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PHARMACOKINETICS OF TOREMIFENE

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Summary—The pharmacokinetics of toremifene has been investigated in man after single and multiple oral doses. Toremifene was completely absorbed without first-pass metabolism. Peak concentration in serum was achieved in 4 h. Mean half-lives of distribution and elimination were 4 h and 5 days, respectively. Kinetics was linear in the studied dose-range of 10–680 mg. Toremifene was over 99% bound to plasma proteins and extensively metabolized. The main metabolites in serum were demethyl- and deaminohydroxytoremifene. In patients receiving multiple dosing of 60 mg/day serum steady-state level of toremifene was 0.8 μg/ml on average. The level of demethyl metabolite was twice and that of deaminohydroxy metabolite was one tenth of toremifene.

INTRODUCTION

Toremifene is a new antiestrogen under investigation for its antitumor properties for breast cancer [1, 2]. The pharmacokinetics of toremifene has been studied at the Research Center of Farmos Group Ltd in laboratory animals and in more than 100 human subjects after single and multiple dosing. The purpose of this article is to summarize the results of these studies. Human pharmacokinetic data are the main topic.

MATERIALS AND METHODS

Pharmacokinetic studies after single dose and repeated doses for 5 days were performed in connection with phase I studies at different dose-levels in a total of 70 postmenopausal female volunteers. Toremifene steady-state levels in serum were determined in patients participating in a phase II study. The studied patients had been on therapy for at least 42 weeks. In order to estimate the bioavailability of tablet formulation, a cross-over study was designed using twelve healthy male volunteers.

Toremifene and its two metabolites in serum were determined by a specific method based on quantitative thin-layer chromatography: an aliquot of serum was extracted at pH 7 with cyclohexane–butanol (9:1). The organic phase was evaporated to dryness, and a part of the dissolved residue was applied on a silica gel TLC plate with an autospotter. The plate was developed in chloroform/cyclohexane/triethylamine/ethanol (25:20:5:1) and dried on a thermoplate. The analytes were converted into fluorescing compounds by exposing the plate to strong u.v. irradiation. The fluorescence was measured by scanning with a chromatogram spectrophotometer using 315 nm as excitation wavelength and a 390 nm cut-off filter. Quantification was achieved by comparison of the peak heights for samples and standards. The detection limit was about 5 ng/ml, and the variance was found to be 6% on average for all three compounds.

Serum toremifene concentration/time data were analyzed with PCNONLIN computer program [3] according to a two-compartment model or by standard model independent methods.

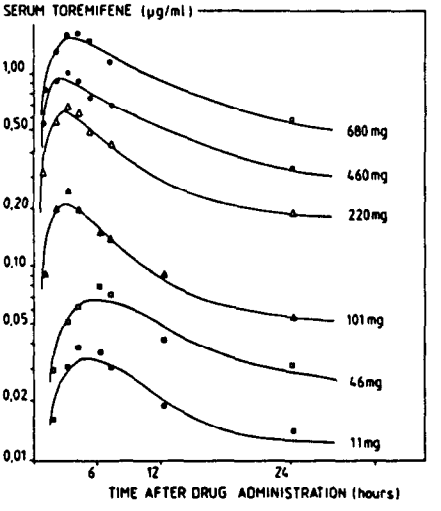

Fig. 1. Mean serum toremifene levels in female subjects after a single dose of toremifene (n = 3–5/dose).

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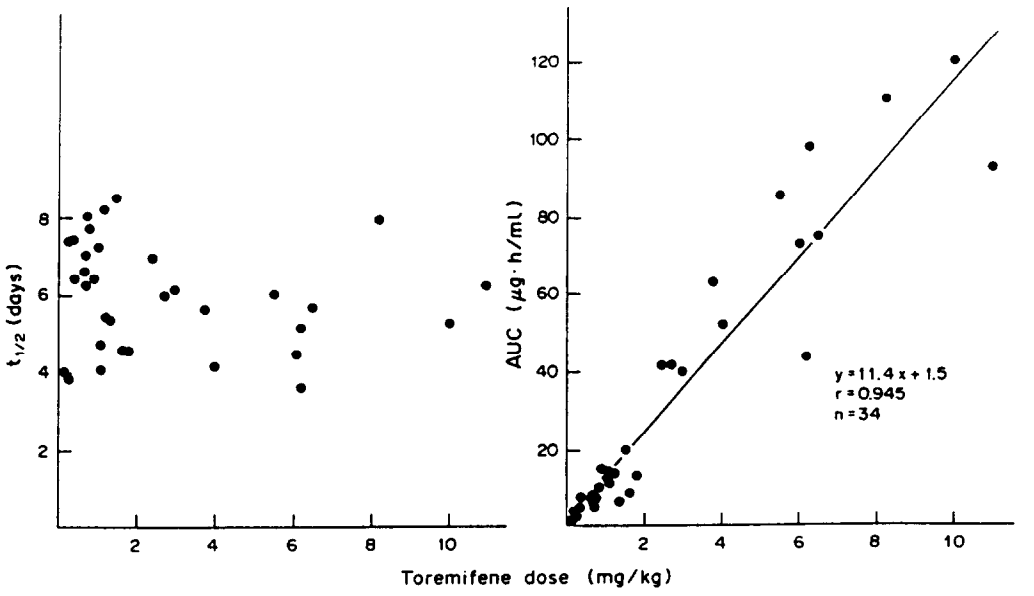

