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Bioequivalence Study of Nabumetone Tablets in Man

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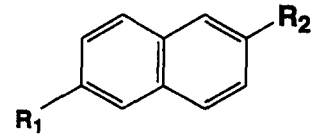
A nabumetone tablet in development (Nabuton^R) was tested for its bioequivalence to the reference tablet (Uniton^R). Seventeen healthy Korean male subjects participated in this study. Each subject received a 1-g dose of nabumetone (2 tablets each) in an unbalanced, randomized, two-way crossover investigation. Serum concentrations of 6-methoxy-2-naphthylacetic acid (6-MNA), a major metabolite of nabumetone, were measured over 120 hr interval by a high-performance liquid chromatography. The maximum serum concentration (C_{max}) and time to reach the maximum concentration (T_{max}) were read directly, but area under the serum concentration time curve from time 0 to 120 hr (AUC) and mean residence time (MRT) of 6-MNA were calculated from the serum 6-MNA concentration-time curves. The serum curves showed multiple peaks of 6-MNA in most subjects, and the C_{max} and T_{max} were read from the highest serum peaks. Calculated bioavailability parameters for test and reference tablets were 1498.6 : 1377.9 μg·hr/ml for AUC; 25.2: 23.1 μg/ml for C_{max}; 11.8: 16.4 hr for T_{max}, and 42.6 : 43.8 hr for MRT, respectively. The paired *t*-test revealed no significant differences in all the parameters between the two tablets. Analysis of variance (ANOVA) revealed no significant differences between groups and formulations in all the parameters (C_{max}, T_{max}, AUC and MRT) indicating the crossover design of the experiment was properly performed. But significant differences ($p<0.05$) between subject/groups and periods were found for all the parameters indicating substantial intersubject and interperiodic variations for these parameters.

Key words : Nabumetone, 6-Methoxy-2-naphthylacetic acid (6-MNA), Bioequivalence, AUC, C_{max}, T_{max}, MRT, Multiple peaks, ANOVA

INTRODUCTION

Nabumetone [4-(6-methoxy-2-naphthyl)-butan-2-one] is an anti-inflammatory drug developed by Beecham Pharmaceuticals. Nabumetone is one of the naphthylalkanone derivatives (Fig. 1) with great potency and fewer gastrointestinal adverse effects (Mangan *et al.*, 1987; Friedel and Todd, 1988). Nabumetone (1 g) is orally administered to patients with painful rheumatoid arthritis once daily since the biological half-life of 6-MNA is about 24 hr (Von Schrader *et al.*, 1983). After oral dose, nabumetone is absorbed from small intestine and undergoes extensive first-pass metabolism by the liver (Mangan *et al.*, 1987; Friedel and Todd, 1988). A major metabolite of nabumetone in serum is 6-methoxy-2-naphthylacetic acid (6-MNA) (Fig.1) formed by side-chain oxidation (Haddock *et al.*, 1984). 6-MNA shows more potent anti-inflammatory effect than nabumetone itself. Due to extensive first-pass metabolism of nabumetone to 6-MNA in the body, 6-MNA in serum needs to be determined to assess the bioavailability of nabumetone preparations.

In this study, bioequivalence of a test tablet (Nabuton^R) and reference tablet (Unimeton^R) of nabumetone was tested in 17 healthy male volunteers by comparing peak serum concentration (C_{max}), time to reach peak concentration (T_{max}), area under the serum concentration time curve from time 0 to 120 hr (AUC) and mean residence time (MRT) of 6-MNA



	R_1	R_2
4-(6-methoxy-2-naphthyl)butan-2-one (Nabumetone)	OCH_3	$CH_2CH_2COCH_3$
6-methoxy-2-naphthylacetic acid (6-MNA)	OCH_3	CH_2COOH
2-naphthol (internal standard)	H	OH

Fig. 1. Chemical structures of nabumetone, its major metabolite 6-MNA and 2-naphthol (internal standard)

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according to the Korean Guidelines of Bioequivalence Test (KGBT, 1988). We did not compare the logarithmic transformed values of the above-mentioned parameters in the test, although these are now recommended by some researchers and regulatory authorities (Schuirmann 1991; Steinijans *et al.*, 1992).

