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PHARMACOKINETICS AND DISPOSITION

Effects of erythromycin on voriconazole pharmacokinetics and association with *CYP2C19* polymorphism

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Abstract
Purpose To assess the impacts of erythromycin on the pharmacokinetics of voriconazole and its association with *CYP2C19* genotypes in healthy Chinese male subjects.
Methods A single-center, open, crossover clinical study with two treatment phases was carried out. Eighteen healthy male volunteers, including 6 *CYP2C19* homozygous extensive metabolizers (EMs, *1/*1), 6 heterozygous EMs (HEMs, *1/*2 or *1/*3), and 6 *CYP2C19* poor metabolizers (PMs, *2/*2 or *2/*3), were enrolled in this study. A single oral dose of 200 mg voriconazole was administrated to all subjects after 3-day pretreatment with either 500 mg erythromycin or placebo three times daily. Periods were separated by a washout period of 14 days. Serial venous blood samples were collected, and plasma concentrations of voriconazole were determined by HPLC.
Results C_{max}, AUC_{0-24}, and $AUC_{0-\infty}$ of voriconazole were increased significantly, while oral clearance of voriconazole was decreased significantly by erythromycin administration ($p<0.001$, respectively). Compared with individuals with *CYP2C19* PM genotypes, individuals with *CYP2C19* EM and HEM genotypes showed significantly decreased $T_{½}$, AUC_{0-24}, $AUC_{0-\infty}$, and increased oral clearance of voriconazole ($p<0.05$, respectively). In addition, significant increases in AUC_{0-24} and $AUC_{0-\infty}$ and decreases in oral clearance of voriconazole after erythromycin treatment were observed in *CYP2C19* HEMs and PMs ($p<0.05$, respectively), but not in *CYP2C19* EMs.
Conclusion Both *CYP2C19* genotypes and CYP3A4 inhibitor erythromycin can influence the plasma concentration of voriconazole, and erythromycin increases plasma concentration of voriconazole in a *CYP2C19* genotype-dependent manner.

Keywords Voriconazole · Erythromycin · CYP2C19 · Genetic polymorphism · Chinese

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Introduction

Voriconazole is a second-generation triazole antifungal agent that is structurally related to fluconazole. The mechanism of action of voriconazole is similar to that of other azoles, i.e., it inhibits the cytochrome P450-dependent 14-α-lanosterol demethylase and disrupts fungal ergosterol synthesis [1–4]. Voriconazole is used for the treatment of invasive aspergillosis and other serious infections [5–8].

Voriconazole undergoes extensive oxidative metabolism mediated by cytochrome P450 (CYP) isoforms CYP2C19 and CYP3A4, and to a lesser extent, by CYP2C9 [9, 10]. Mutations in the *CYP2C19* gene that result in the CYP2C19 poor metabolism (PM) phenotype are common in Asians. About 13–23% of Asians inherit *CYP2C19* PM genotypes, which is a much higher prevalence than 3–5% observed in Caucasians [11–14]. Evidence has shown that 49% of the variance in apparent oral clearance of voriconazole can be

explained solely by *CYP2C19* polymorphisms [15]. It is suggested that the initiation dose of voriconazole dosage should be adjusted according to *CYP2C19* genotypes to avoid hepatotoxicity [16]. Preliminary observations also suggest that *CYP2C19* genotypes should be evaluated as a factor that may affect the pharmacokinetics of voriconazole and perhaps drug interactions or adverse events related to voriconazole [17–19].

CYP3A4 is a major drug metabolic enzyme in adult humans, and contributes to the metabolism of about 70% clinically important medications [20]. Induction or inhibition of CYP3A4 as a result of drug interactions is common in clinical practice. During the treatment of systemic fungal infection, antifungal agents such as voriconazole are often prescribed concomitantly with other medicines, and some of these latter medicines are CYP3A4 inhibitors [21]. Erythromycin has proven to be a potent CYP3A4 inhibitor that can result in mechanism-based inactivation of CYP3A4 [22–24]. Results from in vitro study indicate that erythromycin affects voriconazole metabolism [10], although the clinic relevance of this drug interaction remains to be explored.

