Influence of Absorption Rate on the Metabolic Kinetics of Theophylline

S.A. Hotchkiss, J. Caldwell,
Department of Pharmacology, St. Mary’s Hospital Medical School,
London W2 1PG, U.K.

Summary

Theophylline is administered orally to patients primarily in the form of sustained-release preparations. In view of the widespread use of these formulations and the non-linear kinetics reported to exist for theophylline, it is important to assess the effect of slow delivery upon the metabolic kinetics of the drug. If certain metabolic pathways are saturated when a conventional preparation is administered, this may occur as a result of the immediate high concentration of drug reaching the liver overwhelming the enzymes responsible for metabolism. If this is the case, one might expect that if a drug is delivered slowly to the liver, as occurs when a sustained-release preparation is administered, this may not saturate the metabolic pathway concerned and hence metabolism will not become zero-order.

Single doses of conventional and sustained-release theophylline preparations were administered to 5 healthy volunteers on separate occasions. After conventional preparations, high plasma theophylline levels were observed, together with zero-order elimination of the 3 major metabolites, 3-methylxanthine, 1-methyluric acid and 1,3-dimethyluric acid. Plasma levels were lower after roughly equivalent doses of sustained-release theophylline, and elimination was only observed to become zero-order for the metabolite 3-methylxanthine.

These observations indicate that the rate of absorption of theophylline from the gastrointestinal tract can affect its pharmacokinetic disposition. This may be of significance in the clinical situation for the safe and effective use of theophylline in the management of asthma.

Introduction

Enzymic metabolism is an important determinant of the pharmacokinetic profile of many drugs. Enzyme kinetics follow the Michaelis-Menten equation, with the rate of conversion of metabolite(s) being a function of enzyme affinity and concentration and the concentration of drug, such that the rate becomes constant above certain substrate concentrations.

There have been a number of reports that the pharmacokinetics of theophylline are dose-dependent, arising from observations of a disproportionate increase in plasma concentration with increasing dose (non-linear kinetics) [1, 2]. More specifically, certain authors have found that the plasma elimination kinetics for theophylline are dose-dependent
within the therapeutic dose range [3], which has been explained in terms of the saturation of metabolic pathways. Monks et al. [4, 5] reported that the rate and extent of theophylline metabolism was enhanced when other methylxanthines were removed from the diet, possibly due to saturation of the N-demethylation pathway giving rise to 3-methylxanthine by the normal body pool (ca. 300 mg) of methylxanthines. Other authors have presented evidence for the occurrence of non-linear elimination kinetics for all three major theophylline metabolites [3, 6].

Considering the fact that there are a great variety of sustained-release preparations of theophylline in widespread use, it is surprising that the influence of delivery rate upon the kinetics of its metabolism has not been investigated. It is possible that delayed, slowed or prolonged absorption may affect the metabolic disposition of certain drugs, especially where saturation of metabolic pathways or first-pass metabolism are involved.

When a conventional theophylline preparation is administered, from which absorption is rapid and complete, high concentrations of the drug will reach the liver which may saturate the enzymes responsible for metabolism. However, if absorption is retarded, and the drug is delivered more slowly to the liver, as occurs when a sustained-release preparation is administered, saturation of these metabolic pathway(s) may not occur and metabolism will not become zero-order.

The present study was designed to investigate the effect of absorption rate upon the metabolic kinetics of theophylline in healthy human volunteers. In order to achieve different rates of absorption, both conventional and sustained-release formulations of theophylline were administered, the former giving immediate and the latter delayed delivery to the site of metabolism.

Materials and Methods

Conventional-release aminophylline (theophylline ethylenediamine) tablets (100 mg Aminophylline BP containing 80 mg theophylline) and controlled-release aminophylline (350 mg Phyllocontin Forte containing 280 mg theophylline) were used in the study. 5 healthy volunteers (3M, 2F, 23–37 y; 54–70 kg) received each medication orally on separate occasions after an overnight fast and 4 days abstention from all dietary methylxanthines. Food was withheld for 2 hours after dosing. Serial blood and urine samples were taken up to 30 h and theophylline in plasma was determined by the HPLC method of Cotgreave & Caldwell [7], and theophylline and metabolites in urine were determined by the HPLC method of Hotchkiss & Caldwell [8].

Results

Maximum plasma levels (C\text{max}) of theophylline were achieved after 1.5–3 h with the conventional tablets, and were up to 3 times greater than after the sustained-release preparation (eg. 11.1 vs. 3.4 \(\mu\)g/ml), the latter being achieved only after 10 h. When C\text{max} values were corrected for dose they were significantly lower (by 100%) after the sustained release formulation.

From plasma concentration-time graphs (Fig. 1) the elimination phase of theophylline was monoexponential. Although the elimination rate constant (k) appeared to be smaller