MATERIALS AND METHODS

Materials

The test tablet, Nabuton[R] (500 mg as nabumetone), was supplied by Dong Sung Pharm. Co., Seoul, Korea, and the reference tablet, Unimeton[R] (500 mg as nabumetone), was purchased from Dong Kwang Pharm. Co., Seoul, Korea. The tablets showed almost similar dissolution profiles in our previous study (Shim, 1994). The dissolution of 6-MNA from each tablet into 40% (v/v) ethanol was almost complete when determined at 37°C and 80 rpm for 45 min by paddle method, and showed no significant difference between the two tablets. 6-MNA was purchased from Syntex Research (Palo Alto, CA). 2-naphthol (Fig. 1) was purchased from Showa Chemical Inc. (Tokyo, Japan) and used as internal standard (IS) in HPLC assay of 6-MNA in serum. Hydrochloric acid (37%), ether, citric acid, sodium hydroxide and acetic acid were reagent grade and also purchased from Showa Chemical Inc.

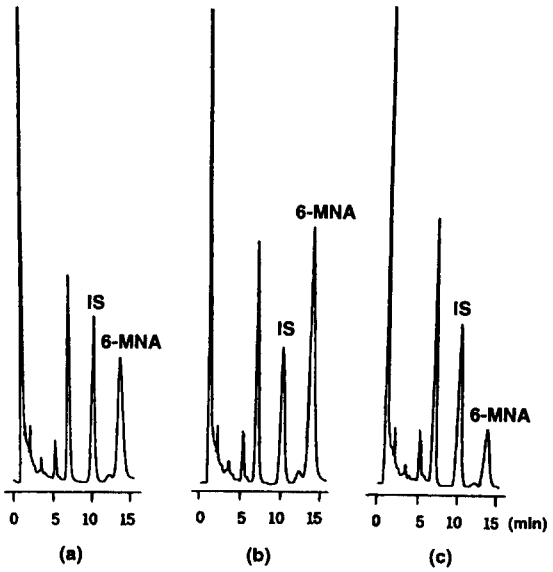

Fig. 2. HPLC chromatograms of serum samples collected from a subject (65 kg) at (a) 1, (b) 24 and (c) 96 hr after a single oral dose of nabumetone (1 g). HPLC was performed according to the modified method (Jang *et al.*, 1995)

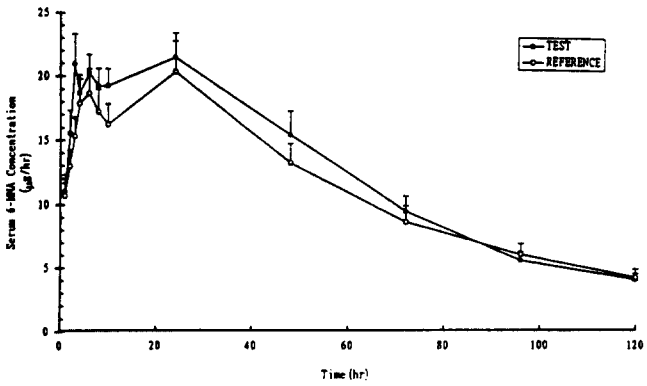

Fig. 3. Average serum concentrations of 6-MNA as a function of time after a single oral dose of nabumetone (1 g) to a male subject (65 kg). Each point represents the mean±SE of seventeen subjects. ○ reference tablet, ● test tablet

Subjects

Seventeen healthy male Korean volunteers, ranging in age from 23 to 33 years (25.6±2.2), in weight from 61 to 74 kg (67.2±4.5 kg), and in height from 165 to 185 cm (174.3±5.4 cm), were selected after passing a clinical screening procedure including a physical examination and laboratory tests (complete blood count, serum urea, creatinine, total protein, albumin, alkaline phosphatase, glucose, SGOT and SGPT and complete urine analysis). Volunteers were excluded if they were possibly sensitive to this type of medication, had any illness of hepatic, renal, or cardiovascular systems, or had taken alcohol or other medication. This was done to ensure that the existing degree of variation would not be due to influence of illness or other medication.

