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Pharmacokinetics of Benzbromarone in Normal Chinese Males

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ABSTRACT

Pharmacokinetics of benzbromarone, a potent hypo-uricemics, have been investigated employing 26 normal Chinese males. Following oral administration of 100 mg dose (Desuric 100 mg/tablet, Labaz France), the pharmacokinetics of benzbromarone based on plasma data were C_{max} (3.51 ± 0.90 μg/mL, mean ± SD), AUC_t (0-14 h, 17.94 ± 4.53 μg·h/mL), total AUC (19.00 ± 4.73 μg·h/mL), T_{max} (3.08 ± 1.15 h), terminal phase $T_{1/2}$ (2.97 ± 0.85 h), MRT (5.70 ± 1.25 h) and Cl/F (89.5 ± 26.2 mL/min). Wagner-Nelson absorption plots of the mean benzbromarone plasma concentrations suggest that there are competing reactions in the absorption process. The 90% confidence regions for C_{max} and AUC, and for C_{max}, AUC and MRT, and their log-transformed vectors were also estimated. No evidence to show that the pharmacokinetics of benzbromarone in Chinese are different from those reported in Caucasian subjects, and none of the slow elimination phenotype with benzbromarone have been observed in this study.

Key words: **benzbromarone, HPLC, pharmacokinetics, Chinese.**

INTRODUCTION

Benzbromarone, 2-ethyl-3(4-hydroxy-3,5-dibromo-benzoyl)-benzofuran,developed by Labaz Lab. (France) is a popular potent inhibitor of renal urate reabsorption and shows significant hypo-uricemic and uricosuric activity in both non-gouty and gouty subjects at doses of 50-100 mg per day[1-3]. A single oral dose of benzbromarone reduces serum uric acid by about 30 to 60% of the pre-treatment level[4]. This effect is apparent 3 h following oral administration and the maximum effect is attained after 8 to 12 h[4,5]. Following the administration of an oral dose of 100 mg ^{3}H-labelled benzbromarone, approximately 50 to 55% of the dose was absorbed[6]. Excretion of benzbromarone and its metabolites is mainly via the bile, only 6% of radioactivity can be recovered in the urine[6]. Studies suggested that benzbromarone under went debromination in the liver to form major metabolite benzarone[6,7]. However, it was revealed in the subsequent study[8] that benzbromarone is not debrominated but hydroxylated to form hydroxyalkyl-, hydroxyaryl-, oxo- and hydroxymethoxyaryl-benzbromarone. The major metabolite in plasma and urine was a

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hydroxybenzofuranoyl species, and the hydroxybenzofuranoyl metabolite has been mistaken for benzarone in the previous studies[9]. Since benzbromarone is practicably insoluble in water and in gastric juice, the rate of absorption from gastrointestinal tract depends on the particle size of the preparation, the maximum serum levels are obtained 2 and 3 h, respectively following oral administration of micronized and non-micronized benzbromarone[10]. In spite of the popular use of this drug in Taiwan, the available data on the pharmacokinetic behavior of benzbromarone are based on studies which used Caucasian subjects[10-12]. The current study aims to reveal the pharmacokinetics of benzbromarone in normal Chinese males.

MATERIALS AND METHODS

I. *Benzbromarone Products*

Original innovator's Desuric tablets (reference product, Lot No. 56, Labaz, France), each unit containing 100 mg benzbromarone were used.

II. *Subjects*

After a review of their personal history, plus medical and laboratory examinations, 26 normal Chinese males in Taiwan whose age ranged from 20 to 43 years were selected to participate in two randomized 2x2 single dose bioequivalence studies (n_1=12, n_2=14) using Desuric tablet and a generic product (Narcaricin, 100 and 50 mg per capsule, Swiss Pharm. Taiwan). The data obtained following the oral administration of Desuric tablets in the two studies are compiled in this report. The demographic data of subjects are listed in Table 1.

