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Pharmacokinetics of Nifedipine in Taiwanese

Shu-Chen Chien, Yow-Shieng Uang, Hsiu-Yi Lin and Kuang-Yang Hsu*
School of Pharmacy, Taipei Medical University, 250 Wu-Hsing Street, Taipei 110, Taiwan, ROC

ABSTRACT: To elucidate the pharmacokinetics of nifedipine in Taiwanese, a retrospective review of nifedipine bioequivalence studies completed in Taiwan in the past 5 years was conducted. A total of 198 healthy male volunteers were given a single dose of a 10 mg Adalat® capsule as a reference drug after overnight fasting. Pharmacokinetic parameters derived from Adalat® administration were calculated by non-compartmental analysis with the WinNonlin program. After oral administration of an immediate-release dosage form of a 10 mg nifedipine capsule to Taiwan residents, a skewed distribution with no clear evidence of bimodality of pharmacokinetic parameters was observed. The mean C_{max} was 143.12 ± 53.48 ng/ml, the mean *AUC* was 293.77 ± 115.62 ng · h/ml, the mean $T_{1/2}$ was 3.08 ± 1.61 h, and the median value of T_{max} was 0.61 h. Compared with other published studies, the C_{max} and *AUC* of nifedipine after 10 mg administration were significantly higher in Taiwanese than in British and American subjects. However, the C_{max} and *AUC* were similar to those of Indian and Mexican subjects. According to the antimode of *AUC* distribution of 22.5 ng · h/ml/mg proposed by Kleinbloesem, 69.7% of Taiwanese can be categorized as slow metabolizers. Based on the results in this study, the majority of Taiwanese show lower activity of nifedipine metabolism. Copyright © 2004 John Wiley & Sons, Ltd.

Key words: nifedipine; pharmacokinetics; Taiwanese

Introduction

Nifedipine (NF) was the first dihydropyridine calcium channel blocker and is widely used in the treatment of arterial hypertension, angina pectoris and other cardiovascular diseases. Its therapeutic effect is the result of potent vasodilatory activity produced by a blockade of calcium entry to smooth muscles [1]. NF shows a high body clearance, which is primarily attributed to its first-pass metabolism. NF has a short half-life, ranging from 1 to 5 h, and undergoes biotransformation to pharmacologically inactive metabolites [2–4]. Different pharmacokinetics of oral NF has been obtained from people of different ethnic origins [5–7]. After oral administration of an immediate-release formulation, NF is absorbed rapidly with peak blood concentrations within 30–90 min. NF is almost completely absorbed from the GI tract [8]. However, the overall absorption varies among individuals (absolute bioavailability ranged from 31% to 92%) due to differences in the extent of extraction of NF by first-pass metabolism [4]. Values of the area under the plasma concentration-time curve (*AUC*) and peak concentration (C_{max}) after NF administration were higher in Mexicans than in Europeans and Americans [7]. In another study, the drug showed a significantly higher *AUC* and a longer terminal half-life in South Asians than in Caucasians [10]. There are several possible reasons for these differences. (I) The metabolism of NF is apparently via oxidation to the pyridine analogue, followed by conversion to acid

*Correspondence to: School of Pharmacy, Taipei Medical University, 250 Wu-Hsin Street, Taipei 110, Taiwan, ROC.

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metabolites that are excreted in the urine [3]. The oxidation process is mainly performed by the microsomal cytochrome enzyme known as CYP3A4, which can be inhibited by certain compounds, such as flavonoids, present in foodstuffs. Hence different bioavailabilities in oral NF among populations may result from differences in dietary habits [5]. (II) Possible differences in phenotypes of NF metabolizers may play a role in interethnic distinctions between fast and slow NF metabolizers as well. The pharmacokinetics of NF has been studied in various populations including British [9–12], Germans [4, 13], Americans [2, 15], Dutch [14], Nigerians [10], Mexicans [7, 16], South Asians [10] and Japanese [17], but not in ethnic Chinese. In this study, a retrospective review was conducted of data from NF bioequivalence studies completed in the past 5 years in Taiwan. In total, 198 healthy male volunteers who participated in NF bioequivalence studies were given a 10 mg Adalat® capsule as a reference drug. Then the pharmacokinetic parameters of NF derived from Adalat® administration in Taiwanese were compared with those of other populations.