Study implementation

Selected volunteers were cloistered and underwent fasting for 10 hr before medication. Each volunteer gave his informed consent before participation in the study. The study was unbalanced, randomized, open-label, two-period crossover (2×2 crossover design, Table I) for the evaluation of the bioavailability of the two tablets with different formulations. Seventeen healthy male subjects received either a single dose (1 g, two tablets) of the test or the reference tablets in the morning (between 8 and 9 o'clock a.m.). There was a nine-day washout period between medication. The tablets were administered with 200 ml of water. No sleeping was allowed during the experiment. Blood samples (10 ml) were collected by venipuncture from a forearm into heparinized (25-unit) va-

Table I. Dosing schedule of test (Nabuton[R]) and reference (Unimeton[R]) tablets

Group	Subject		
	Period	I	II
1	1-8	Reference	Test tablet
2	9-17	Test tablet	Reference tablet

cuum tubes through an indwelling butterfly needle (21 G Scalp-vein set) at 0, 1, 2, 3, 4, 6, 8, 10, 24, 48, 72, 96 and 120 hr after dosing. After four-hour blood collection, the volunteers were permitted to have standard meals with 200 ml of water. The serum was separated by centrifuging blood specimens at 6000 g for 5 min, and frozen at -20°C until the analysis by high-performance liquid chromatography (HPLC).

HPLC assay of 6-MNA in serum

Daigneault *et al's* method (1987) was modified according to Jang *et al.*, (1995). A stock solution was prepared by dissolving 6-MNA in acetonitrile and serially diluted with acetonitrile to obtain 3 sets of 6-MNA standard solutions of 20, 100, 200, 500 and 1000 μg/ml. Of human blank serum, 950 μl was placed in a 15 ml conical tube and 50 μl of standard solutions were spiked so that the final concentrations of 6-MNA in each tube were 1, 5, 10, 25, 50 μg/ml (standard samples), respectively. To these standard (0.1 ml) and serum samples (0.1 ml) taken from the subjects, 0.1 ml of IS solution containing 100 μg/ml of 2-naphthol in acetonitrile was added and vortexed for 3 min. The samples were acidified by adding 0.5 ml of 0.1N hydrochloric acid and 1.0 ml of 0.5 M citrate buffer (pH 3) with vortexing for 5 min, then extracted with 4 ml of ether by mechanical shaking for 15 min and centrifuged at 3500 rpm for 10 min. The organic layer was transferred into another conical tube and evaporated under a gentle stream of nitrogen. The residue was reconstituted in 0.5 ml of acetonitrile and 20 μl aliquots were injected onto the HPLC column.

The HPLC system consisted of a Shimadzu liquid chromatography system, pump (LC-10A), a UV-spectrophotometric detector (SPD-6AV) and an integrator (C-R6A). Samples were injected with a Rheodyne 7125 injection valve fitted with a 20-μl sample loop. Separations were performed on a μ-Bondapak C18 column (3.9×300 mm, 10 μm particle sizes, Waters) with a Econosphere guard column (Alltech, Carnforth, UK) under ambient temperature. The mobile phase used in the separation was a mixture of acetonitrile (HPLC grade) and 1.5% acetic acid solution with the volume ratio of 25 : 75 (v/v), and adjusted pH 3.7 with 1N sodium hydroxide and filtered through a 45 μm MF membrane filter. The solvents were degassed before use and delivered at a flow rate of 3.0 ml/min. Detection was performed at the wavelength of 280 nm. Retention times of 6-MNA and IS were 13 and 9 min, respectively. Serum concentration of 6-MNA was quantitated by comparing peak height of 6-MNA to internal standard from a linear calibration curve within 1~50 μg/ml (r^2=0.9997). The detection limit of this method was 1 μg/ml.