Table 1. Demographic data of subjects

Subjects	Age (years)	Height (cm)	Weight (kg)
1	31	178	78
2	24	173	85
3	20	170	70
4	29	172	66
5	20	168.5	72
6	28	164.5	58
7	28	170	61.5
8	34	169	63
9	25	164	58
10	25	177	75
11	25	171	58
12	24	173	63
13	26	179	62.5
14	24	172.5	74
15	34	172	72
16	24	171	52
17	24	173	90
18	23	160	52
19	29	178.5	78.5
20	29	168	59
21	43	175	85
22	36	171	69
23	28	176	69
24	29	170	70
25	35	166	63
26	21	165	55
Mean(SD)	27.6(5.4)	171.0(4.7)	67.6(10.2)

III. *Study Design*

A Desuric tablet was administered orally on the morning under fasting condition with a 150 mL of drinking water. Blood samples (10 mL) were serially collected via heparin lock pre-dose and at 0.5, 1, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, and 14 h post-dose. Plasma was separated immediately subsequent to the blood collection, and the plasma was stored in a freezer (-20°C) until assayed. The assays were accomplished within one month after the blood had been collected. A stability study revealed that benzbromarone was stable at least for one month in the freezer.

VI. *Determination of Benzbromarone in Plasma*

A clean-up procedure and a specific HPLC method have been developed and validated. Briefly, 1 mL of plasma was acidified with 50 μL of 0.1% phosphoric acid solution, and then added 2 mL of acetonitrile to precipitate plasma proteins. The supernatant was aspirated to a new test tube and subsequently extracted with 3 mL of

dichloromethane. The organic layer was transferred to another new test tube and dried at 35°C with N_2 gas. The residue was redissolved in a 250 μL of HPLC mobile phase. A 20 to 50 μL of the solution was injected into HPLC. An HPLC apparatus, Shimadzu LC-6A equipped with SPD-10A detector, CR-4A chromatopac data workstation, SCL-6A system controller and SIL-6A autoinjector was used. The separation was accomplished with a NOVA-PAK C18 column (3.9 x 150 mm, 4 μm, Waters) and a Guard-Pak μBondapak C18 (8.0 x 10 mm, Waters). Benzbromarone was detected using 350 nm. A mobile phase consisting of 10 mM NaH_2PO_4 (pH 5.4)/CH_3CN = 60/40 (v/v) was run at a flow rate of 1 mL/min and a detector attenuation of 0.005 aufs under room temperature. In order to avoid the response error due to the day-to-day retention time shift, peak area rather than peak height was measured[13]. The day-to-day retention time shift may have resulted from decreasing efficiency of analytical column and small perturbation of analytical conditions in the assays of biological samples. Linearity of response and plasma concentrations of benzbromarone was established by the Lack-of-Fit test. The linear dynamic concentrations ranged from 0.04 to 5.0 μg/mL. The calibration line passed through the origin without constant bias (e.g. Y=200781X, Y: peak area, X: concentration, μg/mL). The recovery was larger than 90% and inter-assay variability was smaller than 8% (coefficient of variation, CV) for the linear dynamic concentration range. The limit of quantitation (LOQ) was 0.04 μg/mL.

V. *Pharmacokinetic Parameters*

The maximum observed plasma concentration (C_{max}) and the time to reach the maximum concentration (T_{max}) were recorded for each subject. The partial AUC (AUC_t, 0-14 h) was calculated using the linear trapezoidal method; whereas the remaining area was estimated through dividing the last observed concentration by the slope of the terminal phase. Partial mean residence time (MRT_t, 0-14 h) and total mean residence time (MRT) were computed using the statistical moment method[14]. The apparent oral clearance (Cl/F) was estimated through dividing the dose by the total area under the concentration curve (AUC).

VI. *Wagner-Nelson Absorption Plots*

Wagner-Nelson absorption plots[15] was used to evaluate the absorption kinetics of benzbromarone with the mean plasma concentration data.

