Determinants of free theophylline clearance in asthma

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1 The free and total plasma and saliva concentrations of theophylline were measured during a dosing interval at steady state in nineteen asthmatic subjects receiving a once-daily theophylline preparation (Riker TCR-1).

2 Saliva theophylline clearance (mean $\pm$ s.d. 5.8 ± 2.1 l h⁻¹) was closely related to total plasma theophylline clearance (mean 3.6 ± 1.2 l h⁻¹) ($r = 0.958$, $n = 19$, $P < 0.001$).

3 Saliva theophylline clearance was closely related ($r = 0.967$, $n = 19$, $P < 0.001$) and numerically very similar to the free plasma theophylline clearance (mean 5.8 ± 1.9 l h⁻¹) (mean difference = 0.06 ± 0.12 s.e. mean).

4 Free plasma theophylline clearance was significantly, although weakly, related to body weight and to the plasma free thyroxine concentration which together accounted for over 40 per cent of the variability in free clearance.

5 Theophylline administered for 2 weeks did not affect plasma free thyroxine (FT4) free tri-iodothyronine (FT3) or reverse tri-iodothyronine (rT3) concentrations compared with placebo.

Keywords theophylline clearance asthma

Introduction

Asthmatic subjects show wide variation in their ability to metabolise the antiasthmatic drug, theophylline. Although several determinants of the rate of theophylline metabolism have been identified, none of these appear to be particularly strong (Jusko *et al.*, 1978). It has been recently suggested that theophylline metabolism may be related to thyroid status, even in euthyroid subjects (Vozech *et al.*, 1984). We therefore decided to investigate the relationship between thyroid status and theophylline clearance in euthyroid asthmatic subjects receiving the drug chronically (rather than acutely) and using free as well as total clearance as a measure of drug metabolism. In addition, the effect of theophylline administration on thyroid hormone concentrations in plasma were investigated to assess whether

theophylline administration might itself affect thyroid hormone concentrations in man.

Methods

Nineteen clinically euthyroid non-smoking asthmatic patients (eight males) aged between 19 and 67 years were studied. They constituted a part of the population of asthmatic subjects who had volunteered for a study of a new once daily preparation of theophylline which has been reported elsewhere (Williams *et al.*, 1986; Alwazir *et al.*, 1987). In brief, subjects were started on 300 mg daily of theophylline or, in those patients already taking theophylline, were changed to the once daily preparation at the same dose. The

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daily dose was increased by 300 mg every week to achieve either a pre-dose plasma concentration of more than 8 mg l⁻¹ or until a maximum daily dose of 1200 mg day⁻¹ had been achieved. The dose was taken after breakfast. The subjects were also receiving other drugs for asthma including inhaled sympathomimetic agents and inhaled corticosteroids.

After 7 days, when steady-state had been achieved, patients attended hospital having fasted from midnight and having not taken theophylline tablets on that morning. Coffee, tea, chocolate and caffeine containing soft drinks were denied for the following 24 h. An intravenous cannula was inserted and blood taken for measurement of total plasma theophylline concentration by h.p.l.c. (Miksic & Hodes, 1979) at 12 h after the index dose. The h.p.l.c. method had a lower limit of sensitivity of 0.1 mg l⁻¹ and within and between-day precisions of 3.5 and 5.4% respectively. Saliva was collected after stimulation by chewing Teflon® tape and analysed by the same h.p.l.c. method, using the appropriate saliva standards. The free fraction of theophylline was measured by equilibrium dialysis at 37° C as described elsewhere (Ebden *et al.*, 1984) and the free concentration calculated by multiplying the total plasma theophylline concentration by the free fraction. Total plasma theophylline clearance (CL) at steady-state was calculated using the formula:

$$CL = \frac{F \cdot D}{AUC}$$

where *D* was the daily theophylline dose, *F* (the bioavailability) was assumed to be unity (data on file, Riker Laboratories), AUC was the area under the plasma concentration-time curve measured by the trapezoidal method 0–24 h. Saliva and free plasma theophylline clearances were calculated using the same equation but substituting the area under the saliva or free plasma concentration-time curve for AUC.

