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Influence of Droloxifene (3-Hydroxytamoxifen), 40 mg daily, on Plasma Gonadotrophins, Sex Hormone Binding Globulin and Estrogen Levels in Postmenopausal Breast Cancer Patients

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Droloxifene (3-hydroxytamoxifen) is a novel antiestrogen currently undergoing clinical investigations for treatment of breast cancer patients. We measured plasma levels of sex hormone binding globulin (SHBG) and the gonadotrophins (LH and FSH) at baseline and after 3 months on treatment in a group of fourteen postmenopausal women treated with droloxifene 40 mg daily. Plasma levels of estrone (E_1), estradiol (E_2) and estrone sulphate (E_1S) were measured in a subgroup of eight patients. Plasma SHBG increased during treatment with droloxifene by a mean value of 16.6% ($P < 0.05$), while plasma levels of LH and FSH decreased by a mean value of 15.7% (n.s.) and 18.1% ($P < 0.05$), respectively. Plasma levels of E_2 and E_1 fell slightly (mean decrease 19.4 and 16.7% respectively, n.s.). On the contrary, plasma levels of E_1S increased by a mean value of 23.5% ($P = 0.068$). The ratio of E_1S to E_1 and E_1S to E_2 increased by a mean value of 48.3% ($P < 0.025$) and 53.2% ($P < 0.025$), respectively. The effect of droloxifene 40 mg daily on plasma levels of SHBG resembles what is seen during treatment with tamoxifen but occurs to a smaller extent. Contrary to tamoxifen, droloxifene caused a minor suppression of plasma LH levels, suggesting droloxifene to have less estrogen agonistic effects on the pituitary.

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INTRODUCTION

Endocrine therapy plays a key role in adjuvant therapy as well as in the treatment of advanced breast cancer [1, 2]. The antiestrogen tamoxifen is used in adjuvant therapy and is currently first line therapy in postmenopausal women with metastatic disease. Tamoxifen is known to act as an estrogen antagonist but also to express partial estrogen agonistic activity [3]. The estrogen agonistic effects of tamoxifen have led to the development of novel anti-estrogens with the aim to achieve drugs with more potent estrogen antagonistic activity and less agonistic activity.

Droloxifene is a novel antiestrogen currently undergoing clinical investigations for treatment of breast cancer. Preclinical data suggest droloxifene to express less estrogen agonistic activity compared to tamoxifen [4–6].

Tamoxifen is known to suppress plasma gonadotrophins and to increase plasma levels of sex hormone binding globulin (SHBG) in postmenopausal breast cancer patients, probably by acting as an estrogen agonist on the pituitary and the liver. In a recent study [7], we found tamoxifen to also elevate plasma levels of estrone sulphate (E_1S).

In this study, we measured plasma levels of SHBG together with the gonadotrophins in a group of 14 postmenopausal breast cancer patients treated with droloxifene 40 mg o.d. Due to the limited amount of plasma available, plasma estrogen levels could be determined in a subgroup of 8 patients only.

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PATIENTS AND METHODS

The files of a phase II study [8] were examined leaving 14 patients from whom plasma samples before and following 3 months on treatment with droloxifene 40 mg o.d. were available for analysis of SHBG and the gonadotrophins. From eight of these patients sufficient plasma was available for plasma estrogen determinations.

The median age of the patients was 62 years (range 51–83 years). None of the patients received any other form of endocrine treatment known to influence drug or hormone disposition.

Plasma estrone (E_1), estradiol (E_2) and E_1S was measured as described elsewhere [9]. Plasma gonadotrophins (LH and FSH) and SHBG were determined by commercial IRMA (LH/FSH) and RIA (SHBG) assay kits obtained from Orion Diagnostica (Espoo, Finland).

As previous work in our laboratory has revealed plasma levels of these hormones to be best fitted to a log normal distribution [10], plasma hormone levels and the percentage change in their levels were expressed as their geometrical mean value with 95% confidence intervals.

Plasma hormone levels obtained before and during treatment were compared using the Wilcoxon matched pair signed rank test. All P-values are expressed as two-tailed.

