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Clinical Pharmacology of Tamoxifen and *N*-Desmethyltamoxifen in Patients with Advanced Breast Cancer

Peter Wilkinson[1], Gerald Ribeiro[1], Hugh Adam[2], and John Patterson[2]

[1] Christie Hospital,
Withington, Manchester M20 9BX
[2] Imperial Chemical Industries Ltd, Pharmaceuticals Division,
Alderley Park, Macclesfield SK10 4TG, Cheshire, England

Summary. *Serum concentrations of tamoxifen and its metabolite, N-desmethyltamoxifen (DMT) were determined in six post-menopausal patients with advanced breast cancer. Following a single 10-mg dose PO parent drug was detected in the serum, with a peak concentration of 17.5 ng/ml. Concentrations of the N-desmethyl metabolite were below the limit of detection (< 2.5 ng/ml). After 21 days' oral therapy with 10 mg b.i.d. the serum concentration of tamoxifen had increased ten fold, while DMT was now present in comparable amounts. Two patients were further studied for a longer time period. There was little change in the serum concentration of tamoxifen, while the DMT increased two fold above its value at 21 days.*

Introduction

Although the antioestrogenic drug tamoxifen (Nolvadex[1]) is being used increasingly for the treatment of metastatic breast cancer, to date pharmacokinetic data have been scanty because of the absence of a suitable cold drug assay. The recent development of a densitometric analytical procedure by Adam et al. [1] for tamoxifen and its main metabolite *N*-desmethyltamoxifen has facilitated this. This paper describes the pharmacokinetics of parent drug and its metabolite in female patients with metastatic breast carcinoma.

Patients, Materials, and Methods

Patients

Six post-menopausal patients (mean age 54 years, mean weight 62 kg) with histologically proven metastatic breast cancer gave informed consent to the study. In no subject was evidence of impaired renal or hepatic function revealed by routine biochemical procedures.

Procedure

Each patient took one 10-mg tablet of tamoxifen after an overnight fast. Serial blood samples were taken over the following 48 h after which the women took 10 mg b.i.d. for the following 21 days. They were readmitted to the hospital and, after the morning 10-mg tamoxifen tablet on the 22nd day, underwent serial venesection identical to the initial sequence. Samples were taken into plain tubes and allowed to clot at room temperature; and serum was obtained by centrifugation and stored at –20° C prior to assay. In two of the patients, further single samples were obtained after an additional 6 and 33 weeks of therapy, respectively.

Methodology

Tamoxifen and *N*-desmethyltamoxifen (DMT) concentrations were determined by the method of Adam et al. [1]. Serum (1 ml) was extracted with hexane-amyl alcohol (98.5 : 1.5 v/v), 5 ml at pH 7. After a volume reduction, the organic extract was applied to a thin-layer plate and eluted with toluene-ethanol-triethylamine-liquid paraffin (8 : 1 : 1 : 1, by volume). The dried plate was irradiated with UV light and the resultant phenanthrene derivatives quantified by fluorescence densitometry (410 nm). All unknowns and standards were quantified by reference to the internal standard, ICI 99,311, which was added to all serum samples before extraction. Under these assay conditions DMN (Rf 0.36) is resolved from 4-hydroxytamoxifen (4-HT) (Rf 0.32), but when the ratio of DMN to 4-HT exceeds 20 : 1 the latter is masked and is not detectable.

The apparent $T_{1/2}$ of the single dose was calculated by a regression on the apparent terminal decay phase in individual patients. The area under the concentration/time curve (AUC) was calculated by the trapezoidal method to 12 h followed by integration. The AUC_{0-12} on day 22 was calculated by the trapezoidal method.

Results

The serum concentration/time curve following the initial dose of 10 mg tamoxifen is shown in Fig. 1.

Reprint requests should be addressed to: P. Wilkinson

1 Nolvadex is a trade mark, the property of Imperial Chemical Industries Limited

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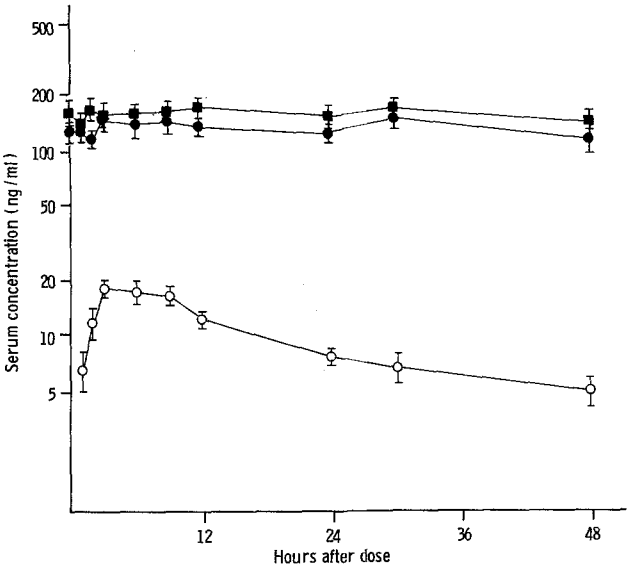

Fig. 1. Serum concentration/time curve (mean ± SEM) in six patients following a single dose of tamoxifen 10 mg PO (○) and 21 days after 10 mg b.d. tamoxifen (●) or desmethyltamoxifen (■)

The mean peak tamoxifen concentration of 17.4 ± 1.6 ng/ml was observed 3 h after administration. Thereafter, the drug decayed with a mean apparent terminal half-life of 44 h. No metabolite was detected.