Fig. 2. The relationship between pharmacokinetic parameters and toremifene dose.

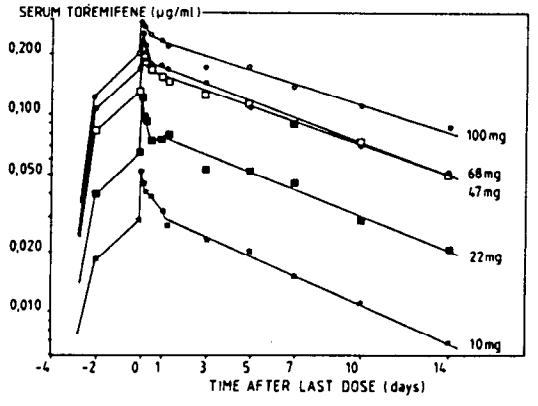

Fig. 3. Mean serum toremifene levels in female subjects following once daily dosing of toremifene during five days (n = 3–5/dose level).

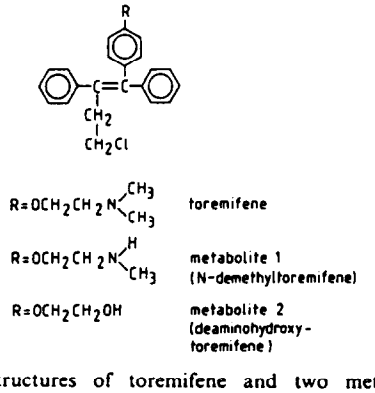

Fig. 4. Structures of toremifene and two metabolites quantified in human serum.

RESULTS AND DISCUSSION

Toremifene is readily absorbed from the gastrointestinal tract. The absolute bioavailability for oral toremifene was estimated to be almost 100% in

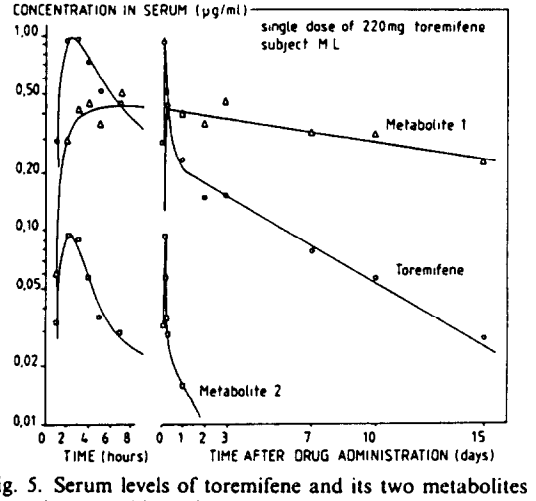

Fig. 5. Serum levels of toremifene and its two metabolites in one subject after single dose of toremifene

laboratory animals. In man peak concentrations in serum were achieved approximately 4 h after oral administration (Fig. 1). After the peak, the disappearance occurs in two phases, with a distribution half-life of about 4 h and a mean elimination half-life of 5 days. In the studied dose-range, 10–680 mg, the kinetics of toremifene was linear: absorption and elimination rates did not change but AUCs increased linearly with increasing dose (Fig. 2). After five days treatment with toremifene, using once daily dosing, the accumulation of toremifene in serum was evident and the linearity of the kinetics was confirmed (Fig. 3).

