CORRESPONDENCE

Statistical Tests and Small Samples

To the Editor—In a recently published paper, 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 (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 is more appropriate.

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REFERENCES


(Accepted for publication October 23, 1991.)

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.

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(Accepted for publication October 23, 1991.)

Antagonism of Sulfonamides by Benzocaine and Chlorprocaine

To the Editor—In addition to causing methemoglobinemia, 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. 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 and in experimental infections. Drugs that release para-aminobenzoic acid are thus expected to antagonize the antibiotic activity in patients treated with sulfonamides. Similar considerations apply to chlorprocaine 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.

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 5 ml 20% benzocaine or 16 ml 3% chlorprocaine 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...