RESULTS

Plasma hormone levels before and during treatment with droloxifene are given in Table 1.

Plasma levels of SHBG increased during treatment with droloxifene by a mean value of 16.6% ($P < 0.05$), while values for LH and FSH decreased by a mean of 15.7% (n.s.) and 18.1% ($P < 0.05$), respectively. E_1 and E_2 fell slightly (mean decrease of 16.7 and 19.4%, respectively, n.s.). On the contrary, plasma levels of E_1S increased by a mean value 23.5% ($P = 0.068$).

Droloxifene was found to increase the ratio of E_1S to E_1, and E_1S to E_2 by a mean of 48.3% ($P < 0.025$) and 53.2% ($P < 0.025$), respectively. No change in the ratio of E_1 to E_2 was seen.

DISCUSSION

The antiestrogen tamoxifen is known to act as a partial estrogen agonist. It has been found to increase plasma levels of SHBG (mean increase of 50–70%) but to suppress plasma levels of LH and FSH by 40–50% [7]. In a previous study, we found droloxifene 100 mg o.d. to elevate plasma SHBG by 73.8% and to suppress plasma FSH and LH by 19.7 and 20.4%, respectively [11].

In this study, we found droloxifene to increase plasma levels of SHBG by 16.6% and to suppress gonadotrophin levels by about 15–20%. However, if the percentage alterations in plasma hormone levels were described by their arithmetical and not their geometrical mean value, the plasma level of SHBG was increased by a mean value of 25.2% while FSH and LH levels were reduced by 15.0 and 3.2%, respectively. Taken together with previous results from our group [11], our findings suggest droloxifene at different doses to express less estrogen agonistic effects on the liver compared to tamoxifen and to have little estrogen agonistic effect on the pituitary. An explanation for the differential effect of droloxifene on the liver and the pituitary compared to tamoxifen may be that droloxifene has a higher metabolic clearance rate and thus might have a higher first pass metabolic clearance rate compared to tamoxifen, causing a higher ratio between the drug concentration in the portal blood and systemic circulation. It is noteworthy that the estrogen agonistic effects of tamoxifen on liver protein synthesis (like the effects on the lipoproteins, plasma IGF-I and plasma homocysteine) in general are beneficial, while the estrogen effects on other organs (like the endometrium) may be detrimental.

In a previous study [7] we found tamoxifen to increase plasma levels of E_1S but to decrease plasma E_2. Similarly, we found droloxifene given as a dose of 100 mg daily to elevate plasma E_1S [11]. In this study we found droloxifene 40 mg o.d. to cause a

Table 1. Plasma hormone and SHBG levels before and during treatment with droloxifene and % change of each hormone; geometrical mean values (with 95% confidence limits of the mean)

	Before treatment		On droloxifene		Change (%)		P-value
Compounds							
E_2	23.4 pM	(11.1–49.3)	18.9 pM	(12.1–29.5)	− 19.4	(− 44.5 + 17.0)	> 0.10
E_1	102.4 pM	(74.9–140.1)	85.3 pM	(66.0–110.1)	− 16.7	(− 34.5 + 6.1)	> 0.10
E_1S	663.1 pM	(317–1387)	819.8 pM	(397–1689)	+ 23.5	(− 3.2 + 57.6)	0.068
SHBG	46.2 nM	(34.8–61.5)	53.9 nM	(42.0–69.3)	+ 16.6	(− 9.3 + 50.1)	< 0.05
FSH	70.1 IU/l	(54.4–90.4)	57.5 IU/l	(45.4–72.7)	− 18.1	(− 30.9 − 2.9)	< 0.05
LH	26.8 IU/l	(19.0–37.9)	22.6 IU/l	(16.4–31.1)	− 15.7	(− 38.3 + 15.3)	> 0.10
Ratios							
E_1/E_2	4.37	(2.78–6.88)	4.52	(3.29–6.20)	+ 3.4	(− 15.2 + 25.9)	> 0.10
E_1S/E_1	6.48	(3.27–12.80)	9.61	(5.35–17.24)	+ 48.3	(+ 15.1 + 91.2)	< 0.025
E_1S/E_2	28.3	(12.2–65.8)	43.4	(22.7–83.0)	+ 53.2	(+ 12.2 + 109.4)	< 0.025