This study was designed to assess the impacts of erythromycin on pharmacokinetics of voriconazole, and to identify the potential role of *CYP2C19* variants in the magnitude of this drug–drug interaction in healthy Chinese male subjects. We expect that the results of this study would be helpful in the optimization of voriconazole therapy in the clinic.

Materials and methods

Subjects

Two hundred and ninety-seven unrelated Chinese male healthy volunteers were genotyped for *CYP2C19**2 and *CYP2C19**3 variations. Six individuals homozygous for the wild-type allele (*CYP2C19*1/*1*, denoted EM), 6 individuals heterozygous for the *CYP2C9*2* or *CYP2C9*3* variants (n= 4 for the *CYP2C9*1/*2* genotype and n=2 for the *CYP2C9*1/*3* genotype, denoted HEM) , and 6 individuals carrying two variant alleles simultaneously (n=5 for the *CYP2C19*2/*2* genotype and n=1 for the *CYP2C19*2/*3* genotype, denoted PM) were then selected randomly from these subjects. The mean age of the volunteers ranged from 19 to 23 years and the range of body mass index was approximately 18–25 kg/m^2. No significant difference in either mean age or body mass index was observed among the three genotyped groups.

All subjects were ascertained to be in good health as identified from medical history, routine physical examination, and clinical laboratory tests. None of the volunteers was a smoker or had received any medication of botanical dietary supplements at least 2 weeks before entry into and during the study. All subjects ate a normal diet during the study. The study protocol was approved by the Ethics committee of Xiangya School of Medicine, Central South University. Written informed consent was obtained from all volunteers.

Study design

The study was carried out as a single-center, randomized, open, crossover design with two treatment phases, separated by a 2-week washout period. The subjects were hospitalized during the investigational treatments (from day 1 to the morning in day 5) in each phase. In each phase, the 18 volunteers received oral administration of either placebo or erythromycin (4 tablets erythromycin enteric-coated 125 mg; Baiyunshan, Guangzhou, China; batch No.1060001) three times daily for 4 days (day 1 to day 4) for 12 doses (the tenth dose being administered 30 min ahead of the voriconazole dose on the morning of day 4). On day 4, each subject was given a single oral dose of 200 mg voriconazole (four tablets of voriconazole 50 mg; GeneTech Pharm, Beijing, China; batch No. 20051001, this dose level is recommended in clinical use) along with 200 mL plain water after overnight fasting and rest. The subjects were asked to be recumbent from 30 min before to 4 h after the administration of drugs. Standardized meals were served at 2 h, 4 h, and 10 h respectively, after morning drug dosing. All subjects were under close surveillance by appropriately qualified staff within 24 h after voriconazole administration.

Venous blood samples for the determination of plasma concentrations of voriconazole were collected immediately before and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h after the administration of voriconazole. Blood was collected into 4-mL EDTA-containing vacuum blood-collecting tubes. Immediately after blood collection, the samples were centrifuged at 3,000 rpm for 10 min. The plasma was transferred into polypropylene tubes and stored at −40°C until analysis.

CYP2C19 genotyping

Genomic deoxyribonucleic acid (DNA) samples were extracted from venous blood samples by standard phenol/chloroform extraction. Detection of *CYP2C19*2* and *CYP2C19*3* mutant alleles was performed by PCR/RFLP, as described elsewhere [25–27]. PCR products were digested with the restriction endonucleases *Sma* I and *BamH* I to detect the *CYP2C19*2* allele and the *CYP2C19*3* allele respectively. DNA fragments generated

after restriction enzyme digestion were separated on a 2% agarose gel. Restriction fragments were visualized by use of a UV detector.

High performance liquid chromatography determination of the plasma concentration of voriconazole

Plasma concentrations of voriconazole were determined by high performance liquid chromatography (HPLC) as described with optimization [28]. Plasma samples were extracted with chloroform. Chromatographic column was Diamonsil C_{18} (250 mm×4.6 mm, 5 μm); the mobile phase was composed of acetonitrile: 10 mM ammonium acetate (pH set at 5.4 with acetic acid) with a v:v of 50:50; the flow rate was 1.0 mL/min; the column temperature was 40°C and the detector wavelength was set at 255 nm. The standard curves of voriconazole were constructed with eight non-zero standards ranging from 0.02 μg/mL to 8.86 μg/mL. The lower limit of quantification was 0.02 μg/mL and the concentrations of QC samples were 0.07, 1.10 and 8.80 μg/mL respectively.

