are involved in opioid gastrointestinal effects. Peripheral opioid effects clearly play a major role in the colon: For years, the most effective treatments for severe diarrhea have been loperamide and diphenoxylate, two poorly absorbed opioids. N-methyl naltrexone has already been shown to antagonize the inhibitory effects of morphine on human intestine in vitro and in vivo. It is true that different mechanisms may be involved in gastric emptying and intestinal peristalsis, but the complex apparatus of the enteric nervous system (including opioid receptors and opioid peptides) extends through both areas.

The value of this study, then, is the demonstration that peripheral antagonism may be a clinically useful treatment for this particular opioid side effect. A single dose of morphine produced significant effects in these healthy volunteers. The stomach took four times as long to empty plain water, and there was a threefold decrease in the peak plasma concentration of acetaminophen. The antagonist prevented these changes at a dose that is unlikely to produce toxicity or to reverse analgesia.

Where does this leave us? N-methyl naltrexone is an investigational drug, and it has been given “orphan” status by the Food and Drug Administration. The results of this limited study are clear but not definitive. We will eventually need to have data on a range of antagonist doses and the onset and duration of antagonism. We also need to see the effect of the antagonist alone on gastric emptying—perhaps it will reverse endogenous opioid tone in the stomach! Most importantly, we need to define the clinical populations at risk who might benefit from the prophylactic or therapeutic use of this new drug.

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Transient Neurologic Symptoms

Now, with Phenylephrine?

THE manuscript by Sakura et al. in this issue of Anesthesiology continues the contemporary discussion about the potential temporary tissue toxicity of local anesthetics as manifested by transient neurologic symptoms (TNSs). Such symptoms were demonstrated 24 h after surgery in 10 of 80 patients who received spinal anesthesia with 0.5% tetracaine and 0.125% phenylephrine in 7.5% or 0.75% glucose as compared with those who did not have phenylephrine in the injectate (1 of 80 patients with TNSs). The study is significant because it broadens the concern about local anesthetic toxicity to include tetracaine, a spinal drug for which there has been only a single case report associating TNS with its clinical use, and it implicates phenylephrine. We could question the significance of this finding about phenylephrine until insight is gained into how widely this drug is used as an intrathecal additive. Although it is not commonly used in the United States, the drug is still mentioned in many modern anesthesia textbooks and it is the predominant vasoconstrictor agent used with spinal anesthesia in Sakura’s hospital.

There is no reason to suspect that phenylephrine

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alone is toxic in clinical doses (although this study does not exonerate it). Sakura et al. pique our interest in considering the possible toxic effects of combinations of spinal anesthetic drugs and vasoconstrictors. The report does not illuminate the cause of TNSs, such as induced ischemia from vasoconstriction or increased exposure to the primary local anesthetic agent secondary to delayed absorption. However, it does apply the definition of TNS (pain or dysesthesia in the legs or buttocks starting within 24 h of, but after recovery from, spinal anesthesia) that Schneider et al. originally used in their report of four cases of lower extremity TNS associated with 5% lidocaine in 7.5% dextrose. This fosters continuity in the descriptive language used for this phenomenon and thereby generates consistency in the clinical evaluation of patients for TNS and its subsequent reporting.

We need reports such as this one to encourage research into drugs and adjuncts that fulfill our clinical needs yet do not contribute to patient morbidity or postoperative dysfunction. Thus, although at first glance this report might elicit a “so what” response because it deals with a less-often used local anesthetic and vasoconstrictor agent and a transient phenomenon, we must remain interested in the topic and search for correlations between specific drugs, additives, symptoms, and mechanisms. For instance, it is revealing that, once again, the glucose concentration in the injectate (and by implication the osmolality) does not contribute significantly to TNSs.

Perhaps tetracaine is a better (safer) drug for spinal anesthesia. Compared with lidocaine and bupivacaine, it increases spinal cord blood flow. Based on this fact, perhaps, tetracaine is an agent of choice for spinal anesthesia in any patient, such as in the elderly population, in whom vasoconstriction with either epinephrine or phenylephrine could create the risk for spinal cord ischemia that might contribute to postoperative TNS. Perhaps the increase in blood flow is important in patients who are placed in the lithotomy position, with which an increased incidence of TNS is associated. Perhaps subarachnoid block with tetracaine can more safely provide the duration of anesthesia we strive for when we add epinephrine or phenylephrine to drugs with a shorter duration. This report by Sakura et al. is an interesting stepping stone in our journey from documented clinical events that we do not fully understand to basic science explanations of the causative factors. They have provided us with more reason to carefully choose our patients and the drugs we give them.

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