Therapeutic and Toxic Drug Concentrations: A Correction

To the Editor:
The tabulation by Winek [Clin. Chem. 22, 832 (1976)] provides a concise review of the therapeutic, toxic, and lethal concentrations of drugs or chemicals in the blood. The therapeutic concentration of theophylline and aminophylline is listed as 20–100 mg/liter. Theophylline is a mainstay in the treatment of asthma and constrictive chronic obstructive pulmonary disease, and in fact clinical symptoms and pulmonary function tests begin to improve when serum theophylline concentrations are 5–10 mg/liter, whereas toxic symptoms appear at theophylline concentrations exceeding 15 mg/liter (1–7). Thus a more realistic therapeutic serum concentration of theophylline would be between 10–20 mg/liter. Also, a recent paper (8) reported eight patients who developed grand mal seizures after receiving intravenous theophylline; four of whom subsequently died. Serum theophylline concentrations measured within 1 h of the seizure ranged from 25–70 mg/liter (mean, 53 ± 4.8 mg/liter). Thus Winek’s indication of a therapeutic concentration of 20–100 mg/liter exceeds the therapeutic concentration and extends into the lethal range.

Winek also states that the therapeutic concentration of digitoxin is between 1.7–2.1 µg/liter. It has been demonstrated that mean serum digitoxin concentrations in patients without symptoms of toxicity are about 10-fold higher than those of digoxin, mainly from the substantially greater serum protein binding of digitoxin (9). Serum digitoxin concentrations between 4 and 50 µg/liter have been reported to be therapeutic (9–19). Digitalis intoxication is a well-defined condition (20) and has been shown to correlate with serum concentrations. Beller et al. (10) evaluated the mean serum digitoxin concentrations in toxic and nontoxic patients receiving digitalis leaf and digitoxin. The concentration was 34 ± 18 µg/liter in the toxic group as compared to 20 ± 11 µg/liter in the nontoxic group. Bentley (13) found that digitoxin toxicity was associated with concentrations greater than 45 µg/liter. Butler (19) demonstrated that most nontoxic patients have serum digitoxin concentrations of less than 30 µg/liter while most intoxicated patients have concentrations in excess of 25 µg/liter. A therapeutic range of 20–35 µg/liter has been recommended for digitoxin, with toxicity observed with concentrations exceeding 45 µg/liter (21).

We agree with Mr. Winek that serum concentrations must be interpreted in relation to factors affecting the patient and drug as listed in his Table 1; however, we hope that our corrections will clarify the apparently erroneous therapeutic concentrations for digitoxin and theophylline.

References

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Ed. note: Mr. Winek is obliged to readers Dasta and Slaughter, and also to Thomas J. Persoon and Janice Quinn, (Univ. of Iowa), who also pointed out the error with respect to theophylline, which came from a 1968 reference. Reader Joseph S. Annino points out in addition that “an upper limit of normal for blood lead of 1.3 mg/liter appears high by any standard particularly when the range includes the author’s stated toxic level of 9.7 mg/liter.” Mr. Winek responds: “With regard to lead, this is an old problem. We have [seen concentrations] of 1 mg/liter with no symptoms and have had the same level with symptoms. With lead, the total body burden is important. The expected or ‘normal’ range does overlap with the toxic. . . . The table is to be used as a guide and each case evaluated on its own basis. I suggest reading about Kehre’s lifelong work on lead for enlightenment (In Essays in Toxicology, 1, 1969, chap. 4, ‘Lead Poisoning. An Old Problem with a New Dimension,’ by P. B. Hammond, pp 116–151).”

Inhibition of Alkaline Phosphatase Activity by Serum Albumin

To the Editor:
The diagnostic value of enzyme activity measurements in serum depends on the methodology used and the accuracy and reproducibility of the results. Of importance to these is the suitability of the substrate. For many enzymes, such as the aminotransferases, the choice is restricted to the natural substrate but for others, such as alkaline phosphatase