Safety analysis

All adverse events reported spontaneously by the subjects or observed during the subjects' surveillance were documented, including times of onset and resolution, intensity, and causal relationship to the study drug. Vital signs including blood pressure and pulse rate were surveyed regularly during the hospitalization period.

Pharmacokinetic analysis

The peak concentration (C_{max}) and concentration peak time (t_{max}) were obtained directly from the observed data. The elimination half-life ($t_{½}$), the area under the plasma concentration–time curve (AUC_{0-24}), AUC from zero to infinity (0-∞) and the apparent oral clearance (CL_{oral}/F) were calculated by DAS 2.0 (Gaosi Data Analysis, Wuhu, China).

Statistical analysis

Statistical analyses were carried out with SPSS software version 11.0 for Windows (SPSS, Chicago, IL, USA). Data were expressed as mean±SD. Differences in pharmacokinetic parameters and ratios in different treated phases within the same genotype and pharmacokinetic parameters among different genotypes were compared using *t* test or ANOVA respectively. Wilcoxon's signed-rank test was used to compare difference in t_{max} between or among different groups. A p value <0.05 was considered to be statistically significant.

Results

Safety of voriconazole after oral administration

Voriconazole was generally well tolerated by all participants, without serious adverse events. One participant with the *CYP2C19*2/*2* genotype discontinued the study after the first phase because of a heavy cold.

Erythromycin increased the plasma concentration of voriconazole

Figure 1 showed the plasma concentration–time curves of voriconazole with a 4-day treatment with erythromycin and placebo. Compared with the placebo-treated phase, the C_{max} (2.36±0.78 μg/mL vs 3.16±0.76 μg/mL, p<0.001), AUC_{0-24} (12.65±10.15 μg·h/mL vs 18.97±13.86 μg·h/mL, p<0.001), $AUC_{0-\infty}$ (15.62±15.11 μg·h/mL vs 23.63±20.45 μg·h/mL, p<0.001) of voriconazole was increased significantly in the erythromycin treated phase, while the CL_{oral}/F of voriconazole was decreased significantly by 4-day erythromycin treatment (381±244 mL/min vs 245±171 mL/min, p<0.001, Table 1). No significant difference in $T_{½}$ and T_{max} was observed between the placebo- and erythromycin-treated phases (Table 1).

CYP2C19 PM genotype increased the plasma concentration of voriconazole in the placebo-treated phase

Plasma concentration–time curves of voriconazole according to *CYP2C19* genotypes in the placebo-treated phase are shown in Fig. 2. Significant differences in $T_{½}$, AUC_{0-24}, $AUC_{0-\infty}$, and oral clearance of voriconazole were observed among *CYP2C19* genotypes (p<0.05, Table 1). Compared with individuals with *CYP2C19* PM genotypes, individuals with

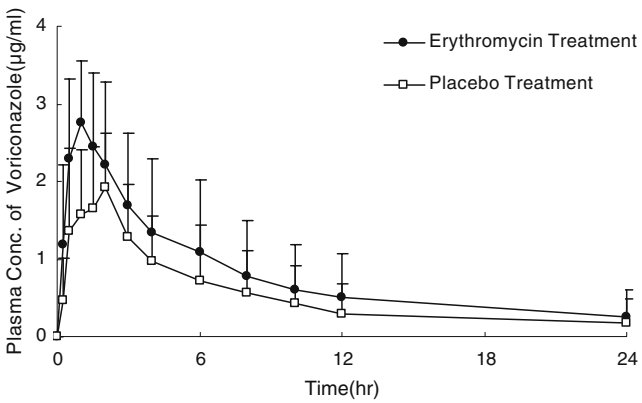

Fig. 1 Mean (± SD) voriconazole plasma concentration–time profile after single oral administration of 200 mg voriconazole in all 18 subjects with a 4-day treatment with placebo (*squares*) or erythromycin (*black circles*)

Table 1 Pharmacokinetic parameters of voriconazole in healthy Chinese volunteers with different *CYP2C19* genotypes with a 4-day treatment with placebo or erythromycin

