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Effect of *Gamiondam-tang* (GMODT), a Polyherbal Formula on the Pharmacokinetics Profiles of Tamoxifen in Male SD Rats (2)

- Single Oral Combination Treatment of Tamoxifen 50 mg/kg with GMODT 100 mg/kg with 2.5 hr-intervals -

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Abstract

Objectives : In our previous study, single co-administration GMODT within 5 min significantly inhibited the oral bioavailability of tamoxifen through variable influences on the absorption and excretion of tamoxifen. Therefore, the object of this study was to elucidate the possible effects on the pharmacokinetics of tamoxifen after single oral co-administration of GMODT with 2.5 hr-intervals.

Methods : After 50 mg/kg of tamoxifen treatment, GMODT 100 mg/kg was administered with 2.5 hr-intervals. The plasma were collected at 30 min before administration, 30 min, 1, 2, 3, 4, 6, 8 and 24 hrs after end of GMODT treatment, and plasma concentrations of tamoxifen were analyzed using LC-MS/MS methods. PK parameters of tamoxifen (Tmax, Cmax, AUC, $t_{1/2}$ and MRT_{inf}) were analysis as compared with tamoxifen single administered rats.

Results : Two-half hr-interval co-administration with GMODT induced variable changes on the plasma tamoxifen concentrations as compared with tamoxifen single treated rats, and especially significant ($p<0.05$) increases of plasma tamoxifen concentrations were demonstrated at 0.5 (199.61%) and 1 hr (101.06%) after end of co-administration with GMODT, and also related significant ($p<0.05$) decreases of $t_{1/2}$ (-39.54%) and MRT_{inf} (-43.94%) as compared with tamoxifen single formula treated rats, at dosage levels of tamoxifen 50 mg/kg and GMODT 100 mg/kg with 2.5 hr-intervals, in this experiment.

Conclusions : According to the results, GMODT critically decreased on the oral bioavailability of tamoxifen through variable influences on the absorption and excretion of tamoxifen. Hence, the co-administration of GMODT and tamoxifen should be avoided in the comprehensive and integrative medicine, combination therapy of tamoxifen with GMODT on the breast cancer.

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I. Introduction

Tamoxifen (Nolvadex™) is a nonsteroidal estrogen agonist-antagonist antineoplastic agent has been used for breast cancer[1]. It is the usual endocrine (anti-estrogen) therapy for estrogen receptor-α (ER α)-positive breast cancer in pre-menopausal women[2),3)]. However, various side effects related to tamoxifen treatment also have been arisen as bone loss in premenopausal women who continue to menstruate after adjuvant chemotherapy[4)], endometrial changes, including cancer, are among tamoxifen's side effects[5)], increased risk of thromboembolism[6)], cause of fatty liver[7)], reduced cognition[8)], semantic memory scores[9)] and libido[10),11)], and premature growth plate fusion[12)]. Tamoxifen also depress the immune response[13),14)], and it also known that hypersensitivity to tamoxifen or any ingredient in the formulation[15),16)].

As results of combination therapies with other drugs to improve the side effects of tamoxifen or to achieve synergic effects, various drug-drug interactions of tamoxifen have been evaluated; because bioactivation of tamoxifen is mediated by polymorphic cytochrome P450 (CYP) enzymes; a substrate of CYP3A4/5, 2C9, 2D6[17-20)], it interacted with various drugs, namely, combinations containing any of the following medications, may also interact with aminoglutethimide, rifampin, medroxyprogesterone and phenobarbital - decreased plasma tamoxifen and/or N-desmethyltamoxifen concentrations[21-24)], bromocriptine - increased plasma tamoxifen and N-desmethyltamoxifen concentrations[25)], anticoagulants - enhanced warfarin effects[26),27)], letrozole - decreased plasma letrozole concentrations[28)], respectively. However, interactions with herbal products have not been established except for some restricted natural compounds; tamoxifen enhanced warfarin effects, and it is contraindicate that co-administration of tamoxifen and warfarin[26),27)]. In addition, our previous studies have been observed the possible interactions with Korean traditional polyherbal formulas; oral co-administration of *Jaeumkang-hwa-tang*, a traditional yin-tonifying herbal medicine has been used for various oriental obstetrical and gynecological fields within 5min did not critically influenced on the pharmacokinetics profiles of tamoxifen after single[29)] and repeated[30)] co-administration at dosage levels of 50 mg/kg in tamoxifen and 100 mg/kg in *Jaeumkanghwa-tang*, respectively.

Gamiondam-tang (GMODT) consisted of 13 types of herbs - *Pinelliae* Rhizoma, *Citri Unshii* Pericarpium, *Hoelen*, *Bambusae Caulis In Taeniam*, *Zingiberis* Rhizoma Crudus, *Ponciri* Fructus, *Polygalae* Radix, *Schizandrae* Fructus, *Ginseng* Radix Alba, *Rehmanniae* Radix Preparata, *Glycyrrhizae* Radix et Rhizoma, *Zizyphi* Semen and *Zizyphi* Fructus and has been traditionally used to treat neuropsychiatric disorders such as neurosis and insomnia in traditional medicine[31),32)]. It has been reported that oral administration of GMODT improves cognitive function in aged rats through the increase of choline acetyltransferase expression in the basal forebrain[33)]. Others also observed that GMODT prevents depressive behavior in thiamine-deficient mice and this may be closely related to the activation of cholinergic functions in the hippocampus[34)]. In our previous study, single co-administration GMODT within 5 min significantly inhibited the oral bioavail-

ability of tamoxifen through variable influences on the absorption and excretion of tamoxifen, can be influenced on the toxicity or pharmaco-dynamic of tamoxifen[35]. It, therefore, the effects of GMODT co-administration with reasonable intervals, 2.5 hrs, on the pharmacokinetics of tamoxifen were observed as a process of the comprehensive and integrative medicine, combi-nation therapy of tamoxifen with GMODT to achieve synergic pharmacodynamics and reduce toxicity in breast cancer.

II. Materials and methods

1. Animals and husbandry

Sprague-Dawley rats (6-wk old upon receipt; OrientBio, Seungnam, Korea) were used after acclimatization for 17 days. Animals were allocated five per polycarbonate cage in a temperature (20-25℃) and humidity (40-45%) controlled room. Light : dark cycle was 12 hr : 12 hr and feed (Samyang, Korea) and water were supplied free to access. After acclimatization, five rats per group were selected based on the body weights. Animal experiments were conducted according to the national regulations of the usage and welfare of laboratory animals, and approved by the Institutional Animal Care and Use Committee in Daegu Haany University (Gyeongsan, Gyeongbuk, Korea) [Approval No DHU2013-059].

2. Test articles and administration

Gamiondam-tang (GMODT; HANZUNG PHARM. CO. LTD., Daejeon, Korea) was used in this experiment, and tamoxifen (Hangzhou Tacon Co., Ltd, Hangzhou, China) was used as control drug. Individual compositions of thirteen kinds of herbs in GMODT were listed in table 1. Tamo-xifen and GMODT were stored in a refrigerator at 4℃ to protect from light and degeneration until use. Both drugs are well dissolved (up to 20 mg/ml solutions in GMODT and up to 10 mg/ml solutions in tamoxifen) in distilled water as vehicle, respectively.

Five rats per group (two groups) were used in this study as follows. The doses of test materials were selected based on our previous pharmaco-

Table 1. Composition of GMODT used in this study

Herbs	Scientific Names	Amounts (g)
Pinelliae Rhizoma	*Pinellia ternata* (Thunb.) Breit.	4.38
Citri Unshii Pericarpium	*Citrus unshiu* S.Marcov.	2.75
Hoelen	*Poria cocos* Wolf	1.25
Bambusae Caulis In Taeniam	*Phyllostachys nigra var. henonis* (Bean.)Stapf	1.88
Zingiberis Rhizoma Crudus	*Zingiber officinale* Roscoe	0.83
Ponciri Fructus	*Poncirus trifoliata*	1.88
Polygalae Radix	*Polygala tenuifolia* Willd.	1.25
Schizandrae Fructus	*Schizandra chinensis* (Turcz.) Baill	1.25
Ginseng Radix Alba	*Panax ginseng* C.A.Meyer.	1.25
Rehmanniae Radix Preparata	*Rehmannia glutinosa* Liboschitz ex Steudel	1.25
Glycyrrhizae Radix et Rhizoma	*Glycyrrhiza uralensis* Fisch	1.25
Zizyphi Semen	*Zizyphus jujuba* Miller	1.25
Zizyphi Fructus	*Zizyphus jujuba var. inermis* (Bunge) Rehder	0.76
Total	13 types	21.23

GMODT = *Gamiondam-tang* purchase from HANZUNG PHARM. CO. LTD. (Daejeon, Korea)

kinetics study after single co-administration of tamoxifen and GMODT within 5 min[35] - 50 mg/kg of tamoxifen with 100 mg/kg of GMODT. 150 mins after 50 mg/kg of tamoxifen treatment, GMODT 100 mg/kg was administered. In tamoxifen single treated rats, 50 mg/kg of tamoxifen was orally administered, and then distilled water 5 ml/kg was orally administered, instead of GMODT solutions with 2.5 hr-intervals. Each tamoxifen or GMODT was single orally administered, in a volume of 5 ml/kg, dissolved in distilled water.

3. Plasma collections

All rats were anesthetized with 2 to 3% isoflurane (Hana Pharm. Co., Hwasung, Korea) in the mixture of 70% N_2O and 28.5% O_2, and blood samples (0.5 ml) were collected into 50 IU heparinized tubes via the orbital plexus at 30 min before treatment (as a control), 30 min, 1, 2, 3, 4, 6, 8 and 24 hrs after end of oral administration. Blood samples were immediately centrifuged for 10 min at 13,000 rpm and about 0.3 ml aliquots of plasma were stored in a −150 ℃ deep freezer until analysis.

4. Sample preparation and calibrations

Primary stock solution, 1.0 mg/ml of tamoxifen in 100% MeOH (Baker, Phillipsburg, NJ, USA) and internal standard working solution, carbamazepine (Sigma-Aldrich, Sigma, St. Louise, MO, USA) 500 ng/ml in acetonitrile were prepared. Working standard solutions were prepared by dilution with acetonitrile. All standard solutions were stored at −20℃ in the dark when not in use, and calibrated the standard samples as 100 μl of blank plasma; working standard solutions and internal standard working solution were mixed with 200 μl of acetonitrile. In addition, 100 μl of sample plasma and internal standard working solution were mixed with 200 μl of acetonitrile. The mixtures were mixed by vortex-mixing and centrifuged at 12,000 rpm for 10 min at 4℃. The clear supernatants (5.0 μl) were transferred to injection vials and the aliquot was injected into the LC-MS/MS system.

5. LC-MS/MS conditions

Concentrations of tamoxifen in the rat plasma samples were determined LC-MS/MS method. Chromatographic analysis was performed using an Agilent 1100 Series HPLC (Agilent Technologies, Santa Clara, CA, USA) equipped with on-line degasser, binary pump, autosampler and column compartment. Separation of the analyte from potentially interfering material was achieved at ambient temperature using Waters Symmetry™ C18 columns (2.1×50 mm, 3.5 μm) (Waters Corp., Milford, MA, USA) at column oven 30℃. The mobile phase used for the chromatographic separation was composed of 50% distilled water (0.1% formic acid)/50% acetonitrile, and was delivered isocratically at a flow rate of 0.35 ml/min. The column effluent was monitored using an API 2000 triple-quadruple mass-spectometric detector (Applied Biosystems, Foster City, CA, USA). The instrument was equipped with an electrospray interface in positive ion mode, and controlled by the Analyst version 1.4.1 software (Applied Biosystems, Foster City, CA, USA) (Linear ($1/x^2$, no Iterate)). Samples were introduced to the interface through a Turbo IonSpray with the temperature set at 500℃. A high positive voltage of 4.0 kV was applied to the ion spray. Nitrogen was used as the nebulizer gas, curtain gas, and collision gas with the settings of 70, 20, and 7, respectively. The multiple reaction monitoring (MRM) detection method was employed for the detection of tamoxifen; the transitions monitored were carbamazepine (IS): m/z 237>194 (Retention time: 0.63min), tamoxifen: 372>178 (Retention time: 0.55 min). Calibration curves of tamoxifen