VII. *The 90% Confidence Region for the Bioavailability Relevant Mean Parameters*

Since the bioavailability relevant parameters, C_{max}, AUC and MRT are mutually correlated variables, when C_{max} and AUC, or C_{max}, AUC and MRT are assessed simultaneously, their confidence region can not be defined by the confidence interval of each variable. Hsu *et al.*[16] have shown that the equations of the confidence region for two or three correlated variables can be derived using Hotelling's T^2 statistics[17]. The 90% confidence regions for the mean vectors of C_{max} and AUC, or $\ln C_{max}$ and lnAUC (confidence ellipse), and C_{max}, AUC and MRT, or $\ln C_{max}$, lnAUC and lnMRT (confidence ellipsoid) after oral administration of Desuric tablets were estimated by the method of Hsu *et al.*[16]

VIII. *Pharmacokinetic Difference between Chinese and Caucasian Subjects*

The pharmacokinetic parameters of benzbromarone obtained in this study were compared to those reported for Caucasian subjects[8,11,12] using Student's t test.

RESULTS AND DISCUSSION

I. *Typical HPLC Chromatogram*

Figure 1 illustrates the typical HPLC chromatogram of clinical plasma samples following clean-up which were obtained at time zero (predose) and at 1, 3, 6 and 14 h post-dose. The solvent front noise drastically increased with time following drug administration. Two new peaks (at about 6 and 18 min) appeared in the samples after

