from all three BCG methods were higher than those from the Beckman rate immunonephelometric method.

We hesitate to accept the results of the rate immunonephelometric method as the "true" values in these cases because the nephelometric measurement process is nonspecific. The manufacturer cautions that "nonspecific interference can occur when the serum is introduced into the polymer-enhanced buffer solution" (9). A carefully controlled study is needed to verify accuracy. Earlier work by Buffone et al. (4) with neonatal specimens demonstrated good agreement between the slide assay, a short-reaction BCG method, and a BCP method when compared with a highly specific electroimmunoassay. We are continuing to investigate the low albumin accuracy and specificity questions raised by Drs. Leerink and Winckers, although they are not unique to our BCG method.

After considering all of the pros and cons, we believe the BCG dye-binding method still offers several practical advantages over the BCP method. Although BCP methods are less affected by globulins and other proteins, they are sensitive to other interferences. They reportedly underestimate albumin in cases of renal insufficiency (5) and obstructive jaundice (6). The twofold greater molar absorptivity for the BCG-albumin dye complex provides better sensitivity and precision than we would obtain with BCP-albumin. And BCG methods can be conveniently standardized and monitored with nonhuman fluids, whereas BCP cannot because it does not bind strongly to bovine albumin. For all of these reasons, BCG continues to be the most widely used method principle for measuring albumin. Of the 4944 laboratories reporting in a recent CAP survey, 76% used a BCG method.

We thank the Clinical Immunology Laboratory at the Mayo Clinic, Rochester, MN, for performing the Beckman rate immunonephelometric albumin assays; The Geese Hospital Clinical Laboratories, Rochester, NY, for performing the Hitachi/BMD BCG albumin assays; Dr. Roberta G. Reed, Imonogene Bassett Memorial Hospital, Cooperstown, NY, for helpful consultations during this investigation; and Drs. C. Bas Leerink and Eduard K. A. Winckers, University Hospital Utrecht, for bringing their concerns to our attention and providing us with their data.

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Theophylline Concentrations Predicted by the Chiu Method

To the Editor:

Pediatric patients in status asthmaticus are treated with an initial aminophylline bolus followed by a constant infusion of the drug. Usually this is an emergency situation, so we need to reach almost immediately concentrations of theophylline in serum between 10 and 20 mg/L, the concentration of the drug being directly related to optimal bronchodilation (1–3).

Thus it would be very useful to individualize pharmacokinetic values before steady-state conditions so we could modify the standard dosage regimens to avoid ineffective or potentially toxic serum concentrations.

The present study was designed to evaluate the predictive value of the method of Chiu et al. (4) for calculating theophylline clearance (CI) in pre-steady-state conditions. We compared the actual (Cₘₐₐ) and the predicted (Cₘₐₚ) steady-state concentrations for the same constant infusion dose, to determine whether Cₘₐₚ is a good estimation of Cₘₐ. We could use such information to modify the dose when the predicted value is too low or exceeds therapeutic values.

Clinicians in the intensive-care unit decided whether the pediatric patients diagnosed as having status asthmaticus could be maintained with the same aminophylline dose until steady-state conditions were reached (at least 48 h). Only 10 patients were in this situation. They were treated with an initial aminophylline bolus of 5 mg/kg of body weight, followed by a constant infusion of a 1–1.5 mg/kg per hour. These doses were chosen by the clinicians: formal pharmacokinetic analysis was not used to determine dosage.

Clearance was calculated from the formula developed by Chiu et al. (4):

\[
CI = \frac{2 \cdot R_0 \cdot 0.82}{C_1 + C_2} + \frac{2 \cdot V_d \cdot (C_1 - C_2)}{(C_1 + C_2) \cdot (t_2 - t_1)}
\]

where CI is clearance (L/kg per hour); C₁ and C₂ are theophylline concentrations (mg/L) at times t₁ and t₂ (h), respectively; R₀ is the aminophylline infusion rate in mg/kg per hour; and V_d is distribution volume (assumed to be 0.45 L/kg).

