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Standards of laboratory practice: theophylline and caffeine monitoring

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Theophylline is used in the treatment of asthma and chronic obstructive pulmonary disease. The use of theophylline has declined with the advent of potent steroid inhalants. Because of the therapeutic index of this drug, monitoring of theophylline concentrations in plasma is essential. Monitoring should be done on trough specimens after steady-state has been reached. Non-steady-state concentrations may be indicated in selected situations. Caffeine is used to treat apnea of the newborn because of its low toxicity. Monitoring is often by clinical effect. Monitoring of serum concentrations should be performed in cases where there is no clinical response or if there is suspected toxicity.

Obstructive lung disease is a common problem, and the incidence of asthma among children in westernized countries has been estimated to be 6–12% *(1, 2)*. The immunological basis of asthma has been well documented *(3)*. Theophylline is one of the therapeutic agents used to treat asthma and chronic obstructive pulmonary disease (COPD) *(4–8)*. The effects on respiration can be assessed through peak lung flow and other lung function tests that provide immediate overall assessment. Patients in respiratory distress can readily die; thus it is important to assess whether the patient has achieved a theophylline blood concentration expected to produce a therapeutic effect. When drug monitoring is performed, the therapeutic range that has been established should be used only as a guide. However, theophylline has a narrow therapeutic index; high concentrations may be toxic, and the drug must be carefully monitored for adult therapy *(5–7)*.

The mechanism of pharmacologic action of theophylline has been studied for half a century *(5–7)*. Theophylline has been shown to have intracellular effects on phosphodiesterases, calcium concentration, and adenosine receptors. The original concept that theophylline relaxes the smooth muscles of the bronchi does not explain its entire pharmacologic effect.

In recent years, theophylline has been replaced in adult therapy by steroid and β-adrenergic bronchial inhalers, and its use and monitoring has been considerably diminished *(4)*. This has been the result of clinical trials and a better understanding of the underlying pathology. One meta-analysis showed that theophylline had little or no effect on relieving symptoms in an asthmatic pediatric population *(9)*. Clinical trials show that inhalers such as fermoterol and budesonide are effective in treating exacerbations of asthma *(10)*. Another study showed that high-dose inhaled budesonide were as effective as theophylline and low-dose budesonide *(11)*. Because of the negative effect of steroids on growth and development in children, theophylline may be used as a first-line therapy or used to decrease dosages of these agents *(12)*. Use of theophylline in acute respiratory distress has been supported by several studies but not supported in others *(13–16)*. Use of theophylline is common in clinical practice *(4)*. Theophylline is not considered the drug of choice in apnea of the neonate.

Indications for Monitoring

Because of the wide variation in metabolism between individuals and the narrow therapeutic index in hospitalized patients, theophylline historically has been initiated as an intravenous infusion and then changed to oral slow-release formulations. Monitoring in hospitals is performed until a stable steady-state is reached. This is most efficiently done by a series of pharmacokinetic calculations using Bayesian or other estimates *(17)*. The pharmacokinetic parameters are presented in Table 1. Once steady-state is reached, the patient should be monitored when the change to oral therapy is made. In pediatric patients, one approach to the use of theophylline is to gradually increase dosage and clinically observe the patients for signs of toxicity *(12)*. The theophylline concentration is then monitored at the usual therapeutic dose.

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Table 1. Theophylline and caffeine information.

Drug	Half-life (range), h	Time to steady-state	V_D,[a] L/kg	Protein binding	Therapeutic range	Critical value	Route/interval
Theophylline	Adults (healthy) nonsmokers, 9 (3–12); smokers, 4; adults (liver cirrhosis), 10–56;	2–3 days	0.5–0.7	55–65%; <36%, neonates and adults with liver cirrhosis	8–20 mg/L, asthma; 6–11 mg/L, neonatal apnea	>20 mg/L	Oral rapid release, 4–6 h; slow release, 12–24 h
	children, 4 (2–10);	1–2 days					
	infants (4–52 weeks of age), 3–14;	1–5 days					
	neonates/premature infants, 30;	~6 days					
	healthy newborn, 24	~5 days					
Caffeine	Neonate, 41–230	NA	0.6–0.7	29–43%	8–20 mg/L	>50 mg/L	

[a] V_D, volume of distribution; and NA, not applicable.

TYPE AND TIMING OF SPECIMENS

Plasma and serum are appropriate samples. Theophylline can be collected in serum separator tubes *(18)*, but the manufacturers of such tubes should be consulted for specific recommendations. If a theophylline loading dose is used in an acute care setting, the serum (or plasma) concentration is measured before loading. A sample is taken ~1 h after the loading dose to verify the concentration and to allow calculation of the infusion dose.

