TDM monograph Theophylline

Synonyms:
Aminofylline, Theolair

Summary

Indication:	Asthma and COPD in adults *Off-label indications:* Asthma and apnea in children Diuresis and prevention of kidney failure in neonates *Indication for TDM:* Debatable for routine TDM, but could be useful with toxicity or absence of efficacy
Sample material:	Serum
Time of sampling:	Through level
Storage conditions:	Refrigerator: 2-8°C. Storage outside the refrigerator for a few hours has negligible impact on stability.
Interpretation:	Therapeutic concentrations: 5 – 15 mg/L Toxic concentrations: > 20 mg/L
Evidence level:	4

Contents

Introduction

Theophylline belongs to the group of xanthine derivatives and is used in acute asthma attacks and apnea in children or for maintenance of asthma and COPD in adults, though its role in treatment is limited [1]. Theophylline induces bronchial dilation by relaxing the smooth muscle cells in the airways. Additionally, theophylline appears to have immunomodulatory and anti-inflammatory properties. Finally, it has positive inotropic and chronotropic effects on the heart and a vasodilatory effect [1].

Dosing guidelines

Treatment of asthma and COPD in adults

Adults [1,2]
Loading Dose: 4.6 mg/kg
(Note: a loading dose should NOT be given to patient who have received theophylline in the previous 24h)

Continuous IV Maintenance Dose:
75-350 mg, with a maximum of 1050 mg per day

Oral dose (maintenance): 10-15 mg/kg/day

Rectal dose (maintenance): enema of 10-50 mg/mL

Asthma and apnea in children

Children [3-8]
Loading Dose: IV 6 mg/kg

Continuous IV Maintenance Dose:
2-6 months: 0.4 mg/kg/hour
0.5-1 year: 0.7 mg/kg/hour
1-6 years: 0.9 mg/kg/hour
7-16 years: 0.7 mg/kg/hour
16 years: 0.5 mg/kg/hour

Oral dose (maintenance): 10-20 mg/kg/day

Rectal dose: 5-6 or 9 mg/kg as enema of 10-50 mg/mL (only based on limited data)

Diuresis and prevention of kidney failure in neonates

Neonates [9-13]
Loading Dose: IV 5-8 mg/kg/dose, once

Dosing guidelines in patients with altered pharmacokinetics

Kidney impairment: No dosage adjustment necessary [14]

Hepatic impairment: Monitoring is required due to risk of toxicity, dose with care.[14]

Indications/Criteria for TDM

The necessity of TDM for theophylline is debatable, as most patients with a standard dosage will fall within the current therapeutic window (5-15 mg/L), despite inter-patient variability. TDM may be useful for patients with pre-existing liver conditions and arrhythmias or those expected to exhibit extreme toxicity. Additionally, TDM is recommended when there is no therapeutic effect or when side effects occur. A trough level should be obtained at least 48-72 hours after the start of treatment.

Background
When considering whether drugs qualify for therapeutic drug monitoring (TDM), the drug must meet certain criteria, namely:

- A clear relationship between serum concentration and effect/toxicity
- Variable pharmacokinetics leading to inter- and intra-patient variability
- A narrow therapeutic window

For theophylline, there is a clear relationship between serum concentrations and therapeutic/toxic effects [15-17]. Additionally, the pharmacokinetics of theophylline exhibit significant inter-patient variability, and the drug is susceptible to interactions via CYP1A2, the primary metabolic route. This leads to the theoretical conclusion that theophylline meets the criteria for TDM, which should be performed when initiating therapy with theophylline.

Beyond the theoretical aspects, it is important to consider practical applications, such as trough levels found after standard dosing and whether higher trough levels lead to more side effects. In 2015 Rugelj *et al*. evaluated 127 theophylline levels after standard dosing (572±148 mg) in a Slovenian hospital. This resulted in levels of 9.7 ± 5.4 mg/L, thereby falling within the current therapeutic window (5-15 mg/L). [18]

A series of covariates were tested, including height, weight, age, smoking status, presence of heart failure, pneumonia, or COPD, presence of potential interacting drugs, and BMI, BSA, and lean body weight (LBW). Of all tested covariates, only LBW and the presence of COPD significantly influenced theophylline clearance and resulting levels. Due to the significance of LBW, dosage adjustments based on LBW were tested, leading to an increase in the average dosage from 572±148 mg to 876±207 mg. The study by McKay *et al*. had previously shown that a daily dose of 1200 mg is necessary to achieve levels within the therapeutic window (10-20 mg/L, average found level 18 mg/L) [19]. Again, with current insights, these outcomes are reassessed, and most patients with a standard dosage fall within the revised therapeutic window, possibly rendering TDM unnecessary [18].

