NSAIDs can produce analgesia by peripheral mechanisms involving decreased calcium entry and cyclic nucleotide generation in sensory afferent endings.^{16,17} Do peripherally applied (intramuscular and infiltration) opioids and NSAIDs interact synergistically for postoperative analgesia? Are side effects from each class of drug affected by the other?

Will this study lead to the spinal use of NSAIDs for analgesia? Appropriate preclinical toxicity testing has not been performed for any commercially available NSAID, and clinical use now is premature. Provided that toxicity is not observed in preclinical testing and synergy is observed in humans between NSAIDs and opioid or α_2 -adrenergic agonists, these drugs could significantly advance therapy for acute and chronic pain.

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