Materials and Methods

Materials

Adalat® (Bayer AG, Germany), containing 10 mg of nifedipine per capsule, was used for this study. A pure standard of NF was obtained from Sigma Chemical (St. Louis, MO, USA). HPLC-grade acetonitrile was purchased from BDH Laboratory Supplies (Poole, England). All other chemicals were of analytical grade and were used without further purification.

Subjects

All clinical procedures of these NF bioequivalence studies, from which the pharmacokinetic data were derived, followed the *Guidance of Good Clinical Practice of Taiwan*. In total, 198 healthy male Taiwan residents, aged between 20 and 40 years old with ideal body weight, participated in these studies. All subjects had an acceptable medical history, physical examination and laboratory tests (including: electrolytes, SGOT, SGPT, alkaline phosphatase, total bilirubin, total protein, albumin, BUN, creatinine, complete blood count of both differential and platelets, and complete urinalysis). They were also questioned to assure that they had no history of sensitivity or allergic reaction to any drugs. No other medications were taken 2 weeks prior to or during the study. Smoking, alcohol and caffeine consumption were not permitted for at least 48 h before and during the study. Written informed consent was obtained from each subject prior to the study.

Sample collection

Blood was sampled from an antecubital vein of the forearm using a green top vacutainer (heparin coated) through an indwelling non-heparinized catheter for 24 h. Blood samples were obtained before and 10, 20, 30, 40 and 50 min, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 h after dosing. After collection, blood samples were centrifuged immediately for 10 min at 3000 rpm at 4°C under light protection. The upper layer of plasma was transferred to an appropriately labelled tube and stored at –20°C until subsequent assays.

Drug assay

The NF concentration in human plasma was determined using a high-performance liquid chromatographic (HPLC) method. The HPLC method was validated according to bioanalytical methods for human studies [18]. Both sample preparation and bioanalysis were performed under light protection to prevent degradation of NF samples.

Pharmacokinetic analysis and statistics

A non-compartmental analysis using the WinNonlin program was performed to calculate the pharmacokinetic parameters obtained from plasma concentrations of NF after oral administration of 10 mg of Adalat® [19]. The *AUC* was determined using the trapezoidal method, and the area extrapolated to infinity was estimated as the last plasma concentration divided by the terminal elimination rate constant (K_{el}). K_{el} was determined by a simple log-linear regression

based on the last three points of plasma concentration. The terminal elimination half-life ($T_{1/2}$) was calculated as ln2 divided by K_{el}. C_{max} and the time at which the peak concentration was reached (T_{max}) were those observed. Pharmacokinetic parameters are reported as the mean $\pm$ SD. The statistical significance ($p < 0.05$) was determined by Student's *t*-test as appropriate for the analysis of pharmacokinetic parameters.

Results

The mean plasma NF concentration-time profile of 198 healthy male Taiwanese after oral administration of 10 mg of Adalat® is shown in Figure 1. The pharmacokinetic parameters of NF after noncompartmental analysis are shown in Table 1. A wide variability among individuals was observed for all parameters. The absorption of NF was very fast with a mean T_{max} of 0.61 h. The frequency distributions of C_{max}, *AUC*, and $T_{1/2}$ are shown in Figures 2–4. They all clearly show that these data are not normally distributed. The values represent a skewed distribution with no clear evidence of bimodality.

Kleinbloesem proposed that individuals could be grouped as either fast or slow metabolizers according to the *AUC* value after a 20 mg dose [6]. Because a linear pharmacokinetic property exists within the 20 mg dose of NF [20], the *AUC* was normalized as *AUC*/dose and 69.7% of subjects in this study were found to be slow metabolizers (*AUC* > 22.5 ng·h/ml/mg) while the other 30.3% were fast metabolizers (Figure 5). This clearly differs from the results with Caucasians.