Reference values

Therapeutic concentrations: 5 – 15 mg/L.
In some cases, higher concentration of 15-20 mg/L may be necessary.

Efficacy

Rugelj *et al.* (2015) evaluated 127 theophylline levels in a Slovenian hospital. The standard dosage was administered (572±148 mg), resulting in levels of 9.7 ± 5.4 mg/L. The study concluded that these are subtherapeutic levels, as the guideline at that time indicated a therapeutic window of 10-20 mg/L. Toxic levels (>20 mg/L) were found in 4% of cases, where doses were reduced. With current insights, most of the above levels fall within the current therapeutic window (5-15 mg/L) [18].

Relationship with occurrence of side effects & toxicity

Ohta *et al.* conducted a prospective study on the safety of theophylline in 3810 elderly patients with COPD or asthma [20]. In this population, a total of 261 adverse effects were observed in 179 patients (4.71%). Gastrointestinal side effects (2.9%), including nausea (1.1%), were most frequently reported, followed by metabolic abnormalities (1.16%), including hyperuricemia (0.42%) and elevated LDH (0.21%). Additionally, factors influencing the occurrence and severity of side effects were investigated. Liver diseases or arrhythmias almost doubled the risk of side effects. All other factors studied, including current disease status, co-medication, and smoking, had no significant impact on the occurrence or severity of side effects [20].

Moreover, the relationship between theophylline dosage/blood levels and the occurrence or severity of side effects was examined. Of the 179 patients with side effects, only 8 had blood levels >20 mg/L. The side effects observed were nausea (n=4), decreased appetite (n=3), diarrhea/bloating (n=1), and elevated alkaline phosphatase (n=1). Serious adverse events occurred in patients with theophylline levels within the therapeutic window. Therefore, there is no relationship between the occurrence and severity of side effects and theophylline blood levels [20].

Sampling & storage conditions

The theophylline levels are measured as through levels at least 48-72 hours after the start of treatment. The determination is performed in serum. The sample is stored in a refrigerator (2-8°C). Storage outside the refrigerator for a few hours has negligible impact on stability.

Toxicity

Toxicity may appear with concentrations above 20 mg/L. Acute toxicity appears with vomiting, nausea, metabolic acidosis, hypopotassemia, hypomagnesemia, hyperglycemia, and tachycardia. Chronic toxicity often results from accumulation of the drug due to saturation of metabolic pathways, decreased clearance, and/or interactions with co-administered drugs or herbal medications.

Theophylline's effects result from the antagonism of adenosine receptor and its indirect adrenergic activity. Consequently, toxic effects are associated with the antagonism of these receptors, leading to bronchodilatation, tachycardia, cardiac arrhythmias, seizures and cerebral vasoconstriction[21-23].

Treatment of toxicity involves reducing absorption (through activated charcoal with laxatives, and potentially gastric lavage or total bowel irrigation), accelerating elimination through hemodialysis, and managing symptoms. For a comprehensive overview of treatment options and corresponding dosages, please refer to toxicologie.org.

Additional information concerning the interpretation of results

Not applicable.

Background information [extended]

Pharmacodynamics

Theophylline, a xanthine derivative, exerts its pharmacodynamic effects primarily through inhibition of phosphodiesterase enzymes (particularly PDE3 and PDE4), leading to increased intracellular cyclic adenosine monophosphate (cAMP) levels in smooth muscle cells of the bronchioles. This mechanism results in relaxation of the bronchial smooth muscle, thereby promoting bronchodilatation, which is the main mechanism in the management of asthma and COPD. Additionally, theophylline antagonizes adenosine receptors, which contributes to its broncho-dilatory effects.

