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Effect of Tamoxifen on the Pharmacokinetics of Theophylline in Rats

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Abstract

The effect of tamoxifen on the pharmacokinetics of theophylline was investigated in male Sprague–Dawley rats.

The oral administration of tamoxifen at a dose equal to 40 mg kg^{-1}, 48 h before the intravenous injection of theophylline 10 mg kg^{-1}, significantly ($P < 0.05$) increased the clearance of theophylline by 39%, with no apparent effect on the volume of distribution. As a consequence, the elimination half-life of theophylline was significantly ($P < 0.05$) shortened in the tamoxifen-treated rats (3.56 ± 0.39 h vs 5.25 ± 0.48 h) as well as its mean residence time (5.04 ± 0.60 h vs 7.50 ± 0.75 h). Although these data cannot be directly extrapolated to the clinical situation, they provide experimental support to suggest that more attention should be paid to the potential risk of pharmacokinetic interactions in the presence of tamoxifen.

The selection of drug interaction studies has usually been based on two main criteria: the likelihood of co-prescription, and therapeutic index (Tucker 1992). This may explain why so many papers have been published on the pharmacokinetic drug interactions with theophylline (Upton 1991a, b). This compound which is extensively metabolized by hepatic cytochrome P-450-dependent enzymes, has also gained considerable interest as a model drug in assessing hepatic drug-metabolizing enzyme activity (Teunissen et al 1985), and because its metabolism is qualitatively similar in humans and rats, this animal has been considered to be a good model for pharmacokinetic investigations (Tang Liu et al 1982).

Tamoxifen is a non-steroïdal anti-oestrogen which has long been used in the treatment of breast cancer (Buckley & Goa 1989) and more recently has been proposed for its prevention (Prentice 1990; Nayfield et al 1991; Powles et al 1994). Tamoxifen is also extensively metabolized by cytochrome P-450 hepatic mixed function oxidase in man and various other mammalian species (Fromson et al 1973a, b; Robinson et al 1991; Mani et al 1993a, b). It has been shown that tamoxifen is a potent inhibitor of some mixed function oxidases in-vitro (Meltzer et al 1984) and may inhibit its own metabolism (Adam 1981; Borgna & Rochefort 1981; Camaggi et al 1983), as well as the biotransformation of other drugs (Ritchie & Grant 1989; Tenni et al 1989). Co-administered drugs such as aminoglutethimide (Lien et al 1990) and methoxyprogesterone (Reid et al 1992) may also interfer with tamoxifen metabolism.

The purpose of this investigation was to examine the influence of tamoxifen on the pharmacokinetics of theophylline administered intravenously to rats.

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Materials and Methods

Drugs and chemicals

Theophylline was purchased from Bruneau Laboratories, Paris (Théophylline Bruneau, 240 mg $(4\,mL)^{-1}$ injectable vials), and tamoxifen was a gift from Zeneca Pharma, Paris (Nolvadex 10-mg tablets). All other chemicals used were of analytical grade.

Animals

Male Sprague-Dawley rats (Elevage Dépré), weighing 245 ± 7 g (mean ± s.e.m.), were used throughout the study. The animals were housed at room temperature in wire cages, and given free access to food and water until 12 h before theophylline administration when they were fasted with free access to water. Animals were randomly distributed into treated or control group. To withdraw blood from the rats, a Silastic catheter (Dow Corning) was inserted under anaesthesia (45 mg kg^{-1} of sodium pentobarbital: Pentobarbital Sodique, Sanofi), in the right jugular vein one day before dosing, it was heparinized and externalized between the two shoulder blades.

Drug administration and sampling

One Nolvadex 10-mg tablet was ground and dispersed in 1 mL of 5% aqueous arabic gum suspension. This preparation (treated group), or vehicle only (control group) was administered orally by gastric intubation approximately 48 h before theophylline injection in a tail vein (10 mg kg^{-1} as a bolus). Blood samples were taken before and at 0.25, 1, 2, 4, 6, 8 and 10 h after injection and transferred to dry tubes. After centrifugation, serum was harvested and frozen at − 20°C until analyzed for theophylline.

