Spinal Administration of Somatostatin in Animals and Humans

To the Editor—In a recent article by Gaumann and Yaksh, the authors suggest that we have administered spinal somatostatin without proper prior studies in animals to rule out toxicity. We wish to point out some inaccuracies on spinal (epidural, intrathecal) use of somatostatin. Our clinical studies were preceded by investigations in dogs which showed that the peptide in a dosage proposed to be used later in humans did not result in any histopathological spinal cord changes. This has to be stated that the intrathecal bolus somatostatin doses used in rats (40–400 μg/kg) and cats (200 μg/kg), as well as the concentrations of the somatostatin solutions employed (0.1–1.0% in rats, 1.0% in cats) tremendously exceeded any that have ever been repeatedly employed in humans (9, 10 (μg/kg) of an 0.225% somatostatin solution intrathecally; 10–15 μg/kg of an 0.1% somatostatin solution epidurally [only small amounts of somatostatin reach the intrathecal space]). Moreover, a species-dependent effect might be assumed. A naloxone-reversible respiratory depression in rats and the occurrence of urinary retention in cats suggest that spinal opiate receptors are involved in the somatostatin effect mechanism. In contrast, somatostatin analgesia could not be reversed by naloxone in humans and investigations using Reed’s rebreathing method revealed that in humans the risk of respiratory depression was negligible following epidural injection of 1 mg somatostatin. Similar to local anesthetics, a segmental dermatome limit of analgesia could be demonstrated that was independent of the injection volume employed and could be maintained during epidural low-dose somatostatin infusion.

Emphasizing a general rule concerning the animal model and the factor by which the clinically effective per body weight dose and the concentration of the solution have to be multiplied and spinally employed without deleterious side effects, we have no doubt that somatostatin will pass, but we do doubt that local anesthetics, for example, would pass those restrictions.

Although the number of patients who have received spinal somatostatin is not large and somatostatin nonresponsiveness is an unresolved problem, we and others who have recently administered somatostatin into the intrathecal or epidural space of some patients have not observed any adverse effects due to the peptide. Careful observation has to be exercised to recognize presently unknown side effects in patients as early as possible.

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REFERENCES

1. Gaumann DM, Yaksh TL: Intrathecal somatostatin in rats: Antinociception only in the presence of toxic effects. ANESTHESIOLOGY 69:753–742, 1988


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In Reply—We would like to comment on the letter of Doctor Chrubasik, as this provides an excellent forum for bringing forth a number of specific issues.

First, in spite of what appears to be extensive citations, the basic animal experiments conducted prior to the application of intrathecal (IT) or epidural somatostatin (SST) in humans were by any index inadequate and insufficient. Only two studies, one in dogs1 and one in rats,2 were conducted, and they provide only limited information. Thus, as we read that literature, the intrathecal dog experiments only included one animal that received IT SST (at total of 30 mg over a period of 3 h) under anesthesia, and which was killed immediately thereafter. This experimental preparation precludes assessment of behavior, analgesia, and motor function. Further, spinal cord histology cannot be assessed for pathological changes due to the abbreviated period of survival. The situation may be somewhat better regarding epidural administration. Thus, in the same paper,1 chronic epidural infusion study in dogs was described, but there is neither information as to the infusion volume nor evidence that the pathological analysis was carried out in a blinded fashion, nor is any representative histology presented with which the saline and drug treated animals may be compared. More importantly, in those animals in which epidural infusion occurred and that were allowed to survive, there is no systematic description of animal behavior. Interestingly, in light of the proposed use of the drug, no apparent efforts were made to assess changes in the pain response. Thus, the doses of the drug employed and alleged to be safe may not have been pharmacologically active. In rat experiments, only one behavioral endpoint (tail pressure) was assessed.2 Ten micrograms SST IT increased the tolerated pressure from “13.4” to “18.5” (arbitrary units) only between 5 and 10 min after SST administration. However, 20 μg SST IT caused acute death due to respiratory arrest in four out of six rats. Thus, these studies only provide evidence for a mild short-lasting analgesia possibly confounded with motor dysfunction and high toxicity of SST with a small margin of safety and no spinal cord histology. In that regard, all of the animal data we have presented are4 are in essential agreement with Doctor Chrubasik’s own data.

We agree that there may be species differences with regard to the susceptibility to toxic and analgesic effects of SST. In order to evaluate possible species differences, we conducted, in addition to studies in rats,2 further studies in cats and mice,4 evaluating analgesia, motor function, behavior, and spinal cord histology following IT SST. Results show that the three species do not qualitatively differ with regard to SST toxicity, which occurs at concentrations of 10 μg/μl of IT SST and that changes in pain sensitivity, if present, only occur in the toxic range.

Due to the fact that SST at low dosages was ineffective in our animal studies, higher dosages than those apparently used in humans had to be employed. It is interesting to note, however, that those dosages employed in humans in recent clinical studies4 are far higher than those initially reported.2 Thus, doses of up to about 10,000 μg of SST epidurally have been infused intraoperatively over unspecified time periods for abdominal procedures. Thus, such cumulative dosing may be significant, for with regard to receptor action, toxicity is best expressed as a function of local concentration. Of similar interest is the reported relative clinical potency of SST given epidurally and intrathecally. Thus, in human experiments,2 equal doses (250 μg) were administered as a bolus IT and epidurally with subsequent infusions of 10 and 125 μg/h, respectively. The reported equivalency of the resulting analgesia is surprising, given that the reported CSF transfer of SST is 2/10,000 (0.02%) of the epidural dose.7 The reason for this similarity between the effects reported with intrathecal and epidural doses and the progressively increasing dose requirements being reported in subsequent publications has never been addressed. We, however, would note that should this tendency continue, there will be little difference between these doses and those reported toxic even in the animal models.

Secondly, we raise the issue of which molecule is actually being examined. In 1985, Doctor Chrubasik kindly provided us with vials of “SST.” We found the content to contain approximately 3.5 mg of material and about 250–275 μg of SST-like immunoreactivity. We do not know the identity of this excess material, but it is not responsible for the toxicity we have observed. As we have documented in all publications, the peptide we have examined is the 1-14 cyclized SST form. We have employed SST from different manufacturers, we have examined the chemical identity to the extent of having assessed its immunoreactivity and its elution on an HPLC column, and we have indicated the vehicle (saline). Outcome was similar in all cases. In none of the studies reported by Doctor Chrubasik et al. in rat,2 dog,1 or humans4 is there any indication of the identity of the molecule, purity