A Rapid Desktop Theophylline Assay*

Evaluation of Use in Clinical Management

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Study objectives: To assess the practicality and precision of a simple desktop theophylline assay (Biotrack 516™) in comparison to a standard laboratory assay system (Abbott TDx™).
Design: A prospective blinded paired sample study.
Setting: The respiratory ward and outpatient clinics, the pulmonary function and biochemistry laboratories of a university teaching hospital.
Patients: Sixty patients with asthma or COPD attending the respiratory service.
Measurements and results: Paired specimens for theophylline assay were collected simultaneously for analysis. There was a highly significant (p<0.001) correlation between the two assay systems for both the total range studied (1.2-39.1 μg/mL; r=0.98), and the clinically important range of 5-15 μg/mL (r=0.95). The limits of agreement for the data by the Bland and Altman method indicated a ±2 μg/mL limit for the 5-15 μg/mL range and a ±2.7 μg/mL limit for the total range studied.
Conclusions: The Biotrack 516 is an easy-to-use system, which provides rapid and reasonably precise measurements of serum theophylline levels. The device should be of particular value in smaller centers without an on-site laboratory assay system. (CHEST 1997; 111:324-26)

Key words: correlation; desktop theophylline assay; precision

Theophyllines have been used for decades in the management of COPD and asthma. New guidelines in these diseases suggest that an optimum therapeutic range of 5 to 15 μg/mL for peak serum theophylline levels would be appropriate to achieve therapeutic goals and minimize side effects.1 The risk of side effects can be reduced by monitoring serum drug levels, but this requires the availability of a theophylline assay system. Such systems are widely available in larger centers, but are not generally available in smaller hospitals or outpatient clinics. We therefore compared the accuracy and reproducibility of a simple theophylline assay system with the standard laboratory assay system used in our hospital.

Materials and Methods

We compared an easy-to-use theophylline assay system (Biotrack 516; Ciba Corning Diagnostics Corp, Medfield, Mass) with a standard laboratory assay system (Abbott TDx; Abbott Diagnostic Laboratories; Abbott Park, Ill).

The study population consisted of 60 patients who were attending this center for the management of COPD or asthma, both as inpatients and outpatients, and who were receiving clinically indicated therapy with standard oral or IV theophylline preparations.2 Measurement of blood theophylline levels was performed as part of their standard clinical care and paired samples for assay were obtained simultaneously by venipuncture.

The Biotrack 516 system is an immunoassay system that measures drug concentration by a turbidimetric latex agglutination inhibition reaction.3 The device is a self-contained unit measuring 21×16×9 cm with an opening in front for the insertion of the test cartridge or calibration cartridge. The disposable test cartridges are similar in size to a standard audio cassette and contain all the dry reagents and liquid diluents. Storage in a refrigerator is recommended for unused test cartridges, and these are valid for up to 6 months. Either whole blood from fingerprick or in lithium-heparin tubes (0.5 mL) may be used as samples and are deposited onto the test cartridge which is then inserted into the Biotrack. No user intervention is required following insertion of the test cartridge and results of each sample are displayed on a digital screen after approximately 4 min. Internal calibration is performed once daily by the operator, using a standard calibration cartridge. Analysis of the specimens by the Biotrack assay was performed in the pulmonary function laboratory, and the investigators who performed these analyses (G. L. and J. L. K.) were blinded as to the standard laboratory assay result.

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The standard laboratory theophylline assay was performed by an experienced biochemical laboratory technician on an Abbott TDx analyzer, which uses a fluorescence polarization immunoassay technique. Samples of whole blood required initial centrifugation to produce serum for use in this assay. Each assay on this system takes approximately 15 min to complete.

The standard assay and Biotrack assay results were not rematched until data collection was completed. Statistical analysis was performed using Spearman’s rank order correlation and the Bland and Altman method for assessing agreement between two methods of clinical measurement.

**Results**

There was a highly significant correlation \((r=0.98; p<0.001)\) between the Biotrack assay \((11.36±6.30 \mu g/mL; \text{mean±SD})\) and the Abbott TDx assay \((11.44±6.63 \mu g/mL)\) across the whole study population of 60 patients (Fig 1). There was also a highly significant correlation between both systems when only those pairs of values \((n=43)\) were analyzed that had serum theophylline concentrations within the 5 to 15 \(\mu g/mL\) range as measured by the standard system \((r=0.95; p<0.001)\). Serum theophylline values for these specimens using Biotrack assay were \(9.57±2.86\) compared to \(9.51±2.94 \mu g/mL\) for the standard laboratory assay.

