The Effect of Tamoxifen on the Serum Concentration of Estradiol, Progesterone and Prolactin in Rats

Xinliang Su, Kainan Wu, Changqing Gan

Department of General Surgery, First Affiliated Hospital of Chongqing Medical University, Chongqing 400016,China

Abstract **Objective** To evaluate the effect of different dosage of tamoxifen on serum levels of estradiol(E_2); Progesterone(P) and prolactin(PRL) in rats. **Methods** Four groups of rats suffering from fibrocystis breast disease induced by exogenous sex hormone, were treated respectively with five, ten, fifteen and twenty times treated dosages of tamoxifen(TAM), at the same time, the blank control group and drug control were designed. Serum E_2, P and PRL were determined by immunoradiological assay after thirty days of experiment. **Results** The level of E_2 of the five-times and more than five-times dosage tamoxifen groups were significantly lower than that of the drug control group($P<0.01$). The level of progesterone and prolactin of ten-times and more than ten-times dose tamoxifen groups were significantly lower than that of the drug control group and five times dosage tamoxifen group. **Conclusion** The results showed that tamoxifen could significantly decrease the serum level of E_2, P and PRL and also provided a theoretical evidence for clinical treatment of the fibrocystis breast disease.

Key words tamoxifen; rat; estradiol; progesterone; prolactin; fibrocystis breast desease

Fibrocystis breast disease, which is throught to be related to disorder of endocrinolsity is common inwomen. Tamoxife(TAM) has effectively been used to treat fibrocystis breast disease in clinic, but its related mechnism is rarely studied. This experiment observed the different dosage of TAM on the serum level of estradiol(E_2), progesterone (P) and prolactin(PRL) and evaluated the possible mechanism of TAM in treating fibrocystis breast disease

MATERIALS AND METHODS

Materials

TAM is a product of Shanghai Hualian Pharmateutical company (lot number: 001003). E_2, P and PRL inmunoradiological reagent case was bought from Tianjin Depu Company. The female un-pregnant Wistar rats weighting from 80 to 120 grams were provided by the animal center of Chongqing medical university. SH-680 immunoradiological r-couter was a product of Rihuan Instrument Factory of Shanghai Nuclear Research Institute.

Methods

180 Wistar rats were randomly divided into 6 groups after adaptable feeding for one week with 30 Wistar rats in each group.

Blank Control Group (A) was freely fed with ordinary food, warter and natural light.

Experimental Group (B,C,D,E and F) were given exogenous sex hormone according to Cheng Zhichun's[1] method: estradiol was injected intraperitoneally (0.5milligram/kg/d for 25 days), then progesterone (4milligram/kg/d for 5 days) to copy the model of fibrocystis breast disease. After one month, 15 rats in each group were randomly killed for drawing 3ml blood sample by picking their eye ball which were centrifuged for 15 minutes (5000r/min), then 0.5 ml serum was taken out and preserved at-20℃. in icebox. The rest rats of B, C, D, E and F group were continuously injected with estrogen and progesterone, at the same time, the rats of group C, D, E and F were fed with 5,10, 15 and 20 times tamxinfen. 30 days later, the blood was gained by the same methods as above. E_2, P and PRL levels were detected by immunoradiological assay, results were expressed with $\bar{x} \pm S$, analysis of variety F test was performed and $p<0.05$ indicated the significant difference in groups.

RESULTS

Table 1 showed that there was the significant difference of C, D, E, F groups'E_2 level before and after the drug was used ($P<0.01$), indicated that five-time dose TAM begin to decrease the concentration of E_2. It also showed the difference between these groups by analysis of variety. $F=140.73$,($P<0.01$), indicated that with the in-

creased dose of the TAM, the E_2 level tended to be significantly decreased.

Table 2 showed there was significant difference of D, E, F groups'P level before and after drug was used ($P<0.01$), indicated that ten-times dose TAM begin to decrease the concentration of P. It also showed the difference between these groups by analysis of varieties, $F=8.089$, ($P<0.01$), indicated that with the increased of dose of the TAM, the P level tended to be significantly lower after the drug was used, especially in ten times and more than ten times group.

Table 3 showed that there was the great difference of D, E, F groups'PRL level before drug and after drug was used ($P<0.01$), indicated that ten-times dose TAM could decrease the concentration of PRL. It also showed that the difference between these group by analysis of varieties, $F=7.6$, ($P<0.01$), indicated that with the increased of dosage of TAM, P level tended to be significantly lower after drug was used, especially in ten-times and more than ten-times dose group.

