■ EDITORIAL VIEWS

Spinal Somatostatin for Patients with Cancer

Risk-Benefit Assessment of an Analgesic

The literature describing the use of spinal somatostatin for pain control is extensive. First examined by Chrubasik *et al.*[1,2] and Meynadier *et al.*,[3] somatostatin was reported to have analgesic actions for postoperative and cancer pain, although its efficacy was considered controversial when examined in blinded studies.[4] The issue that arose early was the observation that spinal somatostatin in concentrations not much greater than those used in humans were found to have deleterious morphologic effects on the spinal cord after bolus intrathecal injections in mice, rats, and cats.[5–9] Concern about those results expressed by several independent laboratories has not diminished and remains widely accepted.

In this issue of the Journal, Mollenholt *et al.*[10] report that the spinal delivery of somatostatin$_{1-28}$ produced some degree of pain relief in six of eight patients in the terminal stages of malignancy. All had undergone radiation treatment and had significant spinal metastasis that encroached on the vertebral canal, factors that in part constitute the complex pain syndrome faced by clinicians treating patients with late-stage cancer. Furthermore, the relief provided by somatostatin$_{1-28}$ was not universal, with two of the eight patients receiving little if any pain relief and all patients requiring rapid increases in drug dose over the brief period. Still, the case could be made that such an outcome, however modest it may appear, is worthy of consideration in patients who have no remittance of their pain through other available therapies.

Do these studies constitute proof that somatostatin is without deleterious effect on spinal function or morphologic features? In my opinion, no. It is true that the lesions observed in the five autopsy cases may be iatrogenic or related to the metastatic process. This possibility, however, does not exclude the likelihood of a drug-induced toxicity. We do not have the appropriate control for the injury in the absence of the drug. Moreover, as the authors note, the worst toxicity was seen in patients who received the largest doses. Furthermore,

although a significant number of humans have already received somatostatin and no deleterious effects have been reported, this consideration should be given little weight in issues related to drug safety. As noted by Mollenholt *et al.*, even "widespread neuronal degeneration may be detected histologically in the absence of neurologic deficits." Indeed, even in preclinical studies, mice were unaffected by spinal peptides,[11] and guinea pigs[12] showed no motor effects. However, in formal histopathologic examinations in mice, spinal lesions have been observed.[6] Thus, one may argue at best that, in the authors' words, "judicious . . . administration of spinal somatostatin appears justified in selected patients with terminal cancer in whom pain remains unrelieved despite large doses of opioid analgesics."

Aside from the issues related to this study, why has somatostatin presented such a conundrum? As noted above, the preclinical studies have clearly shown toxicity. It has been argued, however, that the problem lies in preclinical studies' use of concentrations that are unlikely to be administered to humans.[13] Although that argument is reasonable, it is clear that, as in all studies with somatostatin, the doses required increase considerably over the course of the study and begin to approach those concentrations at which preclinical studies find toxicity. Moreover, as is well known, even lidocaine at a concentration of 50 mg/ml is believed to possess neurotoxic effects in humans.[14,15] In the case of a novel agent, the only rational manner in which to approach its use in humans is initially to define its safety in well-defined preclinical models. In the absence of any toxicity, further evaluation in carefully designed dose-ranging studies can be considered. This has been the approach for several classes of agents, including baclofen,[16] adenosine agonists,[17,18] clonidine,[19] and excitatory amino acid antagonists.[18,20] However, with somatostatin, toxicity has been readily apparent in these models.

The argument that the question revolves only around concentration would be powerful except that that the mechanism of this preclinical toxicity has not been defined. In the absence of an understanding of drug action, we cannot logically exclude the likelihood that there may be circumstances that compromise the ther-

apeutic ratio of the agent (as with lidocaine, for which delivery though a microbore catheter led to an apparent local concentration sufficient to produce toxicity). Moreover, in certain situations, we may be privy to actions of the drug or its class that indeed are likely to be deleterious.

Consider somatostatin. Since its introduction into this field 10 yr ago, several suggestions have been made regarding its local action. First, it has been shown that a local effect produces a significant reduction in perfusion of the spinal parenchyma. A precipitous decrease in spinal cord blood flow has been reported with somatostatin$_{1-28}$,[21,22] and somatostatin-associated lesions often are associated with clearly definable infarcts in various brain regions.[5,6,23]

Second, studies have demonstrated that somatostatin$_{1-28}$ inhibits neuronal depolarization, a phenomenon mediated by a coupling through G protein to hyperpolarize the cell by an inwardly rectifying potassium current[24] and to suppress the opening of coupled calcium channels that reduce transmitter release,[25] effects that potentially underlie any analgesic effect this agonist might have. Nevertheless, it also has been shown that somatostatin$_{1-28}$ can induce a significant state of depolarization.[26-29] Although the specific mechanisms of this excitation are not understood, there is growing evidence that somatostatin$_{1-28}$ augments the synaptic actions of glutamate-releasing terminals,[27,28] perhaps *via* the N-methyl-D-aspartate receptor. Somatostatin may act in part by evoking an increase in the phospholipase A$_2$ activity that releases arachidonic acid.[30] Increased arachidonic acid diminishes glial uptake of glutamate, thereby effectively increasing extracellular glutamate concentrations.[31] Glutamate receptors have been widely shown to mediate a potent neurotoxic effect.[32]

Moreover, as noted, somatostatin$_{1-28}$ has been shown to reduce blood flow. In a recent study, we observed a powerfully synergistic interaction: spinally administered glutamate or mild ischemia, either of which alone had little effect, but produced severe vacuolization and neuronal disruption when accomplished concurrently.[33] If somatostatin$_{1-28}$ or other analogues serve to decrease flow and augment postsynaptic effects of glutamate, then local neuronal injury might occur. There is growing awareness that spinal glutamate release may occur in cases of protracted afferent input.[34] Increased glutamate in the presence of somatostatin, with diminished blood flow, would produce a scenario consistent with neuronal injury.

Third, somatostatin is a 28-amino acid peptide that is widely cleaved at phenylalanine 6–phenylalanine 7 and threonine 10–phenylalanine 11 by a variety of endopeptidases.[35] These cleavage-product molecules can possess activity distinct from their parent. Thus, somatostatin$_{14}$ can enhance voltage-dependent potassium currents, whereas somatostatin$_{28}$ inhibits these currents, sometimes even in the same neurons, by mechanisms not mediated *via* cyclic adenosine monophosphate.[25] The role of the several fragments has not been investigated.

Finally, recent studies have identified the messenger RNA for at least five somatostatin receptor subtypes. Although most of these are believed to be negatively coupled to the synthesis of cyclic adenosine monophosphate,[36] one study has established variants that may not be coupled to it.[37]

In light of these mechanisms, it becomes apparent that the toxicologic processes observed in preclinical models has a logical explanation and thus that we must continue to respect the hypothesis that somatostatin may exert an action deleterious to neuronal function. Ultimately, experience with somatostatin$_{1-28}$ has provided the research and clinical community with an important opportunity to learn about implementation of novel drug therapy for spinal cord and brain disease. Our growing preclinical insights into the spinal pharmacologic mechanisms of pain almost daily raises hope that through rational considerations, the goal of managing these patients' complex pain can be achieved.

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