Discussion

This study reviewed and analysed the pharmacokinetics of oral NF in Taiwanese after oral

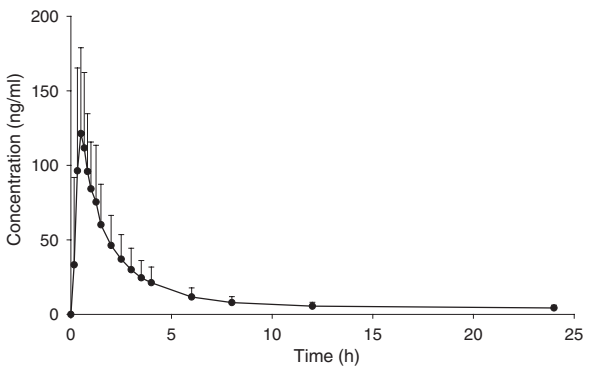

Figure 1. Mean plasma concentration-time curve of nifedipine after oral administration of 10 mg of nifedipine formulation to 198 healthy Taiwanese. Data are shown as the mean $\pm$ SD

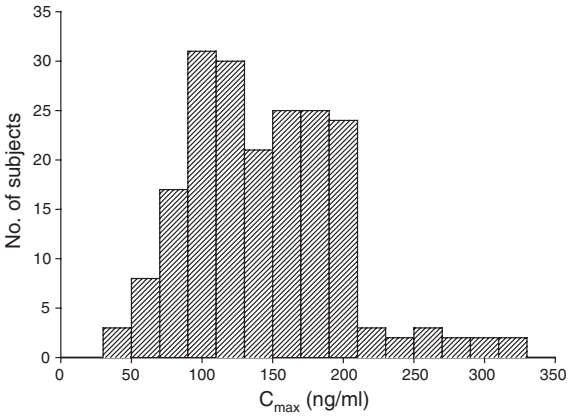

Figure 2. Distribution of nifedipine C_{max} in 198 healthy Taiwanese after oral administration of 10 mg of nifedipine formulation

Table 1. Pharmacokinetic parameters of NF after oral administration of 10 mg of nifedipine formulation *to* 198 healthy Taiwanese

	T_{max} (h)	C_{max} (ng/ml)	*AUC* (ng·h/ml)	$T_{1/2}$ (h)
Mean	0.61	143.12	293.77	3.08
Median	0.50	135.50	272.71	2.65
$\pm$ *SD*	0.38	53.48	115.62	1.61
Minimum	0.17 (Q1, 0.33)	45.00	79.00	1.02
Maximum	3.00 (Q2, 0.67)	322.00	729.15	13.37

Q1: the 25th percentiles.
Q2: the 50th percentiles.

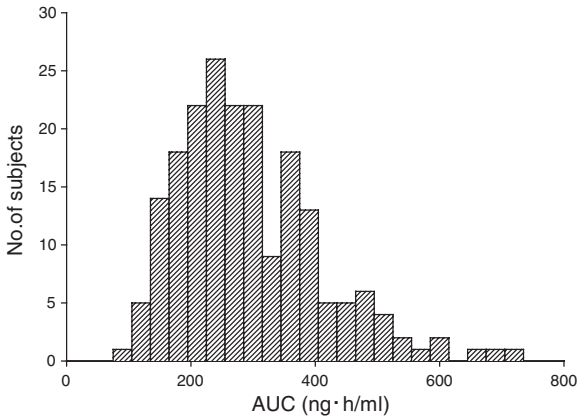

Figure 3. Distribution of nifedipine *AUC* in 198 healthy Taiwanese after oral administration of 10 mg of nifedipine formulation

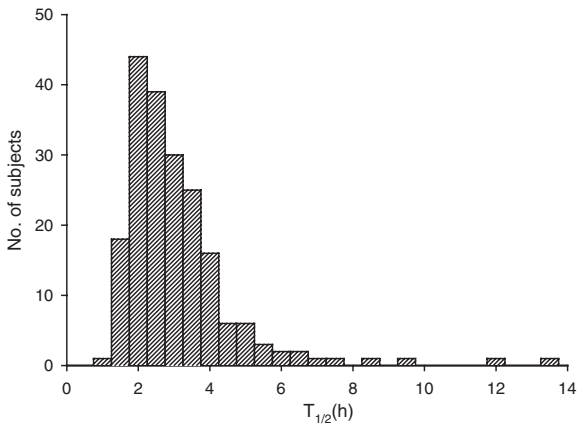

Figure 4. Distribution of nifedipine $T_{1/2}$ in 198 healthy Taiwanese after oral administration of 10 mg of nifedipine formulation

ingestion of a 10 mg Adalat® capsule based on NF bioequivalence studies conducted in the past 5 years in Taiwan. The NF plasma concentration-time data were fitted to a non-compartmental model method, and relevant pharmacokinetic parameters were calculated. After oral administration of an immediate-release dosage form of a 10 mg NF capsule to Taiwanese, a skewed distribution with no clear evidence of bimodality of pharmacokinetic parameters was observed. Great variability among individuals existed. This variability could be attributed to differences in gastrointestinal absorption and/or first-pass

