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Short communication

Serum elimination half-life of tamoxifen and its metabolites in patients with advanced breast cancer

Dick de Vos[1], Peter H. Th. J. Slee[2], Derek Stevenson[3], and Ray J. Briggs[3]

[1] Medical Department, Pharmachemie B.V., P. O. Box 552, 2003 RN Haarlem, The Netherlands
[2] St. Antonius Hospital, Nieuwegein, The Netherlands
[3] The Robens Institute, University of Surrey, Guildford, England

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Summary. In breast cancer patients discontinuing chronic tamoxifen therapy, the serum elimination of metabolites X, Y and E paralleled that of tamoxifen, whereas that of metabolite Z did not. The serum elimination of tamoxifen and metabolites X and B was increased by aminoglutethimide treatment, whereas that of metabolites Z, Y, and E was not

Introduction

The antiestrogen tamoxifen, which is widely used in the endocrine therapy of breast cancer, is extensively metabolised. In patients on chronic tamoxifen therapy, demethylation and hydroxylation constitute important metabolic routes. Demethylation leads to the formation of metabolites X (*N*-desmethyltamoxifen) and Z (*N*-desdimethyltamoxifen), the subsequent removal of an NH_2- group yields metabolite Y, a primary alcohol, and the splitting off of the $HOCH_2CH_2$ group yields metabolite E (4′-hydroxytamoxifen). By hydroxylation, metabolite B (4-hydroxytamoxifen) and metabolite BX (4-hydroxy-*N*-desmethyltamoxifen) are formed [4, 7, 8].

Tamoxifen and its serum metabolites are readily distributed into pericardial, pleural and peritoneal effusions and into saliva and the central nervous system. Conjugated, hydroxylated metabolites prevail in urine and bile [9–11]. Plasma or serum levels of tamoxifen and its metabolites have been described in several reports. The distribution half-life of tamoxifen was found to be in the range of 9–49.2 h, and the terminal half-life lay within the range of 4–7 days [1, 6, 16, 18]. The terminal half-life of metabolite X was found to be twice that of tamoxifen: 9–14 days [1, 16]. In a study in 24 volunteers, the elimination curve of metabolite X paralleled that of tamoxifen, and a terminal half-life of 208 h was calculated for tamoxifen and metabolite X. Due to low concentrations approaching the detection limit, volunteer plasma samples could be measured for up to only 384 h [3]. Lien et al. [11] reported their findings in three patients after the withdrawal of tamoxifen therapy; the metabolite decay curves paralleled the tamoxifen decay curve.

We carried out pharmacokinetics studies in patients who were withdrawn from chronic tamoxifen treatment. The terminal half-lives determined for tamoxifen and its metabolites are reported.

Patients and methods

Patients. A total of 14 patients with metastatic breast cancer who had undergone chronic (>3 months) tamoxifen therapy (30 mg Tamoplex daily) but had to discontinue tamoxifen because of progressive disease gave their informed consent to participate in the present study. Their mean age was 59 ± 10 (range, 44–73) years, their mean height was 165 ± 9 (range, 150–178) cm and their mean weight was 68 ± 10 (range, 50–87) kg. The study was performed under conditions complying with the Helsinki Declaration and with the WHO recommendations for evaluation of drugs for use in man.

Study design. The first blood sample of 5 ml was drawn at 24 h after the last dose. Further blood samples were drawn after 7, 14, 21, 28 and 35 days. Serum was obtained 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 analysed 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 [5, 19]. The availability of samples of pure tamoxifen and metabolites B, E, X, Y and Z enabled proper method development and validation. The unavailability of a pure sample of the relatively new metabolite BX prevented its reliable quantitation. Tamoxifen and its metabolites were converted into phenantrenes by ultraviolet radiation. After their injection onto the HPLC column, these were detected fluorimetrically. The plasma recovery of tamoxifen and metabolites was 90%–100%, standard curves were linear and the sensitivity was 2 ng/ml.

Correspondence to: D. de Vos

Table 1. Serum levels of tamoxifen and its metabolites in breast cancer patients after the cessation of tamoxifen therapy[a]

Time (day)	Concentration (ng/ml)					
	T	X	Z	Y	E	B
No aminoglutethimide medication:						
0	148 (85–217)	280 (134–450)	60 (28–79)	27 (17–39)	26 (18–41)	7 (4–9)
7	59 (45–160)	175 (111–414)	33 (14–84)	14 (7–31)	17 (6–27)	6 (4–6)
14	30 (21– 81)	94 (29–201)	22 (18–58)	8 (4–17)	9 (5–19)	5 (4–6)
21	19 (13– 53)	55 (23– 78)	16 (12–37)	4 (3–14)	4 (3–13)	–[b]
Aminoglutethimide medication:						
0	164 (83–267)	310 (108–444)	36 (23–89)	23 (16–40)	24 (4–47)	5 (4–14)
7	23 (2– 97)	170 (39–236)	49 (25–79)	18 (12–25)	14 (10–38)	–[b]
14	–[b]	82 (12–109)	30 (16–58)	11 (5–16)	8 (6–10)	–[b]
21	–[b]	31 (30– 42)	20 (11–39)	7 (4– 7)	4 (–)	–[b]

[a] Data represent median values; ranges are shown in parentheses
[b] Insufficient data were available for determination of the median value
T, Tamoxifen

