protein，在夜间分别少53.0%和70.9%。褪黑激素和6-氯褪黑激素能竞争性抑制其结合。鸽 im 氢化可的松15 mg·kg^{-1}·d^{-1}×5 d 能明显增加[^{125}I]褪黑激素在脾的结合位点，结果提示褪黑激素对免疫的调节可能有直接作用。

关键词　褪黑激素；碘放射性核素；结合位点；鸽；鹌鹑；氢化可的松；脾

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Pharmacokinetics and relative bioavailability of nimodipine capsules and tablets in 8 Chinese healthy men

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ABSTRACT　A single oral dose of tablets or capsules of 239 μmol nimodipine was given to 8 healthy volunteers of Han nationality in a randomized crossover study. Plasma levels were determined with HPLC method. The plasma concentration-time curve fitted to a first order absorption，1-compartment open model，and the $T_{\frac{1}{2}K}$ was around 2 h. Although the capsules could reach peak level faster，the bioavailability was not significantly different from that of the tablets.

KEY WORDS　nimodipine；capsules；tablets；high pressure liquid chromatography；pharmacokinetics；biological availability

Nimodipine belongs to the second generation of 1，4-dihydropyridine group of Ca^{2+} channel antagonists，and is mainly used for the treatment of cerebrovascular diseases[1]. In relation to this compound，there have been studies abroad on the procedures for drug analysis[2]，the characteristics of pharmacokinetics[3]，and the profiles of biotransformation[4]. Domestically，the focus of research has been on drug stability[5,6] and formulation assessment[6-8]，yet no report has been found on investigation in the human body.

Using a high pressure liquid chromatographic (HPLC) method[2,6]，we studied the pharmacokinetics and relative bioavailability of nimodipine capsules and tablets in 8 Chinese healthy men.

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MATERIALS AND METHODS

Drug manufacturers　Nimodipine standard and tablets (20 mg/tablet)，Tianjin Central Pharmaceutical Factory (tablet lot № 911020). Nimodipine capsules (20 mg/capsule)，Suzhou № 3 Pharmaceutical Factory (lot № 911118). Methanol，Shanghai Zhenxing № 1 Chemical Plant (AR，lot № 9105017). Diethyl ether，Shanghai Malu Pharmaceutical Factory (AR，lot № 90031332)

Instruments　The HPLC system (Shimadzu Corp，Kyoto，Japan) consisted of 2 LC-6A solvent delivery units，a Rheodyne model 7125 injector，a FCV-2AH high-pressure flow channel selection valve，a SPD-6AV uv-vis spectrophotometric detector，a SCL-6B system controller，and a C-R6A data processing unit. Both the 45 mm×4.6 mm precolumn and 250 mm×4.6 mm analytical column (Dalian Institute of Chemical Physics，Dalian，China) were packed with Spherisorb C_{18} 5 μm.

Subjects　Having been informed about the effects of the drug and passed the physical examinations，8 healthy male volunteers of Han nationality were accepted into the study. They were aged 27±*s* 8 a，weighing 64±*s* 6 kg，and all the test results of their blood，urine，liver，kidney，and electrocardiogram were within normal ranges. At least 2 wk before the

study, all were asked to be kept from medications, tobacco, and alcohol until the end of the study.

Study design After a 12-h fasting, the volunteers received at 8 AM a single oral dose of 5 nimodipine tablets or capsules (100 mg or 239 μmol) according to a randomized crossover study design. Regular meals started at 12 noon. The washout period was set to be 1 wk.

Plasma sampling With an iv catheter retained in a forearm vein, blood samples were collected at 0, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, and 9 h after the drug was given. Under darkened conditions, the samples were heparinized and centrifuged immediately at 700×*g* for 5 min. Then plasma (1.50 ml) was extracted with 5.00 ml diethyl ether by vortex shaking for 1 min. After being centrifuged at 700×*g* for 5 min, 4.4 ml of the ether phase was evaporated at 50℃ under a gentle air flow. The residues were dissolved with 50 μl mobile phase, and 25 μl of the solution were injected for HPLC analysis.

Drug analysis The plasma nimodipine concentrations were analyzed with a HPLC system. Methanol-water (725:275, vol·vol) was used as mobile phase at a flow rate of 1 ml·min^{-1} for both the precolumn and analytical column when degassed under vacuum plus sonication. The connection or disconnection of the 2 columns was performed by the FCV-2AH high-pressure flow channel selection valve at the assigned moment in order to avoid most of the interferences. The detector was set at 356 nm and 0.00125 AUFS. The retention time of nimodipine was 9.65 min. The plasma detection limit was 3.58 nmol·L^{-1}. The linear range was between 4—128 nmol·L^{-1} with recoveries of 87±*s* 8% at different levels and *CV* <6% (within-day) and <16% (between-days).