We tried using t₁ and t₂ at 6 and 12 h after the start of the infusion, because t₂ − t₁ must be ≥t₄/₆ (the drug half-life). The C₁ was determined at least 5 h after the initiation of the constant infusion, to try to minimize the effect of bolus (3).

From the CI value we could calculate Cₘₐₚ, the elimination constant (Kₑ) and the drug half-life (t₄/₆), using the following equations (5):

\[
Cₘₐₚ = R_0 \cdot 0.82/CI
\]

\[
Kₑ = CI/V_d
\]

\[
t₄/₆ = 0.693/Kₑ
\]

Cₘₐₚ was obtained at least 48 h after initiating the infusion. Theophylline concentrations were measured by fluorescence polarization immunoassay (FPIA) in a TDx analyzer (Abbott Laboratories, North Chicago, IL).

Prediction performance was done as described by Sheiner and Stuart (6) for determining the mean prediction error. Table 1 summarizes the theophylline concentrations and pharmacokinetic values found.

There were no statistically significant differences between Cₘₐₚ and Cₘₐ: 16.8 (SD 4.0) and 18.1 (SD 4.3) mg/L, respectively, pharmacokinetic values in agreement with previous published data (7, 8). The mean prediction error was −1.3 (95% confidence interval: −0.33 to −2.27).

In our group of patients, whose doses followed usual schedules, 70%
had $C_{\text{m}A}$ between 10 and 20 mg/L, the rest being >20 mg/L. Using this method, we can avoid too-high concentrations by calculating $C_{\text{m}P}$ at 12 h after the start of the constant infusion because $C_{\text{m}P}$ is a good estimation of $C_{\text{m}A}$.

If we desire another steady-state concentration, a new $R_0$ is calculated from the formula

$$C_{\text{m(desired)}} = R_{0(new)} \times 0.82/Cl$$

We conclude that this method can give us reliable and rapid information about the steady-state theophylline concentration obtained after an individual dose, so that both subtherapeutic concentrations and clinical toxicity are avoided.

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Imprecision of the Stratus Immunoassay System for Free Thyroxin

To the Editor:

We recently reported (Clin Chem 1990;36:2148) that estimation of free thyroxin ($fT_4$) by both the Stratus I and II immunoassay systems showed a large and unacceptable range of imprecision when aliquots of individual patient's samples were repeatedly analyzed. Such imprecision was also shown by our Lymphochek and patient pool quality-control material, but not by the Dade quality-control material recommended by the Stratus manufacturers. We concluded that the $fT_4$ assay was subject to significant matrix effects. In their response (Clin Chem 1990;36:2149) Dade suggested that (a) we did not conduct the assay according to the manufacturer's instructions, and (b) our patients' samples were subject to lengthy storage and multiple freeze–thaw cycles.

The extension of incubation time from 60 to 90 s for the $fT_4$ assay conducted on the Stratus II instrument was made on advice we received via the Australian Product Specialist following a visit to Dade in Miami. No other changes to manufacturer's instructions were made, and the Stratus I was operated completely according to manufacturer's instructions. Notwithstanding the minor extension of incubation time, our findings remain valid because (a) the Stratus II method should still respond to patients' samples and quality-control samples in an identical fashion, and (b) the findings for $fT_4$ estimations by the Stratus I and II were the same; i.e., the imprecision for patients' specimens was sample-dependent.

We also clearly stated that each patient's sample and quality-control sample was split into eight aliquots, which were frozen and thawed once and analyzed once. The study was completed within seven days from the time of specimen collection and quality-control preparation. The reference we quoted confirms the stability of $fT_4$ after many months of storage at -20°C.

The response of Dade does not address the problem of apparent matrix effects that are shown by patients' samples but not by Dade quality-control material when the Stratus $fT_4$ assay is used.

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Editor's note: A representative of the manufacturer indicates that they do not wish to reply further.