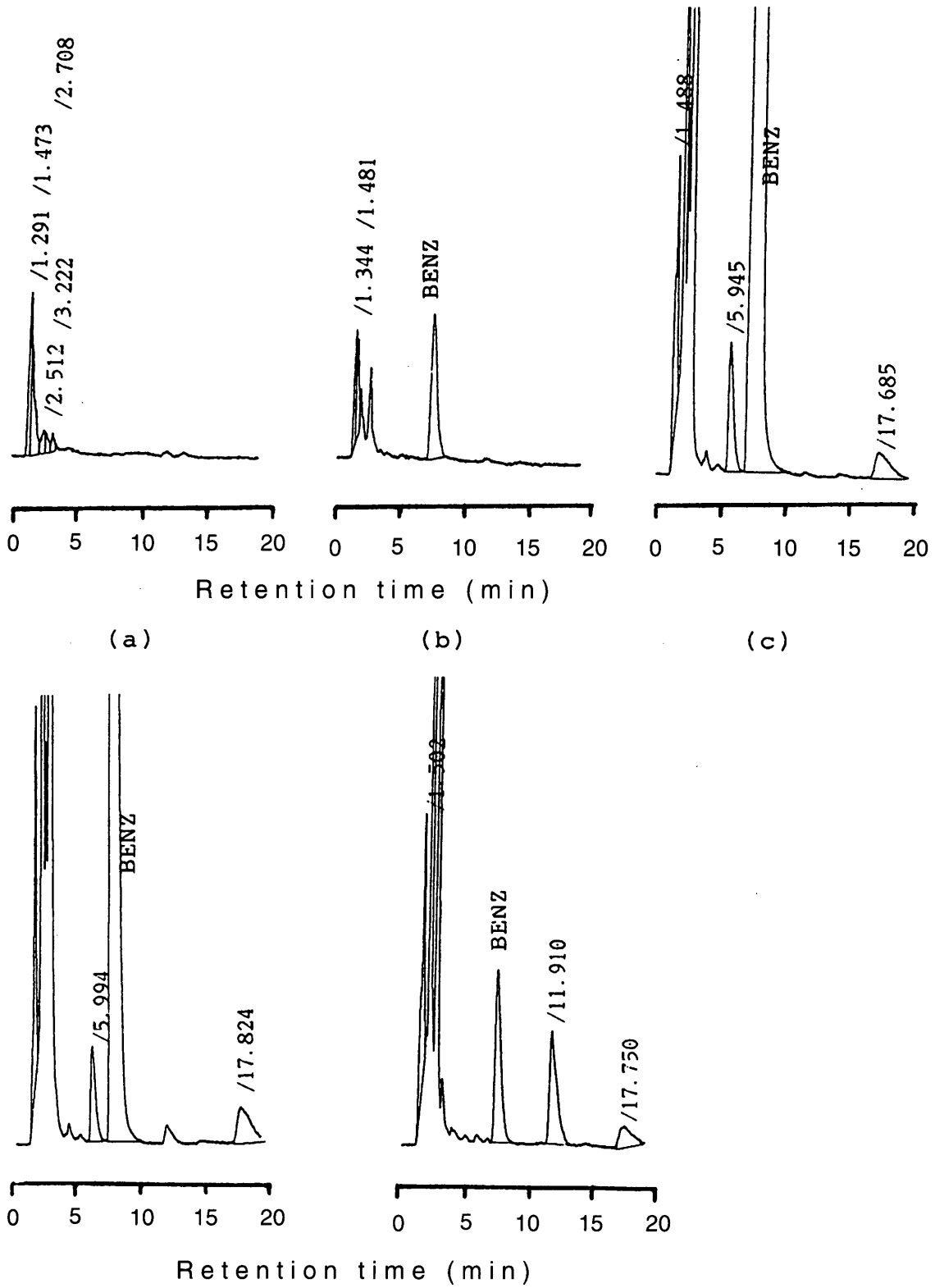

Figure 1. Typical HPLC chromatogram of clinical plasma samples following the clean-up.

(a) Pre-dose (b) 1 h post-dose
(c) 3 h post-dose (d) 6 h post-dose
(e) 14 h post-dose BENZ: benzbromarone peak

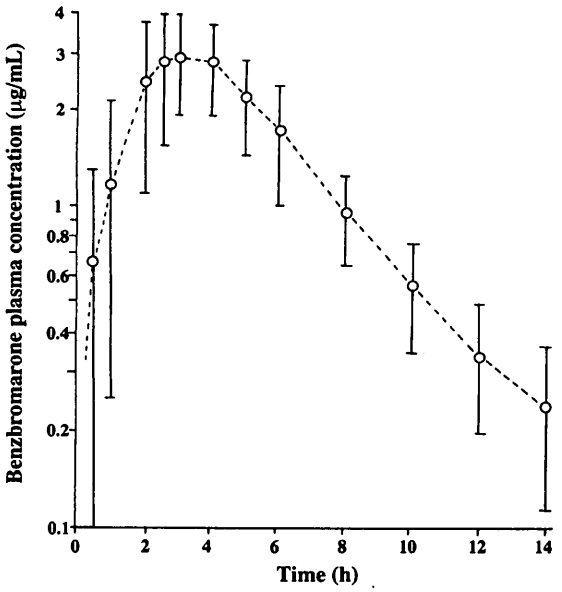

Figure 2. Profile of benzbromarone plasma concentrations (mean ± SD, n=26).

Table 2. Pharmacokinetic parameters of benzbromarone in Chinese (Desuric tablet, 100 mg, n = 26)

Model Independent Parameters	(Mean ± SD)
C_{max}, μg/mL	3.51 ± 0.90
T_{max}, h	3.08 ± 1.15
$AUC_{0\text{-}14\ h}$, μg·h/mL	17.94 ± 4.53
AUC, μg·h/mL	19.00 ± 4.73
$MRT_{0\text{-}14\ h}$, h	4.97 ± 0.80
MRT, h	5.70 ± 1.25
$T_{1/2}$, h	2.97 ± 0.85
Cl/F, mL/min	89.5 ± 26.2

the drug had been administered for 2 h (Figure 1, c), and another peak (at about 12 min) appeared in the samples of 5 h post-dose (Figure 1, d). The peak at about 6 min increased its intensity in the samples obtained at 2 to 4 h, and then gradually decreased its intensity with time, and diminished in the sample of 14 h post-dose. The peak at about 12 min increased its intensity with time in the samples obtained at 5 to 14 h post-dose (Figure 1, d and e). Presumably, the increased solvent front noise, peaks at about 6, 12 and 18 min were related to the biotransformed metabolites of benzbromarone.

