Spinal Cord Toxicity of Epidural and Subarachnoid Analgesics

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Since the introduction of subarachnoid and epidural morphine for the treatment of acute and chronic pain, there has been enormous growth in our understanding of the spinal cord mechanisms of neurotransmission and neuromodulation. Along with this expansion in our knowledge base comes the discovery that a wide variety of receptor agonists and antagonists have analgesic properties when injected intraspinaly in animals. The shortcomings of currently available analgesic techniques provide considerable temptation to quickly introduce these agents into clinical practice. The lesson of the occurrence of cauda equina syndrome following the accidental subarachnoid injection of chloroprocaine (1) or the injection of 5% lidocaine via spinal microcatheters (2) is one that we should heed in developing new categories of therapeutic agents. There has been considerable discussion in recent years regarding what constitutes adequate animal testing prior to clinical trials of drugs intended for neuraxial use. Some agents, such as clonidine and neostigmine, have undergone extensive animal testing prior to the first human tests, while other agents have been introduced clinically with minimal prior scrutiny and, occasionally, despite adverse animal data.

Once animal tests have been completed, there is still the dilemma of determining how much phase 1 human safety experience is adequate and what types of patients or volunteers are appropriate to use in those studies. Finally, once a drug is introduced into clinical practice, there is still the possibility of injecting higher than intended amounts of drug into the subarachnoid space, either through medication errors or through unintentional introduction of epidural doses into this space.

Safety Testing

As recently described by Collins (3), animal testing of new agents has three basic methodologies. The first is behavioral testing, which involves observation of the animal for the expected pharmacologic action of the drug plus any temporary or permanent adverse effects. The second is evaluation of the effect of the agent on spinal cord blood flow. The last is a histologic examination of the spinal cord following exposure to the drug. Tissue pathology or potential harmful reduction in spinal cord blood flow may be evident in the absence of detectable behavioral changes.

In addition to the expected pharmacologic effects of the drugs tested, in this case antinociception, there are also experimentally induced noxious stimulation, where the investigator looks for behavioral changes representing adverse effects that may be transient at lower doses and possibly permanent at high concentrations. Examples of such behavioral changes would include vocalization or agitation immediately following subarachnoid injection, which might suggest tissue irritation related to the chemical or osmotic properties of the drug. Delayed behaviors, expressed as scratching, writhing, and vocalization or touch-evoked agitation (allodynia) would suggest a pharmacologic action related to release of excitatory neurotransmitters, such as excitatory amino acids (EAAs) or peptides, or to suppression of inhibitory neuromodulators, such as gamma-aminobutyric acid (GABA) or glycine (4). There are several examples of irreversible cellular damage and neurologic dysfunction following prolonged enhanced release of EAAs. The EAA agonist alpha-amino-3-hydroxy-5-methyl-isoxazolepropionic-acid has been shown to produce paralysis and urinary incontinence in rats exposed to it for as little as 2 hours of subarachnoid infusion (5), and an EAA agonist N-methyl-D-aspartate (NMDA) produces dose-dependent spinal cord toxicity in rats. Exposure of cultured spinal cord neurons to glutamate produces dose-dependent cell damage. Some glial cells, particularly microglia, are capable of releasing neurotoxic substances, while others, such as astroglia, release proteins that attenuate microglial toxicity (8). It is conceivable that certain drugs might interfere with the normal balance between these opposing activities.

Another example of an adverse behavioral change is an alteration in motor function. Transient weakness may be reflected as failure to use an affected limb or as more subtle changes, such as delay in the...
placing/stepping or righting reflexes or changes in posture or gait. Urinary incontinence may be detected as staining of abdominal fur.

The doses of analgesic agents and the duration of exposure used for animal testing must be adequate to reproduce possible clinical conditions. While drugs used for postoperative analgesia would not require chronic exposure testing, it is likely that many spinal analgesics intended for use in acute pain states would also be used for long-term administration in chronic and cancer pain. Drugs planned for epidural use should be tested by subarachnoid placement in animals, since unintentional subarachnoid administration is a common complication of epidural administration.

Phase 1 clinical studies, which are designed to determine human safety of new agents, are performed either in volunteers or in patients who might benefit from the drug. Terminally ill patients are often used in phase 1 studies of drugs that may have application in cancer pain. While it is often tempting to offer new analgesic agents to terminal cancer patients who fail to achieve reasonable relief of pain with conventional methods, such patients often have other causes for spinal cord pathology, and it may be difficult to rule out neuropathic properties of a new drug in this patient population. In addition, the hope of better pain relief may represent a form of coercion, prompting individuals to expose themselves to a risk they might otherwise be unwilling to accept. Phase 2 studies examine the efficacy of the drug in limited numbers of patients. Phase 3 studies involve larger numbers of patients; they evaluate drug efficacy and address the possibility of uncommon adverse reactions.

**Subarachnoid and Epidural Drugs Used Clinically**

Unfortunately, many of the drugs that have undergone clinical trials of epidural or spinal administration have not been subjected to adequate animal testing and have undergone little or no safety testing prior to initiation of limited efficacy studies. An example of such a situation was the introduction of subarachnoid somatostatin. In one report, subarachnoid somatostatin infusion provided satisfactory analgesia in two patients with cancer pain (9). Another report described effective postoperative analgesia during continuous epidural somatostatin infusion (10). Subsequent to these reports, several animal studies evaluating the safety of subarachnoid somatostatin were published. Two separate studies reported spinal neurotoxicity following subarachnoid somatostatin administration in rats (11,12). Similar results were reported in both cats and mice (13), but studies in guinea pigs showed no behavioral, histopathologic, or spinal cord blood flow abnormalities (14). Since there appear to be species differences in the neurotoxic potential of subarachnoid somatostatin, further human testing would seem advisable. Nevertheless, human studies of neuraxial somatostatin continue to be performed (15,16). In a study of patients with intractable cancer pain (16), autopsies of three patients who had received subarachnoid somatostatin demonstrated demyelination involving nerve roots or the spinal cord (16).