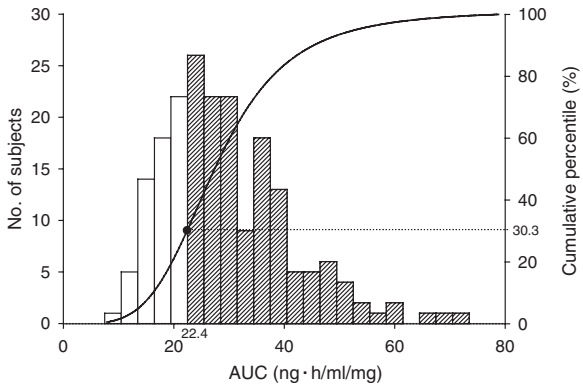

Figure 5. Distribution of normalized nifedipine *AUC* in 198 healthy Taiwanese after oral administration of 10 mg of nifedipine formulation. The shaded area represents 69.7% of Taiwanese who are slow metabolizers (normalized *AUC* > 22.5 ng·h/ml/mg)

metabolism of NF, which involves both intestinal and hepatic CYP 450 enzyme systems. It has been shown that small intestinal metabolism is important in the NF metabolism when the drug is given orally. There is also inter-individual variability in the small intestinal content of CYP 450 [21]. The absorption of NF has been shown to be readily completed [8]. As shown in Table 2, the pharmacokinetic parameters obtained in this study were compared with those obtained in other populations after oral administration of an immediate-release dosage form of NF. There were no statistical differences in T_{max} between that obtained in our study and those of other studies. With the exception of Indian [10] and Dutch [14] subjects, the absorption of NF was very fast in all populations with a mean T_{max} within 1 h. This suggests that gastric emptying of NF was not delayed in Taiwanese. The reason for the variability after NF ingestion may be attributed to differences in the metabolism of NF.

As shown in Figure 4, a wide variability of NF elimination among individual Taiwanese was observed. Variations in the half-life ranged from 1.02 to 13.37 h. Table 2 shows $T_{1/2}$ values that have been reported in healthy subjects from different populations after immediate-release dosage forms of NF were administered (10 or 20 mg). The mean $T_{1/2}$ values for the British reported by Ahsan [9] and Renwick [11] range from 2.3 to 2.5 h, which significantly differ from

Table 2. Pharmacokinetic parameters of an immediate-release dosage form of nifedipine