non-significant drop in the plasma levels of E_1 and E_2 by a mean of 16.7 and 19.4% but a non-significant increase in plasma E_1S of 23.5%. These alterations are in the same range as the alterations observed with tamoxifen 30 mg o.d. and somewhat less than the alterations observed during treatment with droloxifene 100 mg o.d. It is also noteworthy that the increase in the E_1S/E_1 (48.3%) and E_1S/E_2 (53.2%) ratios were of statistical significance. Thus, it is likely that the lack of significant alterations in plasma estrogens in this study may be due to a limited number of observations.

In conclusion, this study suggests a differential estrogen agonistic effect of droloxifene compared to tamoxifen on the liver compared to the pituitary. This may be of clinical importance to the use of these drugs. The effect of droloxifene (as well as tamoxifen) on estrogen disposition merits further investigation.

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REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group: Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy — Part 1 and 2. *The Lancet* **339** (1992) 1–15 and 71–85.
2. Rose C., Theilade K., Boesen E., Salimtschik M., Dombernowsky P., Brünner N., Kjær M., Mouridsen H. T.: Treatment of advanced breast cancer with tamoxifen. *Breast Cancer Res. Treat.* **2** (1982) 395–400.
3. Jordan V. C. and Murphy C. S.: Endocrine pharmacology of anti-estrogens as antitumor agents. *Endocrine Rev.* **11** (1990) 578–610.
4. Löser R., Seibel K., Ross W. and Eppenberger U.: *In vivo* and *in vitro* anti-estrogenic action of 3-hydroxytamoxifen, tamoxifen and 4-hydroxytamoxifen. *Eur. J. Cancer Clin. Oncol.* **21** (1985) 985–990.
5. Hasmann M., Rattel B. and Löser R.: Preclinical data for Droloxifene. *Cancer Lett.* **84** (1994) 101–116.
6. Potter G. A., McCague R. and Jarman M.: A mechanistic hypothesis for DNA adduct formation by tamoxifen following hepatic oxidative metabolism. *Carcinogenesis* **15** (1994) 439–442.
7. Lønning P. E., Johannessen D. C., Lien E. A., Ekse D., Fotsis T. and Adlercreutz H.: Influence of tamoxifen on sex hormones, gonadotrophins and sex hormone binding globulin in postmenopausal breast cancer patients. *J. Steroid. Biochem. Molec. Biol.* **52** (1995) 491–496.
8. Bruning P. F.: Droloxifene, a new anti-oestrogen in postmenopausal advanced breast cancer: preliminary results of a double-blind dose-finding phase II trial. *Eur. J. Cancer* **28A** (1992) 1404–1407.
9. Dowsett M., Goss P. E., Powles T. J., Hutchinson G., Brodie A. M. H., Jeffcoate S. L. and Coombes R. C.: Use of aromatase inhibitor 4-hydroxyandrostenedione in postmenopausal breast cancer: optimization of therapeutic dose and route. *Cancer Res.* **47** (1987) 1957–1961.
10. Lønning P. E., Helle S. I., Johannessen D. C., Adlercreutz H., Lien E. A., Tally M., Ekse D., Fotsis T., Anker G. B. and Hall K.: Relations between sex hormones, sex hormone binding globulin, insulin-like growth factor-I and insulin-like growth factor binding protein-1 in postmenopausal breast cancer patients. *Clin. Endocr.* **42** (1995) 23–30.
11. Geisler J., Haarstadt H., Gundersen S., Raabe N., Kvinnsland S. and Lønning P. E.: Influence of treatment with the anti-oestrogen 3-hydroxytamoxifen (droloxifene) on plasma sex hormone levels in postmenopausal breast cancer patients. *J. Endocr.* **146** (1995) 359–363.