	All volunteers (n=18)		*CYP2C19* EM (n=6)		*CYP2C19* HEM (n=6)		*CYP2C19* PM (n=6)	
	Placebo	Erythromycin	Placebo	Erythromycin	Placebo	Erythromycin	Placebo	Erythromycin
AUC_{0-24} (h·μg/mL)	12.65±10.15	18.97±13.86##	7.05±2.99**	8.54±2.59	8.60±5.62**	15.65±7.36##	24.23±11.05	35.47±13.13#
$AUC_{0-\infty}$ (h · μg/mL)	15.62±15.11	23.63±20.45##	7.70±2.99**	10.75±5.32	10.75±9.42**	16.95±8.10##	30.95±19.20	47.09±23.50##
C_{max} (μg/mL)	2.36±0.78	3.16±0.76##	2.22±0.77	3.04±0.63##	2.29±0.47	2.80±0.68#	3.03±0.75	3.75±0.76
CL_{oral}/F (mL/min)	381±244	245±171##	499±228*	375±176	452±233*	240±125#	153±110	93±64##
$T_{½}$ (h)	5.31±3.96	6.57±4.44	3.72±2.12*	3.76±2.51	4.09±2.84*	5.80±3.14	8.69±5.17	10.87±4.79
T_{max} (h)	1.41±0.64	1.12±0.60	1.25±0.69	0.67±0.26	1.50±0.63	1.00±0.45	1.50±0.71	1.80±0.45

EM, extensive metabolizers; HEM, heterozygous extensive metabolizers; PM, poor metabolizers, AUC_{0-24}, mean total area under the plasma concentration–time curve from time 0 to 24 h; $AUC_{0-\infty}$, mean total area under the plasma concentration–time curve from time 0 to ∞; C_{max}, peak plasma concentration; CL/F, oral clearance; $T_{½}$, terminal elimination half-life; t_{max}, time to peak plasma concentration

Values are mean±SD

#p<0.05, ##p<0.01 compared with placebo in corresponding *CYP2C19* genotype

*p<0.05, **p<0.01 compared with *CYP2C19* PM genotype after placebo treatment.

EM and HEM genotypes showed significantly decreased $T_{½}$, AUC_{0-24}, $AUC_{0-\infty}$, and increased oral clearance of voriconazole (p<0.05 respectively, Table 1). No significant difference in any of the pharmacokinetics parameters of voriconazole between EM and HEM genotypes was observed in the placebo-treated phase (Table 1).

Effect of erythromycin on voriconazole pharmacokinetics is associated with *CYP2C19* genotypes

We then analyzed the effect of erythromycin on the pharmacokinetics of voriconazole according to *CYP2C19* genotypes. The pharmacokinetics profile and detailed pharmacokinetic parameters are shown in Fig. 3 and Table 1 respectively. Both AUC_{0-24} (p<0.05 for PM, and p<0.01 for HEM) and $AUC_{0-\infty}$ (p<0.01 for both PM and HEM) was increased significantly after erythromycin treatment in *CYP2C19* HEM and PM individuals, but not in *CYP2C19* EM individuals. CL_{oral}/F of voriconazole was decreased obviously after erythromycin treatment in the *CYP2C19* HEM and PM individuals (p<0.05 for PM, and p<0.01 for HEM), but not in the *CYP2C19* EM individuals. However, the C_{max} of voriconazole was increased significantly in individuals with the *CYP2C19* EM (p<0.01) and HEM (p< 0.05) individuals, but not PM individuals after erythromycin treatment. No significant difference in $T_{½}$ and T_{max} of voriconazole was observed between placebo- and erythromycin-treated phases for any of the *CYP2C19* genotypes.