Recommendations

Theophylline should be measured after 1–2 half-lives to insure that it has reached the therapeutic concentration and to recalculate the pharmacokinetic parameters, to adjust the dosage if necessary. The drug should also be measured at five half-lives to ensure steady-state concentration. In addition, it should be measured after five half-lives after a patient has been switched to oral dosage. These analyses can be performed with a turnaround time of 4–24 h.

RECOMMENDATIONS FOR SPECIMENS AND TIMING

Plasma or serum are acceptable specimens; whole blood may be used in some analytical systems *(19)*. Samples for therapeutic monitoring may be drawn 1–4 h after an intravenous dose or immediately if toxic symptoms are observed. Toxic symptoms include seizures with associated morbidity, and it must be kept in mind that high concentrations can lead to death *(20)*.

Samples for monitoring of the overdosed patient will depend on the clinical severity and the nature of the intervention. If withdrawal is the treatment, concentrations are usually measured after several half-lives (12–24 h). If intervention is the chosen treatment, then more frequent requests for monitoring will be made, depending on clinical judgment *(20)*. Usually, monitoring continues until values are <20 mg/L (<20 μg/mL).

ANALYTICAL PRECISION

The CV value for theophylline among laboratories, as judged by the College of American Pathologists ZA 1996 survey of >100 laboratories, was 11.1% at ~10 mg/L (10 μg/mL). The intralaboratory CV should be less than this value.

RECOMMENDATION FOR ANALYTICAL PRECISION AND ACCURACY

Theophylline assay methods should be precise enough to produce a CV <10%, and preferably ~5%, if pharmacokinetic analyses are used to adjust dosage. The precision and accuracy over several days should be such that the CV is <5%. Fraser *(21)* recommends an imprecision (CV) of 12.5%.

Quality Assurance Issues

A result of less than the detectable limit for a therapeutic drug request may be a baseline value before a loading dose or may indicate any of the quality assurance problems indicated among the quality assurance issues elsewhere *(22)*.

Clinical Practice Issues

INITIATION OF THERAPY

Theophylline is used as a second- or third-line therapy in adults where steroidal therapy has failed and the patient is in acute respiratory distress. It is also used to treat patients on mechanical ventilation. The drug is prescribed for patients with structural asthma because of the effect it has on muscle function. The drug is also given to patients with chronic respiratory failure. Theophylline remains in use in pediatric asthma *(12)*. Slow-release forms of theophylline remain the formulations of choice *(8)*, and thus monitoring is performed on this "steady-state" condition, i.e., peak and trough concentrations are not performed.

DISCONTINUATION OF THERAPY

Patients do not need to remain on theophylline long after the episode of respiratory distress is ended.

OVERDOSE

The treatment for theophylline overdose depends on the severity. In terms of increasing severity, the choices are: (*a*) withdrawal of the drug; (*b*) activated charcoal administration; (*c*) dialysis; or (*d*) extracorporeal hemoperfusion *(20)*.

Reporting Issues

THERAPEUTIC RANGES

The accepted therapeutic range is 10–20 mg/L (10–20 μg/mL) *(5–7, 23, 24)*. Toxicity has been reported as low as 15 mg/L (15 μg/mL), but in the majority of cases, toxicity is observed only at >20 mg/L (>20 μg/mL). In our institution, values >25 mg/L (25 μg/mL) are designated as critical values requiring an immediate call to the caregiver.

THEOPHYLLINE–DRUG INTERACTIONS

Theophylline interacts with a large number of drugs *(25)*. Of particular interest for dangerous interactions are enoxacin, fluvoxamine, mexiletine, propanolol, and troleandomycin. These drugs interfere with the cytochrome P450 metabolism of theophylline and increase the elimination half-life, thus increasing the theophylline blood concentration.

Future of Monitoring of Theophylline

The need to monitor theophylline will decline as alternative modes of therapy, such as β-agonists, enter the practice of asthma therapy. Low-dose theophylline may become more prevalent, changing the current therapeutic range.

Caffeine

Apnea with or without bradycardia is a common medical problem in premature infants. Theophylline and caffeine have been shown to be effective in reducing the number of episodes of apnea *(26–28)*. The neonate does not have a well-developed P450 system for metabolism of caffeine, and toxicity is a concern for both of these drugs. The long half-life and intraindividual variability make monitoring a necessary adjunct to therapy (see Table 1 for pharmacokinetic parameters). However, because caffeine is considerably less toxic than theophylline, it is the drug of choice for treatment of neonatal apnea *(29, 30)*.