While there have been extensive animal and human studies demonstrating the safety of subarachnoid and epidural opioids, there are some reports that suggest the possibility of spinal neurotoxicity. A study in sheep by Coombs et al. (17) demonstrated no neuropathology following 9-day epidural infusions of morphine and hydromorphone, but high drug concentrations infused over 30 days were associated with spinal cord damage. Similarly, chronic subarachnoid administration of high doses of butorphanol and sufentanil produced behavioral and histologic abnormalities in sheep (18). Spinal infusion of desecine was shown to produce neuropathologic changes in dogs (19).

Drugs that are clinically available for intravenous or intramuscular injections may undergo trials of subarachnoid or epidural administration. If such drugs contain preservatives, those substances may have neurotoxic effects. A commercially available preparation of ketamine, containing the preservative benzethonium chloride, was shown to be neurotoxic in rabbits (20), but preservative-free ketamine was shown not to produce neurotoxic effects (21). Unfortunately, reformulation of potentially useful drugs to preparations without preservative for spinal and epidural use is a very expensive proposition for the pharmaceutical industry because of the extensive clinical testing and regulatory fees required. Few other agents with EAA antagonist effects have undergone neurotoxicity testing in preparation for human spinal or epidural use. Two NMDA antagonists, 3-(2-carboxypiperazin-4-Y1) propyl-1-phosphonic acid and kynurenic acid, were shown to be devoid of neurotoxic effects following subarachnoid injection in rats (22), and CPP was shown not to affect spinal cord blood flow (23). On the basis of these studies, the drug has been introduced into limited clinical use in patients with neuropathic pain (24).

The introduction of spinal and epidural clonidine into clinical practice represents perhaps the best
organized approach to the neurotoxicity issue as it pertains to neuraxial drug administration. Studies of toxicity were carried out in a coordinated fashion in a few centers, so that duplication of experiments was avoided and optimal testing paradigms could be uniformly employed. Histopathologic and behavioral testing included multiple species (25–28). Spinal cord blood flow studies were done in both sheep (29) and pigs (30).

More recently, series of meticulously designed and implemented studies were performed on the behavioral (31,32), histopathologic (33), and spinal blood flow (34) effects of subarachnoid neostigmine. Similarly, carbachol (carbamyl choline), a combined muscarinic and nicotinic receptor agonist, was shown to be without neurotoxic histopathologic effects in rats (35). Subarachnoid administration of neostigmine or carbachol at or above maximal analgesic doses produced some behavioral abnormalities in rat studies, such as truncal rigidity and mild irritability (32,33,36), and also produced hypertension in sheep (37). We postulated that some of these adverse effects may be related to nicotinic agonist properties of neostigmine and carbachol and carried out a series of studies with subarachnoid bethanechol and methacholine, both of which drugs have potent muscarinic effects but minimal nicotinic actions. Surprisingly, both drugs exhibited minimal analgesic effects and produced marked irritability and delayed upper and lower extremity paresis, which persisted for many hours (38), effects that would not be predicted from previous understanding of the spinal pharmacology of cholinergic agonists.

Several other drugs have been administered epidurally or spinaly in humans. Octreotide, a stable analog of somatostatin, was administered by subarachnoid infusion to seven patients with terminal cancer (38). The animal studies assessing the safety of the technique consisted of chronic subarachnoid infusion in two dogs and chronic intracerebroventricular infusion in three dogs (39). In light of the evidence for neurotoxicity following subarachnoid somatostatin in several animal species, the preclinical testing appears rather meager. Subarachnoid midazolam has been used to treat chronic low back pain (40) and was used in a volunteer study (41). Evidence for safety of the technique derived from animal studies consists of a single study of subarachnoid midazolam administration in rats (42). A report on the analgesic effect of epidural droperidol, conducted by Bach et al. (43), failed to provide any documentation of either analgesic effect or neurotoxicity in intact animals. Likewise, subarachnoid calcitonin has been given to control postoperative pain with no apparent documentation of safety from animal studies (44).

Conclusions

The introduction of new drugs specifically for use as subarachnoid or epidural analgesics is probably very unlikely, given the cost of performing the studies to determine their efficacy and obtain spinal cord toxicity data, the medicolegal risks for the pharmaceutical industry, and the relatively small market for such drugs. It is more likely that drugs previously formulated for intramuscular or intravenous injection, such as clonidine or neostigmine, will be introduced into clinical practice. While the availability of potentially useful drugs approved for other routes of administration provides an opportunity to explore new spinal and epidural treatment possibilities, there are also risks. It is relatively easy and often tempting to undertake "pilot studies" in small groups of patients without prior animal testing to determine whether a particular drug is worth testing on a larger scale. Such studies are often useless in terms of both safety and efficacy determinations. A better approach involves the systematic progression from animal studies of efficacy to animal studies of safety to human studies. A cooperative multicenter group that has a wide range of laboratory and clinical resources is ideal for providing effective and clinically relevant research.

References


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