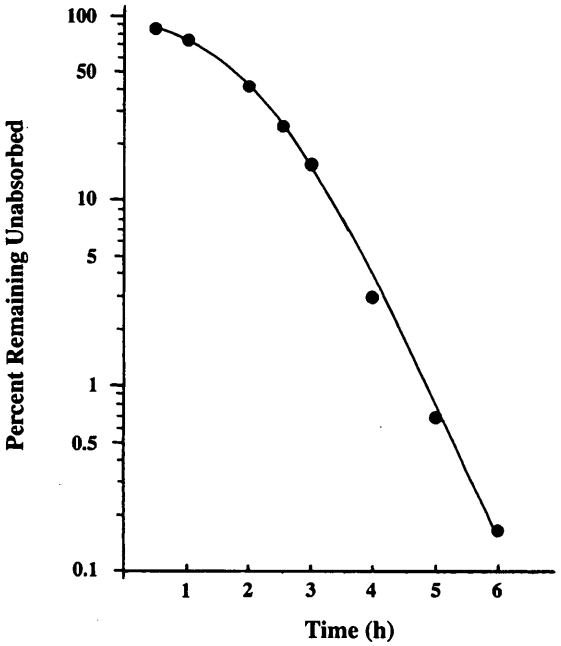

Figure 3. Wagner-Nelson absorption plots.

II. *Profile of Benzbromarone Plasma Concentrations*

The profile of benzbromarone plasma concentrations following oral administration of Desuric tablet is shown in Figure 2. Table 2 shows the pharmacokinetic parameters of benzbromarone in Chinese subjects.

III. *Wagner-Nelson Absorption Plots*

The profile of the apparent percent unabsorbed versus post-dose time is shown in Fig. 3. The profile is a decline curve rather than a straight line which suggests that there are competing reactions in the absorption process of benzbromarone[18]. The most probable competing reactions are the metabolic transformation reactions at the gut wall and liver, because it is known that only about 50 to 55% of the oral dose of benzbromarone is absorbed[6].

IV. *90% Confidence Regions for C_{max} and AUC, and for C_{max}, AUC and MRT*

Table 3 shows the equations of 90% confidence region for C_{max} and AUC (an ellipse), and for C_{max}, AUC and MRT (an ellipsoid); Table 4

Table 3. Equations of 90% confidence ellipse and ellipsoid constructed with vectors (raw scale) obtained following oral administration of Desuric tablet (100 mg, n = 26)

Equation of 90% Confidence Ellipse (C_{max} and AUC)
$0.602(C_{max} - 3.512)^2 - 0.178(C_{max} - 3.512)(AUC - 18.963) + 0.0219(AUC - 18.963)^2 = 1$
Equation of 90% Confidence Ellipsoid (C_{max}, AUC and MRT)
$(C_{max} - 3.512)^2 + 0.0328(AUC - 19)^2 + 0.202(MRT - 5.701)^2 - 0.3(C_{max} - 3.512)(AUC - 19) - 0.071(AUC - 19)(MRT - 5.701) + 0.471(C_{max} - 3.512)(MRT - 5.701) = 1.69$

C_{max}: μg/mL, AUC: μg·h/mL, MRT: h.