DISCUSSION

E_2 and P have a close relationship in occurrence of breast and the growth of ductule, lobular and ductus of breast depends on the action of E_2 and P. The occurrence of fibrosis breast disease is related to the long stimulation of estrogen and inadequate antagonism of progesterone. TAM, which is an antagonist to estrogen receptor, is widely used in treating breast cancer. Recently, there are many clinical data to show that TAM is effective in treating fibrocysis breast disease, but its mechanism is not clear.

The results of our experiment show that E_2 level of experimental group are significantly lower than that of the drug control and E_2 levels get more and more significantly lower with the increase of dose of TAM. It shows that TAM has the effect to decrease the serum level of E_2 which is approved by some reports[2]. There are also some authors taking the decrease of E_2 as an indication of follow-up. However, it is also reported[3,4] that TAM has the effect to increase the serum level of E_2 in postmenopausal woman which indicates that the effects of TAM are related to E_2 level before it was used, when the level of E_2 is high, TAM can have an effect on antiestrogen; when it is low, it acts as similar estrogen.

The study shows that the serum level of progesterone in rats TAM group is lower than before the drug is used and this indicates that TAM can affect the level of progesterone. In ten times and more than ten times TAM groups it is lower significantly. Though the study of 42 postmenpausal patients with breast cancer, it is found that TAM can decrease the level of FSH and LH[5], which will help to decrease serum E_2 and P level. Some authors believe[6] that TAM has a direct effect on ovary.

The experiment also shows that change of prolactin level in ten times and more than ten times TAM groups tends to be decreased and that is accord with what we found in E_2 and P, this is also in agreement with some reports[7] that TAM has effect to inhibit secretion of prolactin. Some other authors suggest[8] that TAM can also inhibit the action of TRH in stimulating secretion of prolactin, and decreasing the serum level of PRL.

TAM is a competitive antagonist for the estrogen receptor. Estrogen receptor mRNA has been detected in the hypothalamus of normal postmenopausal women and normal pituitary tissue. Friend et al found[9] that 50% of the PRL producing cells and more than 50% gonadotroophs in normal human pituitary tissue stained positive for estrogen receptors. TAM can bind the estrogen

Table 1: the effect of tamoxifen on serum concentration of E_2

Group	Number	Before drug	After drug	
		$E2(\overline{\chi} \pm S)$pg/ml	$E2(\overline{\chi} \pm S)$pg/ml	
A	15	4.67 ± 7.78	4.63 ± 4.14	
B	15	[illegible]	[illegible]	
C	15	208.42 ± 17.35	187.14 ± 13.56	*
D	15	207.41 ± 14.76	117.62 ± 13.67	*
E	15	215.18 ± 12.26	97.02 ± 9.21	*
F	15	198.81 ± 11.20	75.24 ± 9.	*

* $P< 0.01$

Table 2: the effect of tamoxifen on serum concentration of P

Group	Number	Before drug	After drug
		P($\bar{\chi}$ ± S)ng/ml	P($\bar{\chi}$ ± S)ng/ml
A	15	14.12 ± 5.76	14.68 ± 4.89
B	15	24.9 ± 3.86	25.1 ± 11.14
C	15	25.67 ± 9.52	23.58 ± 8.54
D	15	26.02 ± 6.49	14.34 ± 5.14 *
E	15	21.10 ± 5.97	9.76 ± 3.60 *
F	15	23.74 ± 9.41	8.14 ± 4.49 *

*$P < 0.01$

Table 3: the effect of tamoxifen on serum concentration of PRL

Group	Number	Before drug	After drug
		PRL($\bar{\chi}$ ± S)ng/ml	P($\bar{\chi}$ ± S)ng/ml
A	15	1.21 ± 0.56	1.19 ± 0.62
B	15	1.83 ± 0.84	1.95 ± 0.81
C	15	1.88 ± 0.83	1.59 ± 0.81
D	15	2.09 ± 0.94	1.26 ± 0.59 *
E	15	2.14 ± 1.07	0.81 ± 0.62 *
F	15	1.92 ± 0.56	0.57 ± 0.52 *

* $P < 0.05$

receptor in the hypothalmo-hypophyseal system and lower gonadotrophins and thus decreases the E_2 and P level. Similarly, TAM might block the E_2 receptor in the hypothalamo-hypophyseal system and act as an antiestrogen, and thus decrease the secretion of PRL. It is provided[10] that in rat's pituitary cells, TAM can inhibits the E_2 -stimulated prolactin release.

The results of this experiment suggested that the acting point of TAM might locate in hypothalamo-hypophyseal system, by decreasing the E_2, P and PRL, especially by lowering the serum E_2 level in treating fibrocysis breast disease. It provided a theoretical evidence for clinical treatment of fibrocysis breast disease.

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