Table II. Estimates of individual pharmacokinetic parameters of 6-MNA (mean±SD, n=17) following *po* administration of test and reference tablets at a nabumetone dose of 1 g (two tablets each)

Parameters	Reference tablet	Test tablet
C_{max} (μg/ml)	23.1±10.4	25.2±9.0
T_{max} (hr)	16.4±12.7	11.8±9.5
AUC (μg.hr/ml)	1377.9±593.0	1498.6±589.3
MRT (hr)	43.8±1.4	42.6±1.0

Pharmacokinetic and statistical analysis

The bioequivalence of the two formulations was decided based on area under the serum 6-MNA concentration-time curve from time 0 to 120 hr (AUC), peak serum concentration (C_{max}), time to reach peak concentration (T_{max}) and mean residence time (MRT). The C_{max} and T_{max} were read directly from the peak of serum concentration time-curve. When the curve showed multiple peaks, the highest peak was selected. The AUC and area under the first moment of the serum 6-MNA concentration-time curve from time 0 to 120 hr (AUMC) were calculated by the trapezoidal method from time 0 to 120 hr. The MRT of 6-MNA following each administration was calculated by Eq. 1.

$$MRT = AUMC/AUC \quad (1)$$

Significant differences of the bioavailability parameters between the formulations were examined by the paired *t*-test at the level of 5%. Analysis of variance (ANOVA) was also carried out in order to determine the source of variation of each bioavailability parame-

Table III. Summary of ANOVA for bioavailability parameters

Source of variation	DF	C_{max}		T_{max}		AUC		MRT	
		MS	F	MS	F	MS	F	MS	F
Groups	1	157.2	0.93	222.5	1.05	847808.1	1.41	32.7	81.00
Subject/groups	15	169.9	7.94*	212.0	5.43*	599462.8	10.93*	32.9	3.36*
Periods	1	2.4	0.11	48.3	1.23	521354.3	9.51*	102.2	10.46*
Formulations	1	38.2	1.78	163.2	4.18	155074.0	2.82	7.7	0.79
Residuals	15	21.4		39.1		54846.1		9.8	

C_{max}: peak concentration, T_{max}: time to peak concentration, AUC: area under the curve, MRT: mean residence time, DF: degree of freedom, MS: mean squares, F: variance. F_1 (0.05)=4.543, F_{15} (0.05)=2.403, * P<0.0.5.

Table IV. Results of bioequivalence test for the test (NabutonR) and reference (UnimetonR) tablets according to the Korean Guidelines for the Bioequivalence Test (KGBT)

Parameter	DB (%)[a]	1-β[b] at α=0.1 (at α=0.05)	90% confidence interval (δ%)
C_{max}	9.1	0.87 (0.77)	-2.99≦δ%≦21.11
T_{max}	27.7	0.43 (0.30)	4.72≦δ%≦50.68
AUC	8.8	0.95 (0.89)	-1.45≦δ%≦18.98
MRT	2.6	0.99 (0.99)	-1.65≦δ%≦6.94
KGBT Range[c]	<±20%	>0.8	-20≦δ%≦20

[a] DB: difference in bioavailability parameter between test and reference formulations against the reference formulation (<± 20%),

[b] 1-β: statistical power to detect the 20% difference.

[c] Ranges permitted by KGBT to guarantee bioequivalence. Calculation procedure of 1-β and 90% confidence interval is exemplified for AUC below: For 1-β, noncentrality l=3.43 was obtained first by incorporating δ*=0.2×1377.9 (from Table II), n=(8+9)/2 and S=V54846.1 (from Table III) to Eq. 2. Then 1-β was read to be 0.89 from the noncentrality table under the condition of a=0.05 and DF=8+9-2=15. The 90 % confidence interval (δ%) was calculated by incorporating following values to Eq. 3. DB=1498.6-1377.9 (from Table II), $t_{0.05}$=1.75 (read from *t*-table at DF=15), S=V54846.1 (from Table III), n=(8+9)/2, XR=1377.9 (from Table II). Then, -1.45<δ%<18.98 was obtained.

ter (Tsuchiya, 1985).

