

Effects of methimazole on the elimination of irinotecan

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Abstract

Purpose To study the possible pharmacokinetic and pharmacodynamic interactions between irinotecan and methimazole.

Methods A patient treated for colorectal cancer with single agent irinotecan received methimazole co-medication for Graves' disease. Irinotecan pharmacokinetics and side effects were followed during a total of four courses (two courses with and two courses without methimazole).

Results Plasma concentrations of the active irinotecan metabolite SN-38 and its inactive metabolite SN-38-Glucuronide were both higher (a mean increase of 14 and 67%, respectively) with methimazole co-medication, compared to irinotecan monotherapy. As a result, the mean SN-38 glucuronidation rate increased with 47% during concurrent treatment. Other possible confounding factors

did not change over time. Specific adverse events due to methimazole co-treatment were not seen.

Conclusions Additional in vitro experiments suggest that these results can be explained by induction of UGT1A1 by methimazole, leading to higher SN-38G concentrations. The prescribed combination of these drugs may lead to highly toxic intestinal SN-38 levels. We therefore advise physicians to be very careful in combining methimazole with regular irinotecan doses, especially in patients who are prone to irinotecan toxicity.

Keywords Irinotecan · Methimazole · Drug interaction · UGT1A · Diarrhea · SN-38 · CYP3A

Abbreviations

APC	7-Ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]-carbonyloxy-camptothecin
CES	Carboxylesterases
CYP3A	Cytochrome P450 3A isoforms
NPC	7-Ethyl-10-[4-amino-1-piperidino]-carbonyloxycamptothecin
SN-38	7-Ethyl-10-hydroxy camptothecin
SN-38G	Glucuronide form of SN-38
UGT1A	Uridine diphosphate glucuronosyltransferase 1A isoforms

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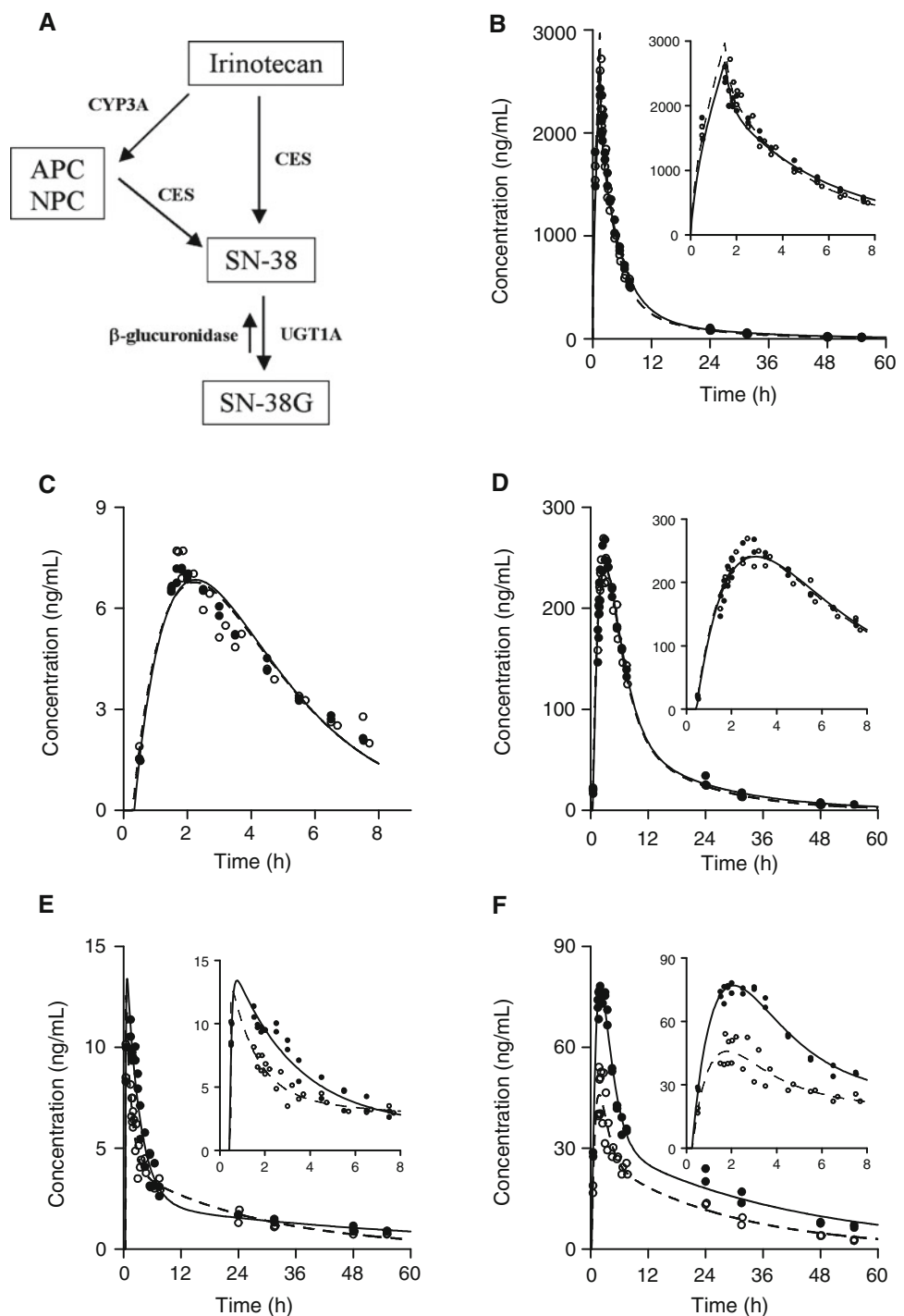
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Introduction

Irinotecan is extensively used in the treatment of advanced colorectal cancer [1]. It is a pro-drug of the active compound SN-38 and is metabolized by cytochrome P450 3A (CYP3A) into inactive metabolites (Fig. 1a). In the liver, uridine diphosphate glucuronosyltransferase 1A (UGT1A) is capable of inactivating SN-38 to its glucuronide form

Fig. 1 Pharmacokinetics of irinotecan and metabolites. **a** Irinotecan is converted into its 1,000 times more active metabolite *SN-38* by carboxylesterases (*CES*), which are predominately found in the liver. The affinity for this reaction is low, since only a fraction of irinotecan is directly converted into *SN-38*. Competing with the formation of *SN-38* is the *CYP3A*-mediated inactivation of irinotecan into the metabolites *APC* and *NPC*. In turn, carboxylesterases also have the ability to convert both of these compounds into *SN-38*. *SN-38* is glucuronidated by *UGT1A* into its inactive metabolite *SN-38G*. In the intestines, β -glucuronidase-producing bacteria can reverse this latter reaction, and thus reactivate *SN-38*, which causes the dose-limiting toxicity diarrhea. Area under the plasma concentration versus time curves for irinotