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SHORT COMMUNICATION

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Serum and urine levels of tamoxifen and its metabolites in patients with advanced breast cancer after a loading dose and at steady-state levels

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Abstract *Purpose*: To compare serum and urine levels of tamoxifen and metabolites after a loading dose and at the steady state. *Methods*: A loading dose of 160 mg of tamoxifen was given to 14 patients with advanced breast cancer. Thereafter a regular daily dose of 30 mg of tamoxifen was given. Serum and urine levels of tamoxifen and metabolites were measured by high-performance liquid chromatography and compared with levels determined in 31 patients with advanced breast cancer at the steady state at a daily dose of 30 mg of tamoxifen. *Results*: Serum and urine levels (24-h values) of tamoxifen and metabolites were lower ($P < 0.05$) after a loading dose than at the steady state. The difference was most pronounced for the metabolites, whereas the tamoxifen loading-dose level was near the steady state. *Conclusion*: Tamoxifen steady state can be reached in 1–2 days by the administration of a loading dose of 160 mg of tamoxifen for 2 days. Tamoxifen metabolite steady-state levels are reached regularly after 4 or more weeks during application of a loading dose. Very little tamoxifen or metabolites are excreted into the urine.

Key words Tamoxifen · Serum levels · Urinary excretion · Loading dose · Steady state

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Introduction

There is a continuing interest in the use of a loading dose of the antiestrogen tamoxifen. Regularly, daily doses of 20–40 mg have been given, whereas loading doses of 80–200 mg have been given for 1–7 days [1–8]. Some data have been published on blood levels of tamoxifen and metabolites after a loading dose of tamoxifen [8–11]. Tamoxifen (T) is hydroxylated, leading to 4-hydroxytamoxifen (B), and demethylated, yielding *N*-desmethyltamoxifen (X). The latter is demethylated again, leading to *N*-desdimethyltamoxifen (Z). Subsequently, the NH_2 group is cleaved, giving metabolite Y, followed by removal of the $HOCH_2CH_2$ group, yielding the 4-hydroxy metabolite E. Following our previous study on the pharmacokinetics of tamoxifen [12] we carried out a comparative investigation of the serum and urine levels of tamoxifen and metabolites in breast cancer patients at the steady state on a daily dose of 30 mg of tamoxifen and after a loading dose of 160 mg followed by a daily dose of 30 mg of tamoxifen.

Patients and methods

Patients and drug administration

The loading-dose group consisted of 14 patients with metastatic breast cancer who started their tamoxifen therapy with a loading dose of 160 mg (4×Tamoplex at 40 mg). Their median age was 70 (range 43–80) years, their median height was 160 (range 150–172) cm and their median weight was 70 (range 43–80) kg. The steady-state group consisted of 31 patients with metastatic breast cancer who had chronic (>3 months) tamoxifen therapy (3×Tamoplex at 10 mg given daily in one dose). Their median age was 70 (range 44–81) years, their median height was 162 (range 148–177) cm and their median weight was 68 (range 50–103) kg. The study was performed under conditions complying with the Helsinki Declaration and with the WHO recommendations for evaluation of drugs in humans.

Study design

Patients in the loading-dose group were sampled before administration of the loading dose and after 1, 8 and 29 days just prior to

the next maintenance dose. Patients in the study-state group were sampled twice before the study period of month to confirm that their serum levels had reached the steady state. Subsequently, they were sampled just prior to dosing after 4 weeks of tamoxifen therapy. The dose was given at noon. Blood samples of 5 ml were drawn and serum was obtained and stored frozen until analysis. Patients collected their 24-h urine specimens following dosing of either 160 or 30 mg. Patients brought the urine container to the outpatient clinic, where the volume of the urine was determined and a sample of 50 ml of urine was taken and stored frozen until analysis. Patients underwent the usual medical examinations; their hematology and blood chemistry were checked and they were prescribed drugs according to their treatment plan. All data, including those on medication, were annotated on clinical flow charts.

Drug assay

The serum samples were analyzed for tamoxifen and metabolites B, E, X, Y and Z by high-performance liquid chromatography (HPLC) according to the modified method of Golander and Sternson [13, 14]. The availability of samples of pure tamoxifen and metabolites B, E, X, Y and Z enabled proper method development and validation. Other metabolites were not available as reference compounds. Tamoxifen and metabolites were converted into phenantrenes by ultraviolet radiation. After their injection onto the HPLC column, these were detected fluorimetrically. The serum and urine recovery of tamoxifen and metabolites was 85–97%, standard curves were linear and the sensitivity was 2–5 ng/ml.

Results

Serum levels of tamoxifen and its metabolites are presented in Table 1. Urine data are summarized in Table 2. Steady-state and loading-dose data on tamoxifen and metabolites were analyzed by the Wilcoxon test for unpaired observations for all comparisons $P < 0.05$. Hematology and blood chemistry revealed no important or unexplainable abnormality.

Discussion

The day-1 serum levels determined for the tamoxifen metabolites after a 160-mg loading dose were considerably lower than the steady-state levels recorded after a 30-mg daily dose. Also the 24-h urine data showed a striking difference. Very little tamoxifen and metabolites were excreted into the urine. This confirms that tamoxifen is metabolized extensively and excreted not via the urinary route but via the biliary route. Tamoxifen and metabolites inhibit their own liver metabolism in vitro and in vivo (e.g., [15–17]). After a first loading dose of tamoxifen the tamoxifen metabolic capacity remains fully intact, whereas in the steady-state situation there is a completed distribution of tamoxifen and its metabolites and maximal auto-inhibition of tamoxifen metabolism. There was no significant difference between the two groups of patients e.g. in co-medication. The 24-h tamoxifen level after a loading dose was near the steady-state level, which was somewhat lower than usual in this patient group and comparable with levels published earlier [18]. To be sure that the tamoxifen steady-state level is reached quickly a 160-mg loading dose should be given for 2 days. Whereas steady-state tamoxifen levels can be reached after a loading dose in 1–2 days, steady-state levels of the tamoxifen metabolite are reached as with normal tamoxifen dosing in several weeks. The data presented further contribute to our knowledge of the steady-state pharmacokinetics and metabolism of tamoxifen.

Table 1 Serum levels of tamoxifen and metabolites measured in breast cancer patients after a loading dose and at the steady state[a] T Tamoxifen)

	Concentration (ng/ml)					
	T	X	Z	Y	E	B
Loading dose:						
Day 1	82 (56–139)	48 (25–69)	*[b]	5[c]	5[d]	*[b]
Day 8	93 (60–135)	81 (49–183)	8 (5–13)	7 (5–16)	7 (4–15)	*[b]
Day 29	102 (60–177)	177 (83–444)	18 (9–89)	16 (7–55)	13 (5–28)	*[b]
Steady state	143 (60–377)	289 (129–607)	45 (17–127)	31 (18–74)	14 (5–59)	7 (6–9)

[a]Data represent median values; ranges are shown in parentheses
[b]Below the detection limit
[c]Mean of 3 values
[d]Mean of 2 values

Table 2 Tamoxifen and metabolites measured in the 24-h urine specimens of breast cancer patients after a loading dose and at the steady state

	Z of the dose			
	T	X	Y	E
Loading dose	0.0029 (0.0023–0.0034)	0.0053[a]	*[b]	*[b]
Steady state	0.031 (0.008–0.120)	0.076 (0.020–0.282)	0.100 (0.027–0.134)	0.042

[a]Mean of 2 values
[b]Below the detection limit

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