Bioequivalence judgement

Bioequivalence was judged based upon the Korean Guidelines of Bioequivalence Test (KGBT, 1988). KGBT asks first a proper crossover design performed, which can be tested by ANOVA. KGBT also asks following three requirements to be met before claiming bioequivalence of a test formulation to a reference formulation. First of all, the difference of the mean values of each bioavailability parameter between the formulations should be within the range of ±20% of the mean value of the reference formulation. Secondly, the statistical power (1-β) to detect the 20% difference (δ) should not be less than 0.8 when estimated at α=0.05 or 0.1, where α and β represent the probability of type-I and type-II errors, respectively. Thirdly, the 90% confidence intervals of δ should be <±20% of the mean value of the reference formulation.

The 1-β was read from the table of noncentralities (Concise Statistical Tables, 1976) using noncentrality (λ) calculated by Eq. 2 (Ogata and Ejima, 1989),

$$\lambda = \sqrt{n} \cdot \delta^*/S \quad (2)$$

where n, δ* and S represent mean number of subjects per group, difference to detect, and sample standard deviation, respectively. The n, δ* and S are obtained by $(n_1+n_2)/2$, 0.2×(mean value of bioavailbility parameter of reference formulation), and $\sqrt{MS}$, respectively. The n_1, n_2 and MS indicate number of subjects in group 1 and group 2, and mean sum of residuals (or mean squares), respectively. The λ was calculated by incorporating each value to Eq. 2. Then the 1-β value at the given l was read from the table of noncentrality under the condition of α=0.05 or 0.1 and degree of freedom (DF)=n_1+n_2-2. Since n_1 and n_2 were 8 and 9 respectively in this study, 8.5 and 15 were incorporated to n and DF in the calculation.

The 90% confidence interval of the minimum detectable difference (δ) of each bioavailability parameter was calculated by Eq. 3,

$$(DB-t_\alpha \cdot S/\sqrt{n})\times 100/X_R<\delta\%<(DB+t_\alpha \cdot S/\sqrt{n})\times 100/X_R \quad (3)$$

where DB and X_R represent difference between test and reference formulations in bioavailability parameter, and mean value of each parameter of reference formulation, respectively. The ta was read from t-distribution table at α=0.05 (10%) and DF=15. The calculation procedures of 1-b and the 90% confidence interval was exemplified for AUC in Table IV.

RESULTS AND DISCUSSION

The concentration of 6-MNA from the first serum sample taken at 1 hr after the oral administration of nabumetone tablets (1 g) was relatively high (11 μg/ml) indicating rapid first-pass metabolism of nabumetone to 6-MNA in the body (Mangan *et al.*, 1987). The average serum concentrations (±SE) of 6-MNA are illustrated in Fig. 1. 6-MNA appeared in serum so rapidly that no absorption lag-time was observed from both formulations. 6-MNA concentration was measured up to 120 hr, which is 5-fold longer than the reported half-life of 6-MNA (Schrader *et al.*, 1983).

Nabumetone showed unusual pharmacokinetic behavior by producing a significant secondary peak of 6-MNA in the serum concentration-time curve after oral administration. A similar pharmacokinetic behavior was reported for ranitidine, cimetidine, penicillamine, sobrerol, furosemide and aspirin (Shim and Hong, 1989). Interestingly, Daigneqult *et al.* (1987) reported no double serum peaks of 6-MNA in the bioequivalence study of nabumetone tablet versus suspension in twenty four fasted healthy male American subjects after oral administration of 1 g dose. The inconsistency of the two studies with different races is of great interest and under investigation in our laboratory. The mechanism responsible for double peak phenomena of 6-MNA is not clear but more than one potential mechanisms can be considered.

For example, enterohepatic circulation, two absorption site, biphasic gastric emptying and/or biphasic dissolution in the intestine are all consistent with this observation (Shim and Hong, 1989; Shim and Jung, 1992a; Shim and Jung, 1992b; Shim and Suh, 1992). This aspect of nabumetone pharmacokinetics is also under investigation in our laboratory.