were linear over the ranges studied with $r^2 > 0.999$. The lower limit of quantification of the tamoxifen in the rat plasma was 8 ng/ml.

6. Pharmacokinetic analysis

The plasma concentration data were analyzed using a noncompartmental method on commercial pharmacokinetics data analyzer programs (PK solutions2.0; Summit, Montrose, CO, USA)[36),37)]. The elimination rate constant (K_{el}) was calculated by the log-linear regression of tamoxifen concentration data during the elimination phase, and the terminal half-life ($t_{1/2}$) was calculated by $0.693/K_{el}$. The peak concentration (Cmax) and time to reach the peak concentration (Tmax) of tamoxifen in the plasma were obtained by visual inspection of the data in the concentration-time curve. The area under the plasma concentration-time curve (AUC_{0-t}) from time zero to the time of the last measured concentration (C_{last}) was calculated using the linear trapezoidal rule[38)]. The AUC zero to infinity (AUC_{0-inf}) was obtained by adding AUC_{0-t} and the extrapolated area was determined by C_{last}/K_{el}. The mean residence time infinity (MRT_{inf}) was calculated by dividing the first moment of AUC ($AUMC_{0-inf}$) by AUC_{0-inf}.

7. Statistical analyses

All the means are presented with their standard deviation of five rats (Mean ± S.D. of five rat plasma concentrations of tamoxifen). The pharmacokinetic parameters were compared using a non-parametric comparison test, Mann-Whitney U (MW) test, on the SPSS for Windows (Release 14.0K, SPSS Inc., USA). A p-value <0.05 was considered statistically significant.

III. Results

1. Changes on the plasma concentrations of tamoxifen

Tamoxifen was detected from 30 min to 24 hrs after end of administration in the both tamoxifen single or 2.5 hr-interval co-administered rats with GMODT, respectively. Variable changes on the plasma concentration of tamoxifen were

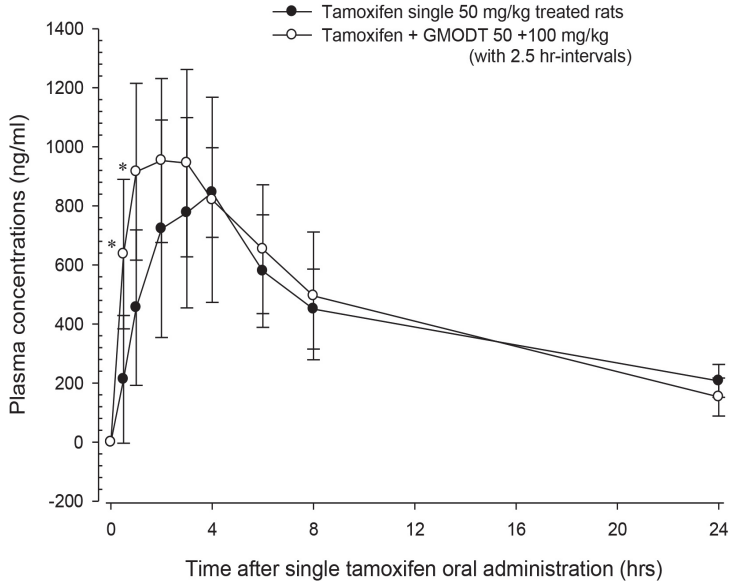

Figure 1. Plasma concentrations of tamoxifen with and without GMODT co-administration with 2.5 hr-intervals in male rats. Values are expressed as mean ± S.D. of five rats (ng/ml). GMODT = *Gamiondam-tang*.
* $p<0.05$ as compared with tamoxifen single treated rats.

demonstrated throughout all blood collecting points in co-administrated rats as compared with tamoxifen single treated rats, and especially significant ($p<0.05$) increases of plasma tamoxifen concentrations were demonstrated at 0.5 and 1 hr after end of co-administration with GMODT, in the present study (Fig 1).

