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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 criteria² (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 test³ is more appropriate.

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2. Bland M: *An Introduction to Medical Statistics*. Oxford, Oxford University Press, 1987, pp 241-264
3. Armitage P: *Statistical Methods in Medical Research*. Oxford, Blackwell Scientific, 1971, pp 135-138

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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 rigorous 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 culture³ 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