Concomitant administration of theophylline and oxamniquine in rats: Effect on theophylline clearance

ABUGA O.K., BOSIRE AND KOKWARO G.O.*

Department of Pharmaceutics & Pharmacy Practice, Faculty of Pharmacy, College of Health sciences, University of Nairobi, P.o. Box 19676, Nairobi, Kenya.

*Author to whom correspondence should be addressed.

This report describes an investigation into the effect of oxamniquine on systemic clearance of theophylline in rat. Male Wistar rats (N=12, 5 weeks old) were divided into 3 groups (N=4 per group) and administered buffer plus theophylline (10mg kg^{-1}; controls, oxamniquine (5 mg kg^{-1};) and theophylline (10mg kg^{-1}) or oxamniquine (20 mg kg^{-1}) and theophylline (10mg kg^{-1}) intravenously. Theophylline clearance was estimated from a single plasma sample obtained 6 hours post drug administration. Oxamniquine administration had no effect on theophylline clearance compared to controls. It was concluded that clinically important interaction between oxamniquine and theophylline is unlikely to occur.

Key Words: Theophylline, metabolism, effect of oxamniquine.

INTRODUCTION

Inhibition of hepatic drug metabolism can result in toxicity if the inhibited pathway contributes significantly to the overall clearance of a drug. We have recently reported [1] that the schistosomicidal drug oxamniquine inhibits the metabolism of caffeine, hexobarbitone and antipyrine in vivo in mice.

The metabolism of caffeine, a widely consumed compound, is mediated by the isoenzyme cytochrome P450 1A2 (CYP1A20 [2].

This is the same isoenzyme that metabolises theophylline [3]. Oxamniquine is no longer widely used but may still be prescribed when the broad spectrum schitosomicidal drug praziquantel is not available. Theophylline is a widely used bronchodilator with a narrow therapeutic index, and its clearance is significantly reduced by factors affecting liver enzyme activities, e.g liver disease [4,5]. It is possible that some patients taking oxamniquine may be prescribed theophylline or may take large quantities of beverages containing caffeine. The aim of the present study was to investigate the effect of oxamniquine on CYP1A2 activity, using theophylline as the probe compound.

The rat was used since CYP1A2 in rat liver is orthologous to that in human liver [2]. In addition, the clearance of theophylline in rat can be estimated from a single plasma sample [6], thus avoiding repeated sampling which may cause trauma to small animals.

EXPERIMENTAL

Chemicals and solvents

Theophylline and 8-chlorotheophylline (the internal standard) were purchased from the Sigma Chemical Co. (Poole, England). Oxamniquine was kindly donated by Pfizer Ltd. (Sandwich, England) while methanol and acetonitrile (HPLC grade) were purchased from Fisons Ltd (Loughborough, England).

Preparation of drug solutions

Solutions of oxamniquine [7] and theophylline [8] were prepared as previously described.

Animals and treatments

Male Wistar rats (5 weeks old, N=12) were obtained from the Faculty of Pharmacy animal house, and divided into three groups (N=4 per group). Group 1 (controls) received citrate-phosphate buffer, pH 5.0 (i.e the vehicle used to dissolve oxamniquine; 0.3 ml via the tail vein), followed by theophylline via the same route. Group II received oxamniquine (5 mg kg^{-1}) followed by theophylline (10 mg kg^{-1}), while group III received oxamniquine (20 mg kg^{-1}) and theophylline (10 mg kg^{-1}).

A single blood sample (0.3ml) was obtained by cardiac puncture, 6 hours post drug administration [6]. Both drug administration and blood sample collection were performed on rats under light ether anaesthesia. Blood was collected into heparinised plastic tubes and plasma obtained by centrifugation (600xg; 10 min.). Plasma was stored at -20°C, until analyzed for theophylline levels by HPLC [9].

Calculations

The total clearance (CL) of theophylline was calculated from the estimated plasma theophylline concentration (C), the dose (D) of theophylline administered, the

volume of distribution (V) and the sampling time (T) thus [10]:

$CL = [\ln (D/V) - \ln C) \times (V/T)$

V was assumed to be 0.49 1 kg^{-1} [6]. Mean clearance values in oxamniquine-treated rats were compared with the mean value in control rats using the student's t-test for unpaired data. $P<0.05$ was taken as significant.

RESULTS AND DISCUSSION

Estimated mean (± sd) clearance values were 3.05 ± 0.4, 3.04 ± 0.2 and 3.14 ± 0.6 ml min-1 kg^{-1} in group I (controls), group II and group III animals, respectively. Treatment with oxamniquine had no significant effect on theophylline clearance in rats.

In a previous study [1], we reported that oxamniquine significantly inhibits the metabolism of caffeine, a substrate for CYP1A2. However, the results of the present study indicate that the metabolism of theophylline, another substrate for CYP1A2, is not affected by oxamniquine. This apparent discrepancy is probably due to the differences in the doses of the two substrates used. Therapeutic concentrations of oxamniquine show wide variability [11], but the doses used in the present and previous study [11] probably resulted in vivo concentrations within the therapeutic range. In the previous study [1], however, tracer doses of radio labelled caffeine were used. The tracer doses better reflected the concentrations of caffeine that would be expected in circulation following consumption of caffeine containing foods and beverages. The dose of theophylline used in the present study has been previously used to screen for potential inhibitors of theophylline metabolism at therapeutic doses [6]. Thus, although the present results suggest that oxamniquine has no significant effect on theophylline metabolism, further investigations are required.

CONCLUSIONS

Although the results of the present study suggest that no clinically significant interaction between oxamniquine and theophylline is likely to occur following concomitant administration of the two drugs, patients taking oxamniquine need to be cautioned about possibility of interaction with caffeine in foods and beverages. This could lead to manifestations of caffeine-related side effects.

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