Pharmacokinetic analysis The concentrations were analyzed with a PKBP-N1 program on a LASER-3000 personal computer to determine the compartment models, the pharmacokinetic parameters and the relative bioavailability of the capsules *vs* the tablets.

RESULTS

The plasma nimodipine concentration-time curves were fitted to a first order absorption 1-compartment open model (Fig 1). The relative bioavailability of the capsules *vs* the tablets was 1.1±*s* 0.4 ($P>0.05$) (Tab 1).

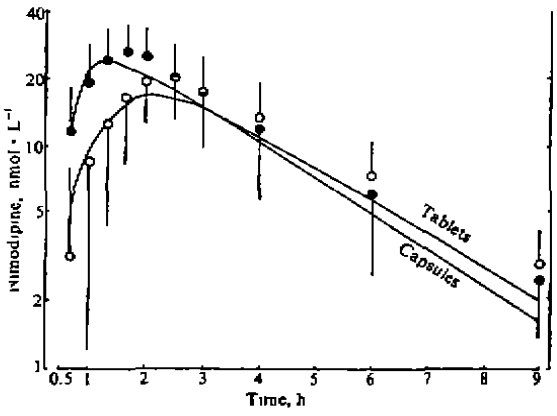

Fig 1. Plasma nimodipine concentrations in 8 Chinese healthy men after a single oral dose of 239 μmol of tablets (○) or capsules (●) in random crossover. $\bar{x}\pm s$.

Tab 1. Pharmacokinetic parameters of nimodipine in 8 Chinese healthy men after a single oral dose of 239 μmol of tablets or capsules in random crossover. $\bar{x}\pm s$. * $P>0.05$, ** $P<0.05$, *** $P<0.01$ *vs* tablets.

Parameters	Tablet	Capsule
Lag time, h	0.8±0.4*	0.56±0.16
K_a, h^{-1}	1.5±0.6**	3.0±1.4
$T_{\frac{1}{2}K_a}$, h	0.53±0.22*	0.29±0.18
A, nmol·L^{-1}	54±47*	43±13
K, h^{-1}	0.34±0.08*	0.37±0.10
$T_{\frac{1}{2}K}$, h	2.2±0.5*	2.0±0.5
V/f, L·kg^{-1}	140±80*	120±40
T_{max}, h	2.2±0.4***	1.4±0.3
C_{max}, nmol·L^{-1}	20±7*	26±9
$AUC_{0-\infty}$, h·nmol·L^{-1}	100±30*	110±50

DISCUSSION

The sensitivity of our method was quite high, because it was approaching the limits of our instruments to detect at ng level. Although the day-to-day precisions were not so satisfactory, it was still acceptable for biological samples.

No difference was found between the 1st and 2nd medication in the randomized crossover study.

Rämsch *et al* (Bayer AG, Germany) studied the pharmacokinetics of nimodipine tablets in 6 healthy volunteers[3]. With some units converted, their results are: oral dosage 143 μmol, $T_{\frac{1}{2}K}$ 1.7±1.1 h, T_{max} 0.8±0.3 h, C_{max} 49±28 nmol·L^{-1}, $AUC_{0-\infty}$ 100±70 h·nmol·L^{-1}. Both the nimodipine products we studied had nearly the same $T_{\frac{1}{2}K}$ as that of the above product. However, even with about double the dosage, it took almost 2 (capsules) to 3 (tablets) as long for the products we studied to reach a level of less than half the maximum concentration, and their relative bioavailabilities were just over 60% *vs* the tablets Rämsch *et al* studied. So it seemed that these domestic products were absorbed more slowly and less in Chinese people than that foreign product was in foreigners. Further investigation is needed to discover whether this is due to quality differences in formulation or caused by genetic variations in human metabolism.

So far as our results are concerned, although the capsules have the same bioavailability as the tablets, they are still clinically advantageous because they can be absorbed faster and reach the peak concentration much earlier. Consequently, the capsules yield therapeutic effects more quickly.

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295-297

尼莫地平胶囊与片剂在8名中国健康人体内的药物动力学与相对生物利用度

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R969.1

摘要 8名男性汉族健康志愿者随机交叉口服单剂量239 μmol国产尼莫地平片剂或胶囊后，用高压液相色谱法测定血浆药物浓度. 血药浓度—时间曲线拟合表明该药体内过程符合一级吸收一室开放模型，消除半衰期为2 h. 统计结果表明胶囊虽达峰时间较快，但生物利用度与片剂无显著性差异.

关键词 尼莫地平；胶囊；片剂；高压液相色谱；药物动力学；生物利用度