Analytical methods

A specific immunoenzymatic assay (Biomérieux) was used for analysis of theophylline in serum. Characteristic features of the

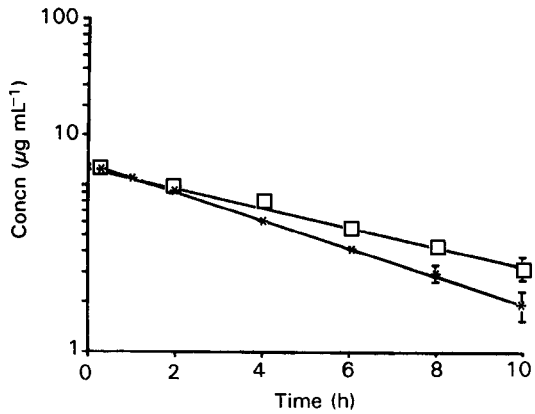

FIG. 1. Serum concentrations (mean ± s.e.m.) of theophylline, after single intravenous administration (10 mg kg^{-1}) to rats pre-treated (*) or untreated (□) with tamoxifen (n = 7 in each group).

assay were 0·25 μg mL^{-1} for the limit of detection, and 0.50 μg mL^{-1} for the lower limit of quantification; the intra-day reproducibility was 2%, inter-day reproducibility, 2%, and accuracy, 2%.

Pharmacokinetic analysis

Non-compartmental pharmacokinetic analysis was conducted using standard formulae (Gibaldi & Perrier 1982), with the Siphar software (SIMED, Créteil). Pharmacokinetic parameters calculated in the control and treated groups were normalized to body weight and compared statistically using a Student's *t*-test, with an α risk of 0·05.

Results

The decay of serum theophylline concentrations with time showed first-order kinetics in the absence and in the presence of tamoxifen as illustrated in Fig. 1. Initial concentrations were similar in the control and treated groups, suggesting that theophylline volume of distribution was unchanged in the presence of tamoxifen. A decrease of theophylline serum concentrations was observed at the terminal phase after co-administration with tamoxifen. Accordingly theophylline elimination half-life was significantly reduced in the presence of tamoxifen. Pharmacokinetic parameters values are presented in Table 1.

Table 1. Pharmacokinetic parameters obtained from theophylline serum concentrations vs time data, after intravenous administration (10 mg kg^{-1}) to rats pre-treated or untreated with tamoxifen.

	Theophylline alone	Theophylline with tamoxifen
CL (mL h^{-1} kg^{-1})	108 ± 9	150 ± 12*
V (mL kg^{-1})	784 ± 33	737 ± 32
$t_{\frac{1}{2}}$ (h)	5·25 ± 0·48	3·56 ± 0·39*
MRT (h)	7·50 ± 0·75	5·04 ± 0·60*

Mean ± s.e.m. values (n = 7 in each group). *Significantly different, $P < 0.05$.

Discussion

The present study shows that tamoxifen has no statistically significant effect on theophylline volume of distribution (Table 1), with an estimated value of this parameter in good agreement with previously published data (675 ± 13 mL kg^{-1} following an intravenous dose of 50 mg kg^{-1} (Arimori & Nakano 1988) and 970 ± 130 mL kg^{-1} following an intravenous dose of 20 mg kg^{-1} (Busby & Lesko 1987). It also shows that tamoxifen has an effect on theophylline elimination, as reflected by a statistically significant increase of clearance (39% on average). As a consequence of this increase of clearance associated with unchanged volume of distribution, theophylline elimination half-life was shortened (by 32% on average ($P < 0.05$)), as well as mean residence time (by 33% on average ($P < 0.05$)).

These data are consistent with a recent demonstration that tamoxifen is an effective enzymatic inducer which can be considered, at least in part, to be a weak phenobarbital-like inducer (Nuwaysir et al 1995). However, many factors, including gender (Mani et al 1993a; Bouquet et al 1996), or dose and route of administration as well as the duration of treatment (Teunissen et al 1985; Zeruersenay et al 1992), may have an effect on such experimental results which should therefore not be directly extrapolated to the clinical situation.

Little attention has been paid until now to the potential risk resulting from pharmacokinetic interactions in patients treated with tamoxifen. Yet several cases of life-threatening interactions between tamoxifen and warfarin have been described (Lodwick et al 1987; Ritchie & Grant 1989; Tenni et al 1989), and there has been a recent report of fatal interaction between tamoxifen and acenocoumarol (Gustovic et al 1994). Our study presents experimental data confirming that tamoxifen may be responsible for pharmacokinetic interactions with associated drugs. Again these results cannot be directly extrapolated to the clinical situation, and every pharmacokinetic interaction with tamoxifen would not necessary be life threatening. However our data suggest that more care should be paid to this potential risk, which should be especially considered for the evaluation of the benefit-to-risk ratio if the drug had to be administered to healthy women in order to prevent breast cancer.

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