Table 4. Equations of 90% confidence ellipse and ellipsoid constructed with vectors (log-transformed) obtained following oral administration of Desuric tablet (100 mg, n = 26)

Equation of 90% Confidence Ellipse (lnC_{max} and lnAUC)
$6.41(lnC_{max} - 1.23)^2 - 9.61(lnC_{max} - 1.23)(lnAUC - 2.92) + 7.24(lnAUC - 2.92)^2 = 1$
Equation of 90% Confidence Ellipsoid (lnC_{max}, lnAUC and lnMRT)
$(lnC_{max} - 1.23)^2 + 0.533(lnAUC - 2.84)^2 + 0.106(lnMRT - 2.03)^2 - 0.105(lnC_{max} - 1.23)(lnAUC - 2.84) - 0.163(lnAUC - 2.84)(lnMRT - 2.03) - 0.251(lnC_{max} - 1.23)(lnMRT - 2.03) = 0.379$

C_{max}: μg/mL, AUC: μg·h/mL, MRT: h.

shows the equations of 90% confidence region for lnC_{max} and lnAUC, and for lnC_{max}, lnAUC and lnMRT following oral administration of Desuric tablets. These confidence regions represent the bioavailability relevant characteristics of the drug product, and can be used in the application of the specification test[16] to determine the comparative bioavailability of generic products. If the vectors of test product are contained in the 90% confidence region of the reference product, then bioequivalence between the test and reference products can be suggested.

V. *Pharmacokinetic Difference between Chinese and Caucasian Subjects*

Among the pharmacokinetic parameters, the values of C_{max}, AUC and $T_{1/2}$ obtained in this study were able to compare to those reported by Feber *et al.* for Caucasian subjects[10] at the same dosage (C_{max}: 1.84 ± 0.87 μg/mL; AUC: 10.32 ± 2.36 μg·h/mL; $T_{1/2}$: 2.77 ± 1.07 h, body weight: 71.6 ± 6.1 kg, n=7). It is intriguing to note that $T_{1/2}$ is not different from Chinese to Caucasian subjects, but there are significant differences in C_{max} and AUC ($p < 0.05$). On the other hand, when the values of parameters in Chinese subjects were compared to those reported by Walter-Sack *et al.* at the same dose[11] (C_{max}: 3.91 ± 0.92 μg/mL, AUC: 18.3 ± 4.12 μg·h/mL, T1/2: 3.34 ± 1.13 h, T_{max}: 1.45 ± 0.55 h, body weight: 76.7 ± 8.7 kg, n=10), only the T_{max} in Caucasian subjects is shorter than that in Chinese subjects ($p < 0.05$). The difference between the results of Feber *et al.* and Walter-Sack *et al.* probably resulted from the different assay methods used since the body weight of subjects are statistically not different between the two studies. Since T_{max} values are dependent on the blood-collection schedule, the difference in T_{max} values between two independent studies may not always be meaningful. Hence, no evidence to suggest that the pharmacokinetics of benzbromarone in Chinese and Caucasian subjects are different. Rapid and slow elimination phenotypes with benzbromarone have been reported[11,12], however, none of slow elimination phenotype with benzbromarone have been observed in this study.

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Benzbromarone在健康華人男性體內的藥物動力學

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摘 要

Benzbromarone爲一有效降尿酸藥劑。26名健康男性口服100mg後所得血漿藥物動力學參數爲：C_{max}（3.51 ± 0.90 μg/mL, mean ± SD），AUC_t（0-14 h, 17.94 ± 4.53 μg·h/mL），total AUC（19.00 ± 4.73 μg·h/mL），T_{max}（3.08 ± 1.15 h），terminal phase $T_{1/2}$（2.97 ± 0.85 h），MRT（5.70 ± 1.25 h） and Cl/F（89.5 ± 26.2 mL/min）. Wagner-Nelson解析結果該藥在吸收過程中有代謝反應。若同時評量C_{max}和AUC，或其對數轉換向量，可得90％可信楕圓，若同時評量C_{max}，AUC和MRT，或其對數轉換向量，可得90％可信楕圓球來描述互爲相關的生體可用率參數的90％可信範圍。

比較benzbromarone在華人和白種人體內的藥物動力學參數值，並未發現有所差異。在本試驗也未發現在白種人中所具有的對該藥物呈消失遲緩的表型。

關鍵詞：benzbromarone，高效液相層析法，藥物動力學，華人。