Pharmacokinetics

Numerous studies have been conducted to elucidate the pharmacokinetic parameters of theophylline. After oral administration, theophylline is almost completely and rapidly absorbed, reaching a C_{max} approximately 2 hours post-dose [24]. The average protein binding is around 60%, and the volume of distribution is 0.5 L/kg. Elimination varies between adults and children, primarily due to the incomplete hepatic function in children. In adults, theophylline is cleared by the liver at >90%, with the primary metabolic pathway being CYP1A2 [25]. In young children, hepatic function is still incomplete, resulting in approximately 50% of theophylline being excreted unchanged via urine [25]. Consequently, the elimination half-life of theophylline also differs between children and adults, being 3.5 hours and 5-6 hours, respectively [26].

Variability
In a review on population pharmacokinetics of theophylline, the following covariates were identified as having a significant impact on theophylline clearance [26]. For neonates, it is crucial to adjust dosing based on body weight, age, and the extent of oxygen support. Age and body weight indirectly describe clearance in neonates, related to the development of liver enzyme function and the overall organ development of the child [27,28]. Notably, the administration of oxygen significantly increases clearance, possibly due to hypoxia in many neonates in the study, which may decrease clearance [29-32]. Alleviating hypoxia consequently increases clearance.

For older children, theophylline clearance depends on age and, to a lesser extent, weight as significant covariates. Age is particularly important in the clearance of theophylline in children. Driscoll *et al*. demonstrated that total clearance increases by 10% for each additional year of age for children between 1 and 15 years old [33]. Other influences, including concomitant medications and gender, require further investigation, as conflicting or non-significant effects have been reported [26].

Adults have fully developed hepatic function, with the primary metabolic pathway via CYP1A2 being used for theophylline elimination. Interactions with this CYP enzyme were also identified as significant covariates in the analyses [34]. This was studied by including the smoking status of patients and the influence of interacting drugs, such as phenobarbital, quinolones, and verapamil [35-37]. Additionally, age and body weight again play roles in the variability among patients. Even when these covariates are included in a predictive model, not all variability can be explained. Genetic variance in CYP1A2 might also play a role, but this has not been investigated to date.

Pharmacogenetics

Not applicable.

Interactions

Theophylline is a substrate of CYP1A2 (major), CYP2E1 (minor), and CYP3A4 (minor). Therefore, interactions with CYP1A2 inhibitors and strong CYP3A4 inducers or inhibitors can be expected.

Decrease in theophylline concentration may occur due to certain inducers (e.g., carbamazepine, efavirenz, etravirine, phenobarbital, phenytoin, St. John's wort, lopinavir, nevirapine, primidone, rifampicin, ritonavir). Additionally, theophylline may lower carbamazepine concentrations (incidentally reported) and potentially also lower the phenytoin and lithium concentration.

Increase in theophylline concentration may result from allopurinol, cimetidine, potent CYP1A2 inhibitors, deferasirox, diltiazem, disulfiram, erythromycin, isoniazid, mexiletine, norfloxacin, anticonceptives, and verapamil. Furthermore, theophylline may reduce the effectiveness of erythromycin and the combination should be avoided.

PK parameters

	F	**Cl** (L/h^{-1})	**Vd** (L/kg)	**$t_{1/2}$** (h^{-1})	**Protein Binding** (%)	**T_{max}** (h)	**Ref.**
Children (> 1 year)	0.8 - 1	0.03 – 0.07	0.4 – 0.7	3.5 – 8.5	53 - 72	*	(26)
Adults	0.8 - 1	0.007 – 0.07	0.35 – 0.65	3 – 30	53 - 72	*	(26)

* dependent on type of sustained-release preparation.

Population models

Population	**Kabs** (h^{-1})	**Vd** (L)	**Kelm** (h^{-1})	**CL** (L/ h^{-1})	**F**	**Ref.**
General	0.3	0.5 ± 0.16	0.064 ± 0.032	0.00016 ± 0.00008	0.96 ± 0.08	(38)

Literature

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Colophon

This guideline has been constituted by S. van der Gaag, hospital pharmacist and clinical pharmacologist in training, under the auspices of TDM, Toxicology and Pharmacogenetics committee (TTF) of the Dutch Association of Hospital Pharmacists (NVZA) and the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT)
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Appendices

Not applicable.

Revision

This guideline has been revised by S. van der Gaag, hospital pharmacist and clinical pharmacologist in training. The guideline was updated based on most recent literature and translated to English.