Table 2. Serum elimination half-lives determined for tamoxifen and its metabolites in breast cancer patients after the cessation of tamoxifen therapy

Patient	T	X	Z	Y	E
1	9.6	9.3	12.3	11.6	11.4
4	7.0	8.4	23.3	10.5	9.5
5	13.2	15.8	19.1	13.2	15.7
8	13.6	13.5	37.6	11.3	14.5
9	8.7	7.9	15.0	7.9	7.8
10	8.3	7.9	10.4	8.4	6.7
12	7.8	9.6	6.4	22.5	7.2
14	8.3	10.0	16.2	10.0	9.4
Mean ± SD (days)	9.6 ± 2.5	10.3 ± 2.9	17.5 ± 9.6	11.9 ± 4.6	10.3 ± 3.3
Aminoglutethimide medication:					
2	1.2	7.0	11.1	8.5	8.1
3	2.5	6.0	–[b]	–[b]	–[b]
6	4.0	7.2	15.9	11.2	7.7
7	2.4	4.4	26.9	5.6	–[b]
11	5.1	5.4	10.4	8.2	5.7
Mean ± SD (days)	3.0 ± 1.5	6.0 ± 1.2	16.1 ± 7.6	8.4 ± 2.3	7.2 ± 1.3
13[a]	12.4	19.1	28.2	19.3	31.3

[a] Patient on medroxyprogesterone acetate
[b] Insufficient data were available for calculation of a representative mean value
T, Tamoxifen

Table 3. Medication of the patients after the cessation of tamoxifen therapy

Patient	Medication
1	Codeine, paracetamol
2	Aminoglutethimide, diclofenac, hydrocortisone
3	Aminoglutethimide, hydrocortisone
4	Indomethacin
5	Cinnarizine, isosorbide dinitrate, methyldopa
6	Aminoglutethimide, beclomethason, hydrocortisone, ibuprofen
7	Aminoglutethimide, diclofenac, hydrocortisone
8	Aspirin, atenolol, digoxin, hydralazine, oxazepam
9	None
10	Morphine
11	Aminoglutethimide, hydrocortisone, ibuprofen
12	Furosemide, prednisone, spironolactone, theophylline
13	Indomethacin, medroxyprogesterone acetate
14	None

Results

Serum levels of tamoxifen and its metabolites are presented in Table 1. After 21 days, insufficient data were available for calculation of representative mean values. The serum elimination curves were monophasic. The serum elimination half-lives calculated for tamoxifen and its metabolites are summarised in Table 2. The medication prescribed to the patients after the cessation of tamoxifen therapy is given in Table 3. Because of the expected difference in pharmacokinetic parameters between patients on aminoglutethimide and those on other therapy, the data in Tables 1 and 2 are presented separately. One patient was given medroxyprogesterone acetate. Hematology and blood chemistry revealed no important abnormalities.

Discussion

From the values calculated, it is evident that the plasma elimination half-lives of metabolites X, Y and E are equal

to that of tamoxifen. This observation is in agreement with the data from a single-dose study in healthy male volunteers, whereby a plasma elimination half-life of 8.7 days was found for tamoxifen as well as metabolite X [3]. Our findings also agree with the results obtained in three patients by Lien et al. [9]. Until recently [15], it was assumed that the plasma elimination half-life of metabolite X was longer than that of tamoxifen [1, 4, 16]; this assumption clearly needs revision.

Although considerable variation was observed, the plasma elimination half-life of metabolite Z seems to be longer than that of tamoxifen. This would indicate that whereas the serum level of metabolite X is production-rate-limited, that of metabolite Z is not.

The aromatase inhibitor aminoglutethimide stimulates the activity of the hepatic mixed-function oxidases, increasing the metabolism of several drugs, including warfarin, digitoxin, antipyrine and theophylline. It also affects oestrone sulphate, medroxyprogesterone acetate and megestrol acetate disposition [12, 13]. Lien et al. [10] found that aminoglutethimide lowered the serum levels of tamoxifen and all metabolites in the steady-state situation. The effect of aminoglutethimide on the elimination phase of tamoxifen and its metabolites was limited to tamoxifen and metabolites X and B. Analysis of the data using Student's *t*-test and Wilcoxon's rank-sum test revealed a statistically significant difference between the serum elimination half-lives found for tamoxifen and metabolite X in the presence versus the absence of aminoglutethimide medication ($P < 0.01$). It is tempting to suggest an inducing effect of aminoglutethimide on the cytochrome P450-mediated demethylation and hydroxylation, which are auto-inhibited by tamoxifen and its metabolites. Such an inducing effect is absent in the deaminase-mediated formation of metabolite Y from metabolite Z [2, 12, 14, 17]. From the data presented for metabolite X, it is not possible to conclude whether aminoglutethimide may have any influence on the disposition of this metabolite or whether the difference in half-life (in the presence versus the absence of aminoglutethimide) mirrors the alterations in the half-life of tamoxifen only.

In conclusion, it can be stated that the serum elimination of metabolites X, Y and E parallels that of tamoxifen. Aminoglutethimide shows metabolic interaction with tamoxifen; the serum elimination of tamoxifen and metabolite X is increased, whereas that of metabolites Z, Y and E is not.

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