

search has been reviewed. Finally, we suspect that the outcome from epinephrine-induced hypertension and arrhythmias will be better than from refractory asystole.

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Pretreatment with an Intrathecal Cholinergic Pressor Agent: Is It Necessary?

To the Editor:—In a recent interesting experimental study by Williams *et al.*, the authors report the effects of pretreatment with an intrathecal cholinergic pressor agent (neostigmine) to “counteract the hypotension produced by intrathecally administered clonidine in conscious sheep.”¹

In the nearly 100-yr experience of intrathecal administration of local anesthetics² and especially during the more informative last four decades,^{3,4} hypotension definitely has been a side effect and has been effectively treated either with head-down position and intravenous fluid-loading alone or in combination with low-dose intravenous catecholamines and parasympatholytic agents.⁴ In other words, the treatment of hypotension produced by spinal local anesthetics never involved intrathecally administered pressor drugs.

On the other hand, intrathecal administration of 150 µg clonidine in humans produces hypotension that can be managed easily with the above mentioned conventional measures.^{5,6} Furthermore, in a recent study, we showed that a two- and threefold increase of this intrathecal clonidine dose (300 and 450 µg, about 4–6 µg/kg) did not reduce blood pressure significantly,⁷ which suggests that the approach to “decrease the dose of α_2 -adrenergic agonists to diminish the side effects”¹ probably is inappropriate, at least after intrathecal administration.

The rationale for the study by Williams *et al.*¹ was to counteract the hypotensive side effects after spinal clonidine administration, which may be “bothersome and could be dangerous in patients with cardiovascular disease.” The authors admit that, although “clonidine could produce delayed hypotension by action at brainstem sites, such delayed hypotension has not been observed in animals or humans,”¹ referring only to clinical studies using epidural clonidine; however, this lack of delayed hypotension has been confirmed in humans after intrathecal administration of clonidine as well.^{5,6} Furthermore, the authors correctly state that “neostigmine is less lipid soluble and could increase mean arterial pressure by actions at cholinergic sites in the brainstem,”¹ probably as a delayed effect. The question raised here is, if the above mentioned conventional measures for the treatment of intrathecal clonidine-induced hypotension could be substi-

tuted by this novel pressor therapy, would this be safer and more effective? Furthermore, if one considers an afterload reduction (using spinal clonidine) preferable compared with a delayed afterload increase (using intrathecal neostigmine), especially in patients with hypertensive cardiovascular disease states, the same question becomes more complicated.

Finally, if the proposed “single-dose spinal neostigmine pretreatment”¹ (intrathecal or epidural?) could be proved safe and effective, it implies technical difficulties in clinical practice, because intrathecal catheters recently were withdrawn as dangerous.

In summary, although information concerning the action of several novel agents in the spinal cord is undoubtedly valuable in understanding pain modulation and improving pain control,⁸ we fail to understand the clinical relevance of the authors’ proposed intrathecal pressor therapy.

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In Reply:—We agree that intravenous fluid administration and low doses of intravenous catecholamine agents are effective and clinically proven treatments for hypotension following spinal injection of local anesthetics and clonidine. However, the rationale for our study examining intrathecal neostigmine was not to propose its use as a "pressor" to supplant these therapies. Rather, we are examining, in this study and in ongoing research, two hypotheses: (1) analgesia from spinal α_2 -adrenergic agonists is mediated *via* acetylcholine (ACh release); and (2) ACh stimulates, whereas α_2 -adrenergic agonists inhibit, preganglionic sympathetic neuron activity.

It follows from these hypotheses that addition of neostigmine to clonidine for intrathecal administration would enhance clonidine's analgesia while counteracting its sympatholytic effect. Should this be the case, a combination injection would reduce clonidine's major

side effects: sedation (which is dose-related) and hypotension. Clearly, we do not need a spinal "pressor," nor has adequate pre-clinical toxicity assessment been presented warranting intrathecal neostigmine use in humans. However, this line of investigation likely will yield better understanding of spinal pharmacology of analgesia and sympathetic nervous system control and may be directly clinically applicable.

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Should Epidural Clonidine Be Used for Reflex Sympathetic Dystrophy?

To the Editor:—We commend the work of Rauck *et al.*,¹ which describes the effects of epidural clonidine for the treatment of reflex sympathetic dystrophy (RSD). We also commend their statement that "the role for such invasive therapy in symptomatic treatment and functional recovery in RSD remains to be assessed." Their study raises several questions that should be addressed at this time:

1. Is there sufficient data to support their conclusion that transdermal clonidine produces analgesia only in its area of application, whereas epidural clonidine produces more "extensive" analgesia? Contrary to Davis *et al.*,² we have found that the effects of transdermal clonidine are not confined to the borders of the patch.³⁻⁵ Given the relatively high rate of serious complications (25% infections) and the cost associated with the use of epidural catheters in their study, should patients first fail a trial with a safer and less

expensive treatment (transdermal clonidine) before a test with epidural clonidine is considered?

2. Is the "analgesic" effect of epidural clonidine a conditioned response to the sedative effect of clonidine experienced by the patients in the study, or might it be the result of the sedation/relaxation produced by the clonidine?

To substantiate the potential therapeutic benefits of epidural clonidine, the authors refer to a book that allegedly supports their position that chronic opioid administration is *not* "recommended" in the treatment of RSD. However, the assertion in the chapter they cite is not supported by reference to clinical data. That is, it represents merely an opinion. On the other hand, published clinical data⁶ and our clinical experience support the position that oral opioids should be considered a viable treatment option in select patients with chronic