Study group	Population	Dose (mg)	T_{max} (h)	C_{max} (ng/ml)	*AUC* (ng·h/ml)	$T_{1/2}$ (h)	Normalized C_{max} (ng/ml/mg)	Normalized *AUC* (ng·h/ml/mg)
Our study, 2001 ($n = 198$)	Taiwanese	10	0.6(± 0.4)	143(± 53)	294(± 116)	3.1(± 1.6)	14.3(± 5.3)	29.4(± 11.6)
Ahsan *et al.*, 1993 ($n = 27$) [9]	British	10	0.7(± 0.4)	93[c](± 49)	169[c](± 74)	2.3[b](± 1.1)	9.3[c](± 4.9)	16.9[c](± 7.4)
Renwick *et al.*, 1988 ($n = 59$) [11]	British	10	–	79[c](± 44)	154[c](± 61)	2.5[b](± 1.3)	7.9[c](± 4.4)	15.4[c](± 6.1)
Renwick *et al.*, 1987 ($n = 6$) [12]	British	10	0.6(± 0.2)	79(± 32)	148[a](± 56)	2.2(± 1.7)	7.9[a](± 3.2)	14.8[c](± 5.6)
Rietbrock *et al.*, 1987 ($n = 8$) [13]	German	10	–	119(± 48)	161(± 68)	–	11.9(± 4.8)	16.1(± 6.8)
Foster *et al.*, 1983 ($n = 12$) [2]	American	10	0.6(± 0.1)	73[c](± 17)	125[c](± 17)	3.4(± 3.0)	7.3[c](± 1.7)	12.5[c](± 1.7)
Retiberg *et al.*, 1987 ($n = 15$) [15]	American	10	1.0(± 0.2)	79[c](± 43)	145[c](± 47)	–	7.9[c](± 4.3)	14.5[c](± 4.7)
Ahsan *et al.*, 1993 ($n = 16$) [9]	Indian	10	1.4(± 1.2)	142(± 102)	382(± 232)	4.8(± 2.5)	14.2(± 10.2)	38.2(± 23.2)
Hoyo-Vadillo *et al.*, 1989 ($n = 12$) [7]	Mexican	10	0.6(± 0.2)	145(± 80)	384(± 142)	5.0(± 2.0)	14.5(± 8.0)	38.4(± 14.2)
Palma-Aguirre *et al.*, 1989 ($n = 6$) [16]	Mexican	10	0.5(0.2)	134(± 17)	267(± 54)	–	13.4(± 1.7)	26.7(± 5.4)
Rämsch *et al.*, 1986 ($n = 6$) [4]	German	20	0.7(± 0.3)	146(± 59)	386(± 82)	3.9(± 2.3)	7.4[b](± 3.0)	19.3[c] (± 4.1)
Kleinbloesem *et al.*, 1984 ($n = 6$) [14]	Dutch	20	1.4(± 0.5)	116(± 15)	–	1.7(± 0.5)	5.8[c](± 0.8)	–
Sowunmi *et al.*, 1995 ($n = 12$) [10]	Nigerian	20	0.8(± 0.5-4.0)	205(± 149)	808(± 250)	5.0(± 2.0)	10.2(± 7.4)	40.4[a](± 12.5)
Tateichi *et al.*, 1989 ($n = 6$) [17]	Japanese	20	1.0(± 0.9)	236(± 71)	598(± 52)	2.5(± 0.6)	11.8(± 3.5)	29.9(± 2.6)

Data are shown as the mean ± SD.
[a] $p < 0.05$; [b] $p < 0.005$; [c] $p < 0.001$.

that in our study. Although the British reported in another paper of Renwick [12] and the Japanese [17] also show a mean $T_{1/2}$ of around 2.5 h, the sample size was too small to obtain a statistical result. Besides the British and Japanese, the mean $T_{1/2}$ values of other reports are all greater than 3 h and show no statistical difference with results of our study. NF is highly first-pass metabolized [4], so the elimination half-life should be mainly determined by hepatic blood flow [22]. Therefore, it should not be easy to obtain a clearly significant difference in the half-life between populations.

The C_{max} in our study varied from 45 to 322 ng/ml in Taiwanese. The mean value of C_{max} was significantly higher than that in the British [9–12], Americans [2, 15], Germans [4] and the Dutch [14], however, no significant differences were seen when compared with values for Indians [9], Mexicans [7, 16], Nigerians [10] and Japanese [17] when the dose was normalized. Although there was no statistical difference in the mean value of C_{max} between the Germans in Riebrock's study and our results [13], the reason may also be the small sample size in that study. Although, C_{max} can be decreased by delayed gastric emptying in an immediate-release dosage form, the mean T_{max} of NF is below 1.4 h in all populations (Table 2) which means delayed gastric emptying of NF did not occur. On the other hand, a lower C_{max} may result from faster metabolic activity of NF. The majority of British, Germans, Dutch and Americans are Caucasians and are all reported to have more extensive CYP3A4 activity than other populations [23].

The bioavailability of NF can be calculated by the *AUC*. The difference between the mean and median *AUC* of NF in Taiwan residents indicates that the data were not normally distributed but skewed. Our data showed significantly higher values of *AUC* than those for the British [9–12], Americans [2, 15] and Germans [4], but lower than that of Nigerians [10]. No statistical difference was seen when compared with Indians [9], Mexicans [7, 16] and Japanese [17] after the NF dose was normalized. In Table 2, the high *AUC* values also show higher values of C_{max}. The higher *AUC* in our study could be due to reduced systemic clearance. Hepatic CYP3A4 has been proven to be involved in the metabolism of NF. Taiwan residents may express a lower level of hepatic CYP3A4 than do the British, Germans and Americans.