The mean concentrations of 6-MNA for each formulation were not different significantly throughout the sampling period. Table II lists pharmacokinetic parameters (mean $\pm$ SE) for the test and reference tablets. Due to distributed appearance of the peaks, the mean peak heights in Fig. 1 look a little lower than C_{max} values in Table II. The C_{max} and T_{max} were read from the higher (major) peak of the double peaks because the comparison of each of the double peaks is not asked by KGBT (1988). Paired *t*-test reveals that there are no significant differences between the formulations in all the pharmacokinetic parameters implying the possible bioequivalence of the two formulations.

In spite of the difference of serum peak profile from Daigneqult *et al.* (1987), the estimates of the C_{max} and AUC for the two formulations in this study were consistent with their reported values for the tablets which showed C_{max} and AUC of 27.56×1.50 μg/ml and $1,269 \pm 83$ μg·hr/ml, respectively. But T_{max} of 4.99 ± 0.41 hr in their study was far smaller than that in this study which showed 16.4 ($\pm$12.7) and 11.8 ($\pm$9.5) hr for reference and test tablets. The inconsistency in Tmax between Daigneqult *et al.* (1987) and present study is also under the study in our laboratory.

Summary of the analysis of variance (ANOVA) is shown in Table III. There was no significance in F values between groups and formulations for all the parameters. It indicates that the crossover design was properly performed and there is no difference between formulations in all the parameters. But there was significance ($P<0.05$) in all the parameters between subject/groups indicating substantial intersubject variations in these parameters. The significance ($p<0.05$) was also found between periods for AUC and MRT indicating substantial interperiodic variation in these parameters.

Results of the bioequivalence test are summarized in Table IV. The differences (DB) in C_{max}, AUC and MRT between the two formulations were within $<\pm$ 20% satisfying the first requirement of the guidelines of KGBT. The statistical powers (1-β) for C_{max}, AUC and MRT at $\alpha=0.1$ were larger than 0.8 satisfying the second requirement. The powers for AUC and MRT were larger than 0.8 even at $\alpha=0.05$. The 90% confidence intervals of δ for AUC and MRT were within the range ($<\pm$20%) of the third requirement. But the 90% confidence interval for C_{max} slightly exceeded the third requirement ($-2.99\%<\delta\%<21.11\%$). However, that subtle exceeding of this parameter is generally allowed unless the pharmacology/toxicology of the drug is critical to this range of drug concentration (KGBT, 1988). For MRT and AUC, the 95% confidence intervals were also within the range of $<\pm$ 20%, respectively. Therefore, it could be concluded that C_{max}, AUC and MRT of the two formulations are bioequivalent when evaluated at $\alpha=0.1$, respectively.

The difference in T_{max} between the two formulations against the reference tablet (27.7%) exceeded the range permitted in the first requirement indicating bioinequivalence. The statistical power (1-β) and confidence interval of δ for T_{max} were calculated to be 0.43 at $\alpha=0.1$, and $4.72\%<\delta\%<50.68\%$, respectively, not satisfying the second and third requirements either.

In conclusion, bioequivalence of the two tablets (Nabuton^R and Unimeton^R) was guaranteed for AUC, MRT and C_{max}, and bioinequivalence was found for T_{max}. The T_{max} is often neglected in judging bioequivalence since it has little meaning especially for a drug that shows multiple peaks (Steinijans *et al.*, 1992). Actually, US FDA (1977, 1986-1988) is moving to exclude T_{max} from the parameters to be examined in judging bioequivalence. Thus, reference tablet appears to be replaceable by test tablet in patients who need multiple dosing of nabumetone if appropriate care is taken on T_{max}. Considering the results of the present study together with Daigneault *et al* (1987) that showed bioequivalence of suspension and tablet of nabumetone, nabumetone seems to seldom cause bioequivalence problem in spite of its poor water solubility and extensive first-pass metabolism to 6-MNA.

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