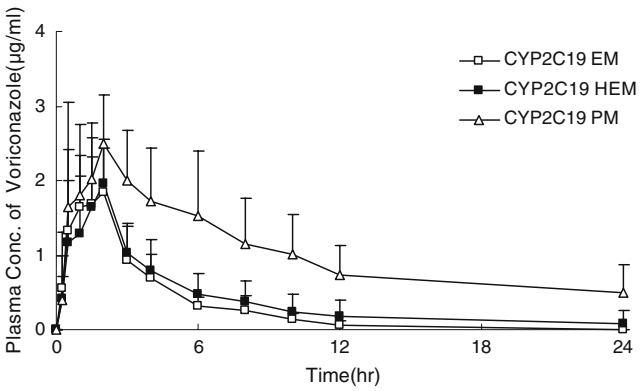

Fig. 2 Mean (± SD) voriconazole plasma concentration–time profile after single oral administration of 200 mg of voriconazole according to *CYP2C19* genotypes in the placebo treatment phase. *EM*extensive metabolizers, *HEM* heterozygous extensive metabolizers, *PM* poor metabolizers

Discussion

In the consideration that the antifungal agent voriconazole might be used concomitantly with the erythromycin, a potent CYP3A4 inhibitor, we observed the effect of 4-day erythromycin administration on the pharmacokinetics of voriconazole, and assessed the association of *CYP2C19* variants (*CYP2C19*2* and *CYP2C19*3*) with this drug–drug interaction in healthy Chinese male subjects. We observed that both 4-day treatment with erythromycin and *CYP2C19* PM genotypes increased the plasma concentration of voriconazole and decreased its oral clearance. We also observed a significant erythromycin–*CYP2C19* genotype interaction influencing plasma concentration of voriconazole in these individuals, and erythromycin treatment increased the AUC and decreased oral clearance of voriconazole limited to *CYP2C19* HEM and PM, but not *CYP2C19* EM individuals.

Our observation that $T_{½}$, C_{max}, AUC_{0-24}, $AUC_{0-\infty}$ was increased and CL_{oral}/F was decreased in *CYP2C19* PMs compared with *CYP2C19* EMs in the placebo-treated phase

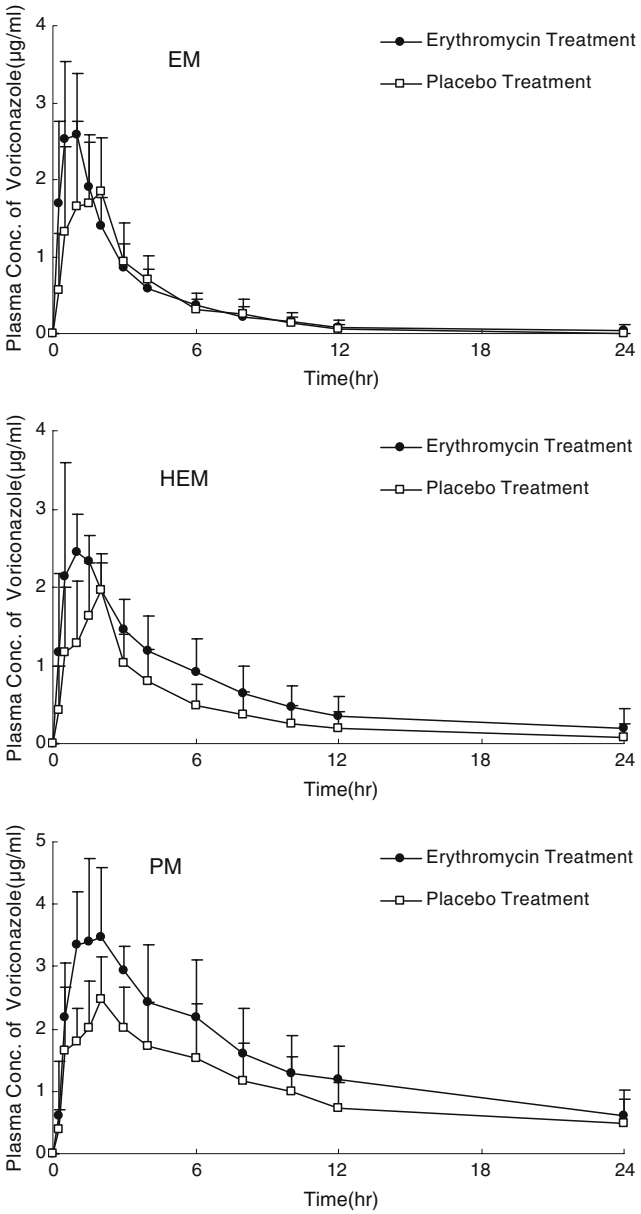

Fig. 3 Mean (± SD)plasma concentration–time profile of voriconazole after a single oral administration of 200 mg of voriconazole pretreated with placebo or erythromycin and association with *CYP2C19* genotypes

is in agreement with several previous studies [18, 19, 29, 30], which indicates that *CYP2C19* genotypes are a key factor in the determination of voriconazole metabolism.