INDICATIONS FOR MONITORING

Because episodes of apnea are well monitored for premature babies, the effectiveness of caffeine therapy is readily observed clinically as a ≥50% reduction of these episodes. Clinical signs of tachycardia, gastrointestinal intolerance, and jitteriness have been reported as indications of toxicity, and monitoring is indicated when these symptoms are present. Because of the long half-life, daily administration is the common dosage procedure. Monitoring is usually performed only on those patients who are unresponsive to high doses of caffeine or who have signs of toxicity.

RECOMMENDATIONS FOR INDICATIONS FOR MONITORING

Monitoring should be performed on those patients who are unresponsive to therapy, as judged by clinical symptoms such as reduction in episodes of apnea, in the presence of high doses of caffeine. Monitoring should also be performed on patients with evidence of toxicity, as indicated by clinical signs of tachycardia, gastrointestinal intolerance, and jitteriness.

Analytical Issues

TYPE AND TIMING OF SAMPLES

Serum and plasma are acceptable samples. Virtually all specimens from the neonate are from heel punctures. The long half-life of caffeine makes monitoring at five half-lives (steady-state) too long a time to determine patient status. Concentrations of caffeine in saliva have been shown in several studies to correlate well with serum concentrations *(31–33)*.

RECOMMENDED SPECIMENS

Serum and plasma are acceptable for current methods. We recommend that saliva testing be explored to reduce the need for heel punctures in this population *(27–29)*.

ANALYTICAL PRECISION

On the basis of the author's experience with other assays, the CV of the enzyme-multiplied immunoassay technique for caffeine depends on the analytical instrument. The precision of the enzyme-multiplied immunoassay technique appears acceptable in view of the wide therapeutic index and low toxicity of caffeine. Because of the infrequent nature of caffeine monitoring and the difficulty of maintaining HPLC equipment, immunoassay is expected to be more precise.

RECOMMENDATIONS FOR ANALYTICAL PRECISION

The current analytical CV of <10% is adequate.

Quality Assurance Issues

A result below the detection limit on a therapeutic drug request for caffeine is potentially life threatening. Refer to the quality assurance issues elsewhere *(22)*. Toxic concentrations because of pharmacy errors have been reported *(34)*. These also require immediate reporting.

METABOLITES

Theophylline is a metabolite of caffeine. It is not necessary to monitor theophylline when caffeine is given.

Practice Issues

INITIATION OF THERAPY

Apnea is a common condition in premature births of <32 weeks of gestation *(35)*. Initiation of therapy is usually immediate.

DISCONTINUATION OF THERAPY

Apnea decreases and disappears as the neonate matures *(35)*. The usual course for infants born at <32 weeks is 20–30 days of therapy *(36)*.

Reporting Issues

THERAPEUTIC RANGES

Several therapeutic ranges have been reported *(29, 30, 37)*. However, because neonates are extensively monitored, clinical observation is used to judge therapeutic effectiveness.

Ranges vary from 12–25 mg/L (12–25 μg/mL) to 23–44 mg/L (23–44 μg/mL) *(29, 30)*.

CAFFEINE–DRUG INTERACTIONS

Caffeine interacts with a number of drugs. The most important are ciprofloxacin, enoxacin, fluconazole, norfloxacin, and pipemidic acid *(25)*. These drugs interfere with the metabolism of caffeine. How these drugs affect caffeine metabolism in the neonate is not known.

RECOMMENDATIONS FOR REPORTING OF RESULTS

Values below the detection limit should be called to the physician as soon as they are verified. Such results may require investigation as part of a quality assurance process because these values frequently represent some type of error in phlebotomy (wrong patient drawn), in the laboratory (clerical, instrument, and so forth), or in the pharmacy (incorrect formulation, wrong patient given drug, and so forth). All these events could lead to serious morbidity or death.

Reference therapeutic ranges for caffeine should be reported along with the value obtained in the patient.

THERAPEUTIC RANGE

When reduction in the number of episodes of apnea is used as a clinical marker, the therapeutic range has been reported to be 26–40 mg/L (26–40 μg/mL). Severe life-threatening toxicity has been reported at concentrations of 346 mg/L (346 μg/mL) *(34)*; one study reported no toxicity at concentrations <80 mg/L (80 μg/mL) *(37)*.

Future of Caffeine Monitoring

Because the use of caffeine is limited to the neonate, it is unlikely that the need for caffeine monitoring will extend beyond the current practice of supporting neonatal intensive care units.

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