not. After all, without surprise as well as innovation, our field would not hold quite the same excitement.

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Studies in Animals Should Precede Human Use of Spinally Administered Drugs

SPINAL (INTRATHECAL AND/OR EPIDURAL) clonidine has been shown to have no effect on spinal histomorphology in rats,[1] cats,[2] dogs,[3] sheep,[4] and in terminal cancer patients at autopsy.[5] In pigs, clonidine has been shown to have no effect on spinal cord blood flow.[6,7] Behaviorally in rats,[8] cats,[9] and primates[2] over extremes of concentration, neither clonidine nor its structural analogues produce any neurological sequelae. In rats, cats,[9] pigs,[6] and sheep,[4] spinal clonidine has no untoward effects on blood pressure that cannot be accounted for by a systemic effect. These studies suggesting the safety margin in well characterized animal models thus provide a firm basis for spinal administration of clonidine in humans. In fact, the lack of neurological sequelae or toxicity have been similarly observed in patients with terminal cancer or postoperative pain receiving spinal clonidine (see ref. 10 for references).

This orderly development of an extensive knowledge base with clonidine given spinally and its apparent lack of physiologic or tissue toxicity leads to the current consideration by Eisenach *et al.* in this issue of ANESTHESIOLOGY of its use in the female with fetus.[10] Clonidine administered epidurally in concentrations that are anticipated to be effective in humans had little effect on maternal or fetal physiologic and biochemical indices. After the fact, these data might be presumed to be not surprising and the experiments in fact trivial, in view of the extensive animal studies which have shown no neurotoxicity, no change in spinal cord blood flow, and no dramatic effects on sympathetic outflow in concentrations that produce a powerful analgesia and ultimately no difficulty when given to humans.

We wish to take this opportunity to pose the rhetorical question: Were these studies necessary, given the extensive toxicology extant with this drug? As pharmacologists closely involved with investigations on mechanisms, we consider the answer, from a scientific standpoint, to be unequivocally yes. As individuals concerned about the continued use of the perispinal route of drug administration, the answer is even more emphatically affirmative. The animal studies have been exceedingly predictive of the efficacy, physiological effects, and toxicity for humans of spinally administered drugs. Yet, the studies noted above reveal mechanisms relevant to the models that are investigated. It may appear simplistic and obvious, but the mother with fetus possesses physiological systems not present in the animals and humans thus far discussed. Regulation of placental transfer, placental blood flow, and the role of circulating hormones in fetal physiology are issues that are not examined in animal or human studies in which the female-fetus is not considered. It might be argued that clonidine taken systemically by hypertensive human mothers has not been shown to possess deleterious side effects.[11] Thus, if experience suggests that the systemic effects are not detrimental, and if clonidine has no central toxicity, then its spinal physiology must be benign. That observation overlooks the fundamental fact that spinally administered drugs may exert physiological actions that are not observed at concentrations reached by systemic doses. Two examples with morphine, the drug most commonly administered via the spinal route, will suffice to make the point.

First, systemic morphine does not routinely inhibit the micturition reflex, but it is quite clear that opioids, with an action limited to the spinal cord, will produce a dose-dependent, naloxone reversible inhibition of the volume evoked micturition reflex in humans and animals.[12,13] Second, systemic morphine at analgesic doses has relatively little effect on peripheral vascular perfusion other than some idiosyncratic reactions or vasodilation due to histamine release. Following spinal administration, morphine has little effect on measures of sympathetic function,

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as measured by blood pressure, on baroreceptor reflexes.[14] However, spinal morphine will attenuate the reflex evoked increase on muscle blood flow otherwise seen in exercising dogs[15] and depress cardiac function secondary to an increased vagal activity.[16] The relevance of these findings is not known, but like the effects of morphine on the micturition reflex they are clearly not predicted on the basis of information hitherto available. The biological systems with which we deal, and certainly those involving the CNS, are exceedingly complex; we can thus anticipate that it is not possible to predict effects without literally asking the specific question in the appropriate model. One can think of many examples: the toxicity of local anesthetics and drug combinations, or the effect of activating specific receptors in spinal *versus* spinal and supraspinal *versus* peripheral loci on somatosympathetic or somatomotor reflexes. Furthermore, we must not assume that a substance normally found in the nervous system can be injected with inpunity. Naturally occurring peptides and amino acids are important to the functioning of the nervous system as probable neurohormones, but they also display neurotoxic effects when applied in high concentrations onto neural membranes (*e.g.*, dynorphin,[17] somatostatin,[18,19] glutamate[20]).

In the present studies, clonidine at concentrations considered adequate to yield analgesia had no effect on fetal physiologic indices. While it might be argued: 1) that this model does not adequately reflect the human condition, 2) that higher doses, in excess of the clonidine concentrations that may be employed, should have been used to correct for unknown model distribution differences, or 3) that the preparation should be challenged with a physiologic insult (*e.g.*, systemic hypo or hypertension) in the presence or absence of clonidine, these studies represent the rational step to be taken in the application of this agent in a special clinical case having a very high risk/benefit ratio. Failure to see injury or deficit in the studies of Eisenach *et al.* thus provides the additional data in a system not modeled by previous studies.

Let us pose parenthetically the question of what would happen had an untoward outcome been observed in the present investigations. The choice in the face of such data would be either to attempt to define the reason for the effect and demonstrate by persuasive experiments that it was a problem not relevant to the human case (as appears to be the case with the clonidine evoked hyperglycemia in the ewe), or, alternatively, argue that the correct experiment had been done and the drug, because of its untoward, and perhaps unpredicted, side effects, is not suitable for human use. Given the high predictive ability of the several animal models, demonstration of toxicity in such a model cannot be dismissed out of hand. In this context, good intentions and diatribe must not substitute for experiment.

This issue of what are the minimum experiments necessary for considering a drug prior to use in humans is not straightforward, but is of major current significance. The relative efficacy of spinal morphine in humans and the attendant problems associated with its use has provided an impetus to consider application of the spinal pharmacology derived from studies in animals in which a variety of receptor systems have been shown to modify pain processing.[21] Unless, however, the risk/benefit ratio is of a life-or-death nature, the doctrine "primare non nocere" makes clinical investigations rise to a standard that the action of the agent has, within the realm of reasonable scientific effort, been characterized. Without such knowledge, the phrase, "informed consent" is but a hollow mockery. As the risk/benefit ratio increases, the level of certainty as to the effects of the drug must rise accordingly. In the present context of analgesia, a person dying of terminal cancer and in whom the agony may only be addressed by stultifying doses of opioid or a surgical intervention in the pain pathway, the required certainty of drug safety may be less than that required for use in a patient recovering from an arthroscopic procedure or, in the extreme, in the context of delivery where two otherwise healthy lives are at stake. Indeed, the matter here merits additional consideration, as there are accepted clinical procedures for managing postoperative pain or pain associated with delivery, although clearly they may not be optimal.

To conclude, this investigation of Eisenach *et al.* was, in one sense, a boring study—nothing untoward transpired, and clonidine as an α_2-agonist may or may not be a good spinal analgesic in humans. Nevertheless, this work with clonidine by Eisenach *et al.* and that from other laboratories throughout the world provides a laboratory notebook describing the patient and step-by-step consideration of the effects of a novel spinally administered drug. This is the manner by which one rationally and ethically advances clinical practice.

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