In vitro study indicates that the Michaelis–Menten constant (Km) of voriconazole oxidase activity by CYP2C19 was obviously lower than that by CYP3A4. Therefore, CYP3A4-mediated metabolism may not be the main pathway of voriconazole elimination [9, 10]. Previous in vivo and in vitro studies have also investigated the effect of CYP3A4 inhibitors on metabolism of voriconazole [10, 29]. However, controversial observations are reported [10, 29]. A study by Purkins et al. suggests that erythromycin does not affect the steady-state pharmacokinetics of voriconazole [29]. However, the study design of ours is very different from that of Purkins et al. In their study, voriconazole was given 200 mg twice daily for 14 days, while erythromycin was given twice daily during day 8 to day 14 after initiation of voriconazole administration, and pharmacokinetics of voriconazole was analyzed on days 7 and 14 [29]. However, it is reported that voriconazole can also inhibit CYP3A4 [9, 10] and thus may inhibit its own metabolism after long-term use, while in our study, erythromycin was administered for 3 days before a single oral dose of voriconazole. Our results suggest that erythromycin can obviously affect the pharmacokinetics of voriconazole. As both erythromycin and voriconazole can inhibit CYP3A4, the interactions between erythromycin and voriconazole are more complicated in vivo, if voriconazole has reached its steady-state after repeated doses, the effects of CYP3A4 inhibitors may not change voriconazole metabolism. However, if CYP3A4 inhibitors are given before voriconazole, voriconazole metabolism will be affected. Further research is needed to study the effects of CYP3A4 inhibitors on the pharmacokinetics of voriconazole.

Because CYP2C19 is a major enzyme involved in voriconazole metabolism [9, 10], and *CYP2C19* genetic polymorphism can also affect the pharmacokinetics of voriconazole, we hypothesize in our study that the *CYP2C19* genetic polymorphism might interact with erythromycin in affecting voriconazole metabolism. We observed that the increases in $AUC_{0-\infty}$ and decreases in CL_{oral}/F of voriconazole by erythromycin pretreatment were significantly different among *CYP2C19* genotypes. In both the *CYP2C19* HEM and PM individuals, AUC of voriconazole increased significantly while oral clearance of voriconazole decreased significantly after erythromycin treatment. However, in individuals with the *CYP2C19* EM genotypes, the changes in AUC and oral clearance of voriconazole were not obvious after erythromycin treatment. These findings indicate a drug–gene interaction in the inhibition of voriconazole metabolism by erythromycin, and CYP3A4 might be important for voriconazole metabolism in *CYP2C19* HEM and PM individuals.

Because *CYP2C19* genetic analysis for this study included only alleles *2 and *3, the two major mutant alleles of *CYP2C19*, comprising almost 100% of the PMs in oriental populations [12, 26], the occurrence of other defective alleles in the study population and thus misclassification of individuals cannot be ruled out.

In conclusion, this study provides further evidence for the determination of *CYP2C19* genotypes in voriconazole metabolism, and find that pretreatment with the CYP3A4 inhibitor erythromycin can increase the plasma concentration of voriconazole in a *CYP2C19* genotype-dependent manner. Therefore, combination therapy with erythromycin or other CYP3A4 inhibitors and voriconazole may result in higher antifungal exposure, especially in *CYP2C19* PM and HEM

individuals. At the same time, attention should be paid to dose-limiting adverse events of voriconazole, such as hepatotoxicity, when *CYP2C19* PM and HEM patients undergo concomitant voriconazole and erythromycin therapy. Considering the results of our study and previous findings, we would suggest that the voriconazole dosage might be reduced for *CYP2C19* PM and HEM individuals, as lower doses in PM and HEM can meet the required effective therapeutic level and decrease the adverse events of voriconazole.

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Conflict of interest None of the authors has any financial or personal relationships to disclose that could potentially be perceived as influencing the described research.

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