Patients received either active theophylline or matching placebo for 2 weeks each in a randomised double-blind, cross-over fashion. Sufficient plasma was obtained from 16 of the 19 subjects to measure free tri-iodothyronine (FT3) and free thyroxine (FT4) after each 2 week period phase and to measure reverse tri-iodothyronine (rT3) from 14 subjects. In the remaining three subjects, the plasma thyroid hormone concentrations at the end of the study were used to assess the relationship with drug clearance after it had been shown that theophylline administration did not affect thyroid hormone concentrations.

Thyroid hormone concentrations (FT4 and FT3) were measured using Amerlex kits (Amer-sham International plc) and rT3 by radioimmuno-assay.

Statistical analysis was performed using Student's paired *t*-test and least squares linear correlation and multiple linear regression analysis when appropriate and *P* < 0.05 was taken as the minimum level of statistical significance.

Results

The age of the subjects varied between 19 and 67 years and their weight from 51.0 to 95.2 kg (mean 72.7 ± 13.1 kg s.d.). Total plasma theophylline clearance varied from 1.9–6.2 l h⁻¹ (mean 3.6 ± 1.2 l h⁻¹) and their free fraction from 0.60–0.70 (mean 0.63 ± 0.02). Saliva theophylline clearance ranged from 2.8–10.4 l h⁻¹ (mean 5.8 ± 2.1 l h⁻¹) and the free plasma clearance from 3.0–10.0 l h⁻¹ (mean 5.8 ± 1.9 l h⁻¹). There was a close relationship between saliva and free plasma clearance (*r* = 0.967, *n* = 19, *P* < 0.001). Saliva clearance = 0.3 + 1.1 × free plasma clearance, (Figure 1a). There was also a highly significant relationship between free clearance and total theophylline clearance (*r* = 0.958, *n* = 19, *P* < 0.001, Figure 1b). Free T3 (FT3) varied from 4.8–8.9 pmol l⁻¹ (mean 6.3 ± 0.98 pmol l⁻¹, reference range 3–9 pmol l⁻¹), the FT4 from 12.6–18.2 pmol l⁻¹ (mean 15.0 ± 1.57 pmol l⁻¹, reference range 8–26 pmol l⁻¹) and the rT3 from 0.24–0.56 nmol l⁻¹ (mean 0.38 ± 0.07 nmol l⁻¹, reference range < 0.54 nmol l⁻¹). There was a significant relationship between FT4 concentration and both total and free theophylline clearance (*r* = 0.519 and *r* = 0.509, *P* < 0.05 in both cases Figures 2a and b). The FT3 was not significantly related to either total or free clearance (*r* = -0.062 and *r* = -0.046 respectively, *P* > 0.05). There was no relationship between rT3 and either total or free clearance (*r* = 0.273 and *r* = 0.237, *P* > 0.05 in both cases). Age did not correlate significantly with either total or free theophylline clearance (*r* = 0.05 and *r* = 0.02, *P* > 0.05) and although the simple correlation between body weight and total and free clearance was not significant (*r* = 0.230 and *r* = 0.265, *P* > 0.05), multiple linear regression analysis showed that body weight as well as FT4 concentrations were significantly related to free plasma theophylline clearance (*t* = 2.031 for body weight and 3.040 for FT4, *P* < 0.05 in both cases). Together these variables contributed 41.1% to the variability in free plasma theophylline clearance.

The FT3 was 6.04 ± 0.86 pmol l⁻¹ during the

Figure 1 Relationship between (a) saliva and free plasma theophylline clearances and (b) plasma free and total theophylline clearances.