2. Changes on the Tmax of tamoxifen

The Tmax of tamoxifen were non-significantly decreased as −35.29% in 2.5 hr-interval co-administrated rats with tamoxifen 50 mg/kg and GMODT 100 mg/kg (2.20±0.84 hr) as compared with tamoxifen single treated rats (3.40±0.89 hr), in the present study (Table 2).

3. Changes on the Cmax of tamoxifen

The Cmax of tamoxifen were non-significantly increased as 17.32% in 2.5 hr-interval co-administrated rats with tamoxifen 50 mg/kg and GMODT 100 mg/kg (1.02±0.32 μg/ml) as compared with tamoxifen single treated rats (0.87±0.20 μg/ml), in the present study (Table 2).

4. Changes on the AUC of tamoxifen

The AUC_{0-t} of tamoxifen were non-significantly increased as 10.24% in 2.5 hr-interval co-administrated rats with tamoxifen 50 mg/kg and GMODT 100 mg/kg (11.12±4.21 hr・μg/ml) as compared with tamoxifen single treated rats (10.09±2.92 hr・μg/ml). However, AUC_{0-inf} of tamoxifen were also non-significantly decreased as −10.49% in 2.5 hr-interval co-administrated rats with tamoxifen and GMODT (13.15±5.09 hr・μg/ml) as compared with tamoxifen single treated rats (14.69±3.16 hr・μg/ml), in the present study (Table 2).

5. Changes on the $t_{1/2}$ of tamoxifen

The $t_{1/2}$ of tamoxifen were significantly ($p<0.05$) decreased as −39.54% in 2.5 hr-interval co-administrated rats with tamoxifen 50 mg/kg and GMODT 100 mg/kg (9.17±0.83 hr) as compared with tamoxifen single treated rats (15.17±7.40 hr), in the present study (Table 2).

Table 2. Pharmacokinetic parameters of tamoxifen with and without GMODT co-administration with 2.5 hr-intervals in male rats

Parameters	Tamoxifen (50 mg/kg)	
	Without GMODT co-administration (Distill water)	With GMODT co-administration (100 mg/kg)
Tmax (hrs)	3.40±0.89	2.20±0.84
Cmax (μg/ml)	0.87±0.20	1.02±0.32
AUC_{0-t}(hr・μg/ml)	10.09±2.92	11.12±4.21
AUC_{0-inf}(hr・μg/ml)	14.69±3.16	13.15±5.09
$t_{1/2}$(hr)	15.17±7.40	9.17±0.83*
MRT_{inf}(hr)	21.57±11.19	12.09±1.22*

Values are expressed as mean ± S.D. of five rats. GMODT = *Gamiondam-tang* purchase from HANZUNG PHARM. CO. LTD. (Daejeon, Korea). * $p<0.05$ as compared with tamoxifen single treated rats. Cmax: The peak plasma concentration; Tmax: Time to reach Cmax; AUC_{0-t}: The total area under the plasma concentration-time curve from time zero to time measured; AUC_{0-inf}: The total area under the plasma concentration-time curve from time zero to time infinity; $t_{1/2}$: half life; MRT_{inf}: mean residence to time infinity.

6. Changes on the MRT_{inf} of tamoxifen

The MRT_{inf} of tamoxifen were significantly ($p<0.01$) decreased as −43.94% in 2.5 hr-interval co-administrated rats with tamoxifen 50 mg/kg and GMODT 100 mg/kg (12.09±1.22 hr) as compared with tamoxifen single treated rats (21.57±11.19 hr), in the present study (Table 2).

