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Statistical Tests and Small Samples

To the Editor:—In a recently published paper,[1] the authors stated that the patient demographic data were compared by chi-square analysis. It is known that the chi-square test is not valid for small samples, which is the case with the Prielipp *et al.* study, wherein 17 subjects were examined. Small samples would not satisfy Cochran's criteria[2] (at least 80% of the expected frequencies exceed 5, and all of the expected frequencies exceed 1) to make the chi-square test valid. Although Prielipp *et al.* failed to give the contingency tables where the chi-square analysis were performed, I assume that 2 × 2 tables were used. In such circumstances (small samples with 2 × 2 tables), Fisher's exact probability test[3] is more appropriate.

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In Reply:—We appreciate the thoughtful comments on our study by Mantha. Demographic categorical data (*e.g.*, number of patients receiving β-blocker therapy, nitrate therapy, calcium-channel blockers, *etc.*) were analyzed using the True Epistat 4.0 computer software program.* This program kindly cautions the user to avoid chi-square analysis whenever the number of observations in any cell is <6 and recommends use of exact case-control tests, *i.e.*, Fisher's exact probability test. Thus, actual statistical testing maintained the vigorous criteria necessary for smaller sample sizes, and we apologize for not stating this clearly in the article.

* True Epistat 4.0, 1991. Epistat Services, 2011 Cap Rock Circle, Richardson, Texas.

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Antagonism of Sulfonamides by Benzocaine and Chloroprocaine

To the Editor:—In addition to causing methemoglobinemia,[1] benzocaine can prevent the therapeutic activity of sulfonamide-type antibiotics. This issue could prove important in patients treated with sulfamethoxazole or other sulfonamides for serious infections, such as *Pneumocystis carinii* pneumonia.

Benzocaine, procaine and, to some extent, procainamide are metabolized to *para*-aminobenzoic acid.[2] *para*-Aminobenzoic acid is a precursor of folic acid in microorganisms, and the sulfonamide antibiotics are structural analogs of *para*-aminobenzoic acid that thereby competitively inhibit microbial synthesis of folic acid. Supplemental *para*-aminobenzoic acid prevents sulfonamide toxicity toward microorganisms in culture[3] and in experimental infections.[4] Drugs that release *para*-aminobenzoic acid are thus expected to antagonize the antibiotic activity in patients treated with sulfonamides.

Similar considerations apply to chloroprocaine even though it is hydrolyzed to the 2-chloro derivative of *para*-aminobenzoic acid. The 2-chloro compound can function as a sulfonamide antagonist in microorganisms that convert the compound to an enzymatically functional analog of folic acid.[5]

There are insufficient data for accurate quantitation of potential clinical impact of local anesthetics on sulfonamide-treated infections in humans. However, a 70-kg patient might receive doses of 1.75 g sulfamethoxazole every 6 h for *Pneumocystis* pneumonia. A patient might also receive doses of 3 ml 20% benzocaine or 16 ml 3% chloroprocaine for anesthetic purposes. These doses correspond to 7 mmol of sulfonamide and to 4 and 2 mmol, respectively, of the sulfonamide antagonists. Although it might be expected that excess sulfonamide would be active in the presence of slightly smaller doses of antagonists, small quantities of *para*-aminobenzoic acid can neutralize large doses of sulfonamides. For instance, Woods showed that one molecule of *para*-aminobenzoic

acid (or of procaine) can reverse the effect of 5,000 molecules of sulfanilamide against hemolytic streptococci in culture.[3] Similarly, 2.5 mg *para*-aminobenzoic acid was shown to substantially reverse the effect of 25 mg sulfanilamide against experimental streptococcal infection in mice.[4] It thus seems prudent to avoid benzocaine and chloroprocaine in sulfonamide-treated patients.

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How to Proceed Following a "Failed Spinal"

To the Editor:—I read with interest the letter of Drasner and Rigler.[1] I agree that with continuous spinal analgesia the caudal direction and sacral position of a subarachnoid catheter can lead to restriction of the spread of local anesthetics,[2] subsequently causing a cauda equina lesion.[3]

The mechanism of failure of a single spinal dose is altogether different. The position of the needle is in the lumbar region, and the local anesthetic is free to move in the subarachnoid space, controlled mainly by its baricity and the curvature of the spine. There are many known causes of failed spinal block, including partial position of the needle bevel in the epidural space, intravascular injection, inadequate dosage, or the use of a local anesthetic drug past its expiration date.

An important cause of failure, which is rarely stressed, however, is the low site of lumbar puncture, *e.g.*, L4–L5 for a cesarean section. An inadequate block may result because of the longer distance the local anesthetic has to travel in order to reach the higher thoracic segments of the spinal cord, together with an appreciable amount of drug loss to the caudal area due to the position of the injection site at the down-slope of the lumbar curvature. Repeated injection of the *same* dose at a higher interspace leads to a successful block. In training centers, failure of spinal anesthesia after a single dose is not a rare event. We have successfully used a second spinal injection in hundreds of cases over many years, without complications. The following precautions should be taken when administering a second dose:

1. One should wait 10 min to make sure that the first block has reached its full extent; spread is slower in some patients than in others. Moreover, this period of time allows fixation of the initial dose, thus minimizing the "free" portion of the local anesthetic in the subarachnoid space.*
2. One should avoid adding epinephrine or opioids to the second dose if these were added to the first. Excessive doses of epinephrine can lead to neurologic complications, and excessive doses of opioids can lead to respiratory depression.[4]

In conclusion, we believe that a second spinal block, especially in situations of high-risk aspiration pneumonitis or potential difficult intubation, is far safer than a hypothetical problem that applies only to continuous spinal anesthesia.

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