Figure 2 Relationship between plasma free thyroxine concentration and (a) total theophylline clearance and (b) free theophylline clearance.

placebo phase and 6.43 ± 0.97 pmol l⁻¹ during the theophylline phase ($n = 16$, $P > 0.05$, Figure 3). FT4 was 14.83 ± 2.32 pmol l⁻¹ during the placebo phase and 15.27 ± 1.52 pmol l⁻¹ during the theophylline phase ($n = 16$, $P > 0.05$, Figure 3). rT3 was 0.37 ± 0.06 nmol l⁻¹ during the

placebo phase and 0.39 ± 0.08 nmol l⁻¹ during the theophylline phase ($n = 15$, $P > 0.05$, Figure 3). Thus theophylline administration did not significantly affect the plasma concentration of any of the thyroid hormones in these euthyroid subjects.

Figure 3 Effect of theophylline on the plasma concentration of (a) FT4 (b) FT3 and (c) rT3. The open circles indicate the mean ($\pm$ s.d.).

Discussion

Since we have already shown a relationship between the saliva and total plasma concentration of theophylline in subjects given this formulation of theophylline (Williams *et al.*, 1986), it is not surprising that the saliva and total theophylline clearances correlated so closely. Since the saliva to plasma concentration ratio was very similar to the free fraction of the drug in plasma, the saliva clearances were not only closely related to the free clearance but were numerically similar and it appears that under the conditions of the study, saliva clearance can be used to assess free theophylline clearance.

This study also confirms that theophylline clearance can vary considerably, even in a non-smoking population and a greater than three-fold variation was seen in our asthmatic subjects. Since theophylline's effect is related to the plasma concentration of the drug then the dose will need to be titrated in order to be optimal. Unfortunately none of the easily measured variables in patients (e.g. age and body weight) are closely related to plasma theophylline clearance and in some small studies, the relationships between weight or age and theophylline clearance have not been significant (Cusak *et al.*, 1980; Blouin *et al.*, 1982). Our study confirms that body weight is a significant (albeit weak) determinant of theophylline clearance when the effect of other factors is kept constant by using multiple linear regression techniques. Nevertheless, the relationship is too weak to be of useful predictive value clinically.

Vozech and co-workers have shown a significant relationship between plasma FT4 concentrations and total plasma theophylline clearance

in euthyroid subjects given a single dose of theophylline (Vozech *et al.*, 1984). There was no relationship between theophylline clearance and FT3 (which is considered to be the active moiety) although the reason for this is unknown. We have found a similar relationship (with a correlation coefficient similar to their value) between FT4 and total (as well as free) plasma theophylline clearance. Our study, however, was at steady-state and in euthyroid asthmatic patients rather than after single doses in a mixed group of asthmatic, chronic bronchitic and treated hyperthyroid subjects, and in addition we have shown no relationship between rT3 and drug clearance. We also have no ready explanation for the relationship between FT4 and theophylline clearance, although the link between the two is highlighted by the finding that in six hyperthyroid subjects rendered euthyroid with drug treatment, the change in FT4 was related to the change in plasma theophylline clearance (Vozech *et al.*, 1984).

One alternative explanation for the relationship between thyroid hormone levels in euthyroid subjects and theophylline metabolism is that theophylline administration might affect plasma thyroid hormone concentrations. It has certainly been shown that in a patient who took a theophylline overdose, the T3 and T4 concentrations rose temporarily although the mechanism for this phenomenon is unknown (Valensi *et al.*, 1986). We have demonstrated that at steady-state using conventional doses of theophylline in asthmatic subjects, no change in the circulating thyroid hormone concentrations occurs as a consequence of theophylline administration. Thus,

although the mechanism of this relationship is unknown, it appears that theophylline metabolism is related to FT4 concentration, even within the euthyroid range, and together with body weight, FT4 concentrations accounted for over 40% of the variability in theophylline clearance observed

in this group of euthyroid asthmatic subjects.

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