Ten metabolites of toremifene have been identified in rat [4] and human feces (unpublished results). In the single and multiple dose studies in man, two metabolites have been quantified in serum samples. The main metabolite is N-demethyltoremifene. The metabolite formed by side chain deamination and

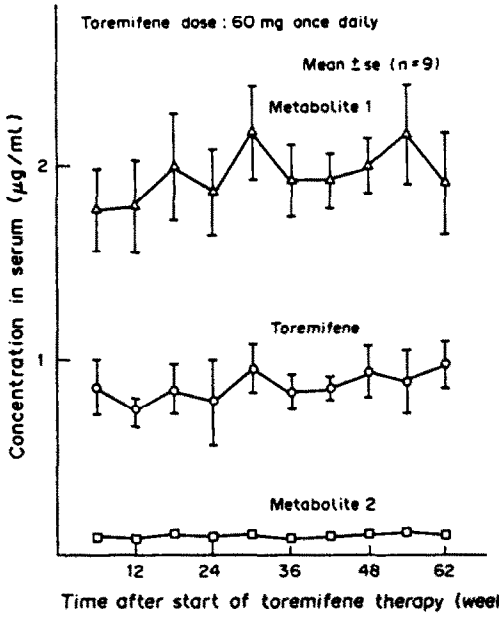

Fig. 6. Mean steady-state levels of toremifene and its two metabolites during toremifene therapy.

subsequent hydroxylation has also been quantified (Fig. 4).

The formation of *N*-demethyltoremifene occurs quite slowly but, by 8 h after administration, the concentration of this metabolite exceeds the level of unchanged drug. The disappearance rate of this metabolite is somewhat slower than that of toremifene. The formation of deaminohydroxytoremifene is relatively fast, but the peak level is less than one tenth of that of toremifene and it disappears much more rapidly (Fig. 5).

The consequence of the long elimination half-life of toremifene is that significant accumulation of the drug occurs during repeated administration. Steady-state levels of toremifene and the main metabolites have been determined in patients from a phase II clinical trial (Fig. 6). The steady-state was achieved within 6 weeks after the start of therapy. The average steady-state level of toremifene was 0.8 μg/ml when using a dose of 60 mg per day. The demethyl metabolite level was twice and deaminohydroxy metabolite level was one tenth of that of toremifene.

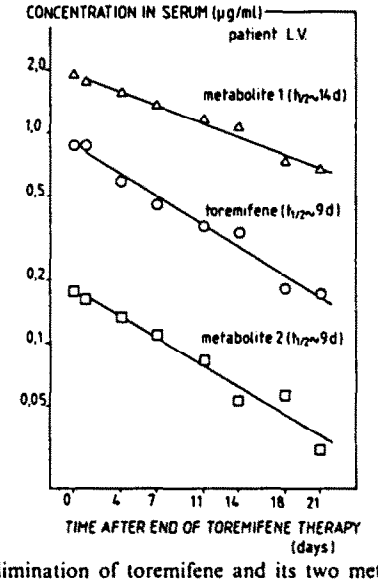

Fig. 7. Elimination of toremifene and its two metabolites after discontinuance of toremifene therapy.

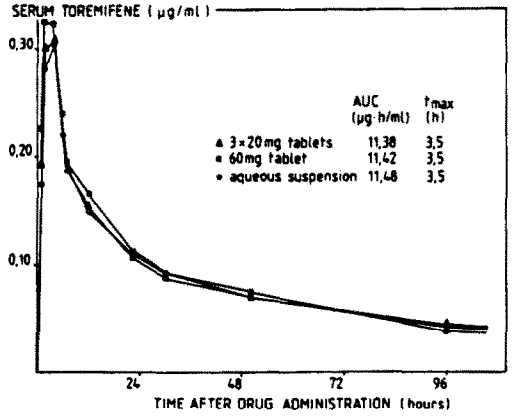

Fig. 8. Mean serum toremifene levels in 12 male volunteers after a single 60 mg dose of three different toremifene citrate preparations.

The concentrations of toremifene and its main metabolites have also been determined in some patients after discontinuation of toremifene after about one year of therapy (Fig. 7). Elimination half-lives were calculated and that of toremifene and metabolite 1 and 2 were in average 6, 11 and 6 days, respectively.

The bioavailability of toremifene tablets compared to toremifene in aqueous suspension was studied in healthy volunteers. The results of this study (Fig. 8) confirm the good bioavailability of the tablet formulation.

In conclusion the pharmacokinetic profile of toremifene is presented: toremifene is well absorbed and over 99% bound to human plasma protein. Elimination is slow with a mean half-life of 5 days. The drug is extensively metabolized without first-pass metabolism. Ten metabolites have been identified, the main metabolites being demethyl- and deaminohydroxytoremifene. After enterohepatic recirculation, the metabolites are excreted mainly in feces.

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