IV. Discussion

Two-half hr-interval single co-administration with GMODT induced variable changes on the plasma tamoxifen concentrations as compared with tamoxifen single treated rats, and especially significant ($p<0.05$) increases of plasma tamoxifen concentrations were demonstrated at 0.5 and 1 hr after end of co-administration with GMODT, and also related significant ($p<0.01$ or $p<0.05$) decreases of $t_{1/2}$ and MRT_{inf} as compared with tamoxifen single formula treated rats, at dosage levels of tamoxifen 50 mg/kg and GMODT 100 mg/kg with 2.5 hr-intervals, in this experiment. These findings are considered as direct evidences that 2.5 hr-interval single co-administration of GMODT also significantly inhibited the oral bioavailability of tamoxifen through variable influences on the absorption and excretion of tamoxifen, can be influenced on the toxicity or pharmacodynamic of tamoxifen, quite similar to those of previous single co-administration within 5 min[35]. Hence, the co-administration of GMODT and tamoxifen should be avoided in the comprehensive and integrative medicine, combination therapy of tamoxifen with GMODT on the breast cancer. I and my colleagues strongly suggested that candidates for breast cancer patient in the comprehensive and integrative medicine should be changed as other than tamoxifen or GMODT.

Tamoxifen was absorbed slowly following oral administration and Tmax of tamoxifen occur about 3-6 hrs after a single dose[39-41] but it rapidly and extensively metabolized in the liver, through a substrate of CYP3A, 2C9, 2D626 including an active major metabolite, N-desmethyltamoxifen has biologic activity similar to that of the parent drug[42),43]. Steady-state concentrations of tamoxifen are attained after 3-4 weeks and those of N-desmethyltamoxifen, an active metabolite, are attained after 3-8 weeks[44]. Tamoxifen excreted principally in feces as polar conjugates[45] with about 5-7 days of $t_{1/2}$ in tamoxifen and 9-14 days in N-desmethyltamoxifen[40]. Clearance of tamoxifen is higher in female children 2-10 years of age than in women[46),47]. In the present study, Tmax of tamoxifen in tamoxifen single oral treated rats was detected as 3.40±0.89 hr, and Cmax, AUC_{0-t}, AUC_{0-inf}, $t_{1/2}$ and MRT_{inf} were detected as 0.87 ±0.20 μg, 10.09±2.92 hr·μg/ml, 14.69±3.16 hr·μg/ml, 15.17±7.40 hr and 21.57±11.19 hr, respectively. In tamoxifen with GMODT co-administered rats with 2.5 hr-intervals, Tmax, Cmax, AUC_{0-t}, AUC_{0-inf}, $t_{1/2}$ and MRT_{inf} of tamoxifen were detected as 2.20±0.84 hr, 1.02 ±0.32 μg, 11.12±4.21 hr·μg/ml, 13.15±5.09 hr ·μg/ml, 9.17±0.83 hr and 12.09±1.22 hr as changed as −35.29, 17.32, 10.24, −10.49, −39.54 and −43.94% as compared with tamoxifen 50 mg/kg single oral treated rats, and especially significant decreases of $t_{1/2}$ and MRT_{inf} were detected in GMODT and tamoxifen single 2.5 hr-interval co-administrated rats as compared with tamoxifen single formula treated rats, at dosage levels of tamoxifen 50 mg/kg and GMODT 100 mg/kg, in this experiment. These results are considered as direct evidences that 2.5 hr-interval single co-administration of GMODT also significantly inhibited the oral bioavailability of tamoxifen through variable influences on the absorption and excretion of tamoxifen, can be influenced on the toxicity or pharmacodynamic of tamoxifen, quite similar to those of previous

single co-administration within 5 min[35].

V. Conclusions

Based on the results of this study, GMODT critically influenced on the oral bioavailability of tamoxifen through variable influences on the absorption and excretion of tamoxifen. Hence, the co-administration of GMODT and tamoxifen should be avoided in the comprehensive and integrative medicine, combination therapy of tamoxifen with GMODT on the breast cancer.

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