A scatterplot of the Bland and Altman type was constructed (Fig 2), which indicates the degree and limits of agreement between the two assays. For the whole group of 60 patients, the limits of agreement (mean difference±2 SDs) for the range of values 1.2 to 39.1 \(\mu g/mL\) (as measured by the standard TDx assay) were \(0.09±2.65 \mu g/mL\). The limits of agreement for the group 5 to 15 \(\mu g/mL\) \((n=43)\) were \(-0.056±1.92 \mu g/mL\).

Within-batch reproducibility was assessed by reanalyzing three separate blood specimens with different theophylline concentrations (Table 1). These specimens were reanalyzed within 1 h of collection.

**Discussion**

Although theophyllines were considered by some to be nearly obsolete at the start of this decade,7 a clearer understanding of their pharmacology and revision of the recommended therapeutic range has renewed interest in their use.2,5 Side effects, including deaths,9 limit the usefulness of these medications, and occur more often when serum levels exceed 15 \(\mu g/mL\).1,2 In view of these considerations, the practice of monitoring blood theophylline concentration has become increasingly important to the practicing clinician. Unacceptable delays in making individual clinical management decisions, as well as extra costs, may result from transporting theophylline samples to a central laboratory for assay, and may be avoided by a simple on-site assay system that can be operated by nonlaboratory staff.

Estimation of serum theophylline concentration is recommended when commencing therapy with theophylline, changing the type of theophylline preparation, when using other medication known to interact with theophylline, or during an intercurrent infection.10 The monitoring of theophylline levels needs to be appropriate to the clinical situation, and knowledge of the pharmacokinetics of the individual preparation will assist the clinician in determining the appropriate timing after the last ingested dose for assaying either peak, trough, or steady-state levels. This factor is important when one considers the time-related differences in serum levels when using rapid release as opposed to modified or sustained-release preparations. In addition, knowledge

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**Figure 1.** Relationship \((p<0.001)\) between the Biotrack assay and the Abbott TDx assay, across the whole range of values recorded from the group studied \((n=60)\).

**Figure 2.** Bland and Altman plot: difference (Abbott TDx assay—Biotrack assay) against mean of both assays for the total group \((n=60)\). Limits of agreement (mean difference±2 SDs) are 0.09±2.62 \(\mu g/mL\).

Within-batch repeatability was satisfactory with less than 10% variation for each specimen on repeated measurements.
of the patient’s smoking habits and liver and heart functions are important as these factors can profoundly affect serum levels. These factors may make the clinician less willing to use theophyllines without easy and rapid access to a method for estimating serum theophylline concentrations.

Various assay kits have been assessed for use in the physician’s office in the past, and are becoming more widely used, such as the AccuLevel immunochromatography method (Syva UK; Maidenhead, Berkshire, England) and the Ektachem DT-60 system (Eastman Kodak Co; Rochester, NY), which demonstrate good degrees of correlation and accuracy with the laboratory-based Abbott TDx system.

The present data indicate that the Biotrack 516 system is a rapid and easily operated desktop system that has a level of accuracy sufficient for taking patient management decisions regarding theophylline therapy. Correlation between the Biotrack and Abbott systems was highly significant (Fig 1) and the agreement (Fig 2) and reproducibility (Table 1) satisfactory enough to make reliable clinical decisions based on the Biotrack measurements, particularly in determining whether patients have toxic serum theophylline concentrations.

The Biotrack system requires minimal training to operate and needs little maintenance, other than daily calibration which takes 8 min. This system is quite durable, having been in operation in our pulmonary laboratory for 18 months without developing any technical fault. The Biotrack assay system is relatively cheap to purchase at approximately $3,000 compared to approximately $36,000 for the Abbott TDx system, but the cost per test cartridge ($9) is approximately double the cost of each measurement using the standard laboratory system. However, cost comparisons will vary widely between hospitals due to the varying costs of laboratory staff time, purchase or leasing costs of equipment, and volume of use. The Biotrack system is not appropriate as a substitute for the standard laboratory assay, but may suit the particular needs of outpatient clinics and some smaller centers where rapid on-site theophylline assay is not available.

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REFERENCES