Kleinbloesem *et al.* proposed that individuals could be grouped as fast and slow metabolizers when *AUC* is normalized by NF dose. They proposed the existence of NF oxidative polymorphism in humans [6]. Linear pharmacokinetic properties exist within a 20 mg dose of NF [20]. Although the *AUC* of NF in our study was widely distributed and skewed, the *AUC* was normalized as *AUC*/dose and 69.7% of subjects in this study were found to be slow metabolizers ($AUC > 22.5$ ng · h/ml/mg) while the other 30.3% were fast metabolizers as shown in Figure 5. Differing from Caucasians, the majority of Taiwan residents are slow metabolizers. The higher *AUC* values are genetically determined. However, the role of environmental factors or nutritional habits in NF absorption and metabolism, which affect *AUC* values cannot be ruled out [5].

Differences in genetic constitution among individuals may result in polymorphic drug metabolism. The metabolism of debrisoquin, which is metabolized by CYP2D6, varies in populations of different ethnic origins and only 0% to 1% of Oriental subjects have been identified as poor metabolizers [24]. Mephenytoin, a substrate of CYP2C9, shows a higher proportion of poor metabolizers in Asians than in Caucasians [25]. CYP2C19 also displays poorer activity in Asians [26]. Among the CYP subfamilies, CYP3A is the most abundant human CYP isoform. The *in vivo* activity of CYP3A measured by NF metabolism shows marked inter-individual variation [27] and suggests the possibility of an ethnic difference in activity level [10, 23]. The human CYP3A subfamily is composed of at least three members, CYP3A4, CYP3A5 and CYP3A7 [28], with CYP3A4 being the dominant subfamily. CYP3A4 is the most prominently expressed P450 in human liver, which was found to account for 29% of the total P450 present [29]. CYP3A4 is also the dominant microsomal P450 in the mucosal epithelial barrier of the small intestine [21]. NF is a high-affinity CYP3A4 substrate that undergoes extensive first-pass metabolism [4]. NF was also the earliest used drug to probe the absence or presence of functionally significant genetic polymorphism of

CYP3A4. Midazolam is another ideal probe for the determination of hepatic and intestinal CYP3A activity since its primary metabolite, 1′-hydoxymidazolam, and minor metabolites, 4-hydroxymidazolam and 1,4-dihydroxymidazolam, are all generated predominantly if not exclusively from CYP3A4/5 in the adult human [30]. In addition, it does not appear to be a substrate for the membranous transporter P-glycoprotein which is an advantage for a CYP3A probe [31]. Evidence reveals that the pharmacokinetics of NF varies among subjects from different populations. A wide variability among individuals was also observed. *AUC* and C_{max} are lower in the British, Germans and Americans after an immediate-release form of NF is administered. Differences in the parameters of pharmacokinetics demonstrate that Caucasians may have higher CYP3A4 activity than Mexicans, Nigerians, Indians and Japanese. After oral administration of an immediate-release dosage form of a 10 mg NF capsule to Taiwan residents, the metabolism of NF in Taiwan residents was significantly slower than that of Caucasians but did not significantly differ from values for Mexicans, Nigerians, Indians and Japanese. The ethnic difference between Caucasian and Japanese hepatic samples was also studied. NF oxidation activity and CPY3A4 protein levels showed marked interindividual variation and were significantly correlated. No significant ethnic difference was found in NF oxidation activity or CYP3A4 protein levels. The contribution of CYP3A5 or CYP3A7 to the purported ethnic difference on the overall CYP3A activity between Caucasians and Japanese seems to be small [32]. Alprazolam is a drug metabolized by CYP3A4. Like NF, Asians are also reported to have lower metabolic activity for alprazolam metabolism [33]. CYP3A4 expression is known to be affected by many factors [34]. The polygenic multifactorial nature of CYP3A4 expression adds to the complexity of delineating the possible role of any one factor on CYP phenotype in an individual at a given time. In conclusion, our data show that the majority of Taiwanese display a lower activity of NF metabolism than Caucasians, but the possibility of an ethnic difference in the CYP3A activity between different populations remains to be studied.

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