The serum concentration/time curve after 21 days of therapy is also shown in Fig. 1. The mean pre-dose concentration of tamoxifen was 125 ± 19.1 ng/ml. Following a further dose of 10 mg, the concentration rose to a peak of 141 ± 20 ng/ml and declined, thereafter, to a concentration of 101 ± 16.5 ng/ml after 48 h. The minimal decay over this time period made it impossible to calculate an accurate $T_{1/2}$. However, an estimate of this value from the four patients who showed some reduction in serum tamoxifen was 5.3 ± 1.6 days.

The mean pre-dose concentration of DMT was higher than that of the parent drug (160 ± 23 ng/ml) on day 22. The serum level did not fall at all over the 48-h observation phase in two of the six patients and only declined slowly in the group as a whole.

The AUC_{00} was 577 ± 97 ng · ml^{-1} · h after the initial dose, and 1,597 ± 205 ng · ml^{-1} · h at the second assessment after 440 mg tamoxifen. As shown in Table 1, there is a considerable increase in the AUC over the study period.

4-Hydroxytamoxifen was not detected in the serum of these patients, although values of < 10 ng/ml would have been masked by the high levels of DMT on day 22.

In the two patients in whom samples were taken at 9 and 36 weeks, tamoxifen levels rose by an average of 24%, while DMT rose by over 100% above the 21-day values.

Discussion

At the time of the present study, the only previous report on the kinetics of tamoxifen in humans was after single oral doses of 20 mg ^{14}C-tamoxifen in female patients [3]. A peak concentration of 100 ng total radioactivity/ml was obtained 5 h after the administration. About one-third of this material was considered to be unchanged drug. The radioactivity appeared to decay in an exponential manner but no calculation of the half-life of tamoxifen was possible because of the low specific activity.

The peak tamoxifen values found in the present study agree with the above findings. It is evident that there is prolonged drug accumulation when tamoxifen is administered in a conventional 10 mg b.d. regime. The tamoxifen concentrations attained after 21 days were similar to those seen in two of the subjects, in whom further samples were obtained at 9 and 36 weeks respectively, suggesting that

Table 1. Kinetic characteristics of tamoxifen in six post-menopausal patients with breast cancer

Subject	Single dose 10 mg on day 1		Multiple dosing 10 mg b.i.d. for 21 days	Ratio AUC_{0-12} : AUC_{00}
	Apparent $T_{1/2}$ (h)	AUC_{00} ng · ml^{-1} · h	AUC_{0-12} ng · ml^{-1} · h	
1	16	389	1,843	4.7
2	32	406	1,039	2.6
3	115	988	2,091	2.1
4	20	395	1,114	2.8
5	27	710	2,178	3.1
6	57	572	1,318	2.3
Mean ± SEM	44.5 ± 15	577 ± 97	1,597 ± 205	2.9 ± 0.4

steady-state levels of parent drug had been approached by 3 weeks of therapy.

The long apparent half-life after 3 weeks' therapy may be inaccurate, in view of the timing of serum samples. This slow decay was unexpected and would not have been predicted from the decay of serum drug levels after a single 10-mg dose, where the decline was followed for only 48 h.

This study also confirms that the major free serum metabolite in patients is DMT [2] and not, as previously suggested, the 4-hydroxy metabolite [3]. DMT could not be detected after a single 10-mg dose of tamoxifen but was easily identified after 21 days' treatment. Continued administration of tamoxifen (10 mg b.d.) led to further increases in the concentration of this metabolite, showing that the elimination of this compound was slower than that of the parent drug. The high concentrations of DMT suggest that it could play a supportive role in tamoxifen therapy, as there is evidence that it possesses antioestrogenic activity in animals equal to that of the parent drug [4].

The marked increase in the AUC at day 21 over the single dose elimination curve suggests either that the true terminal half-life had not been determined owing to the limitations of the assay or that drug retention occurs during daily administration. The mechanism by which this might occur is unknown. The considerable variation between patients in the apparent terminal half-life of tamoxifen may also reflect a combination of genetic and environmental factors related to drug absorption and metabolism, but is more likely to be due to the inaccuracies generated by following the decay curve for 48 h only.

A clinical response to tamoxifen is not usually apparent until at least 4–6 weeks after therapy is started. It is not possible, however, to predict whether these pharmacokinetic observations are related to the clinical response. Further studies are in progress to evaluate the optimal clinical regimen and to assess whether steady-state drug levels – and the time taken to achieve these levels – may be correlated with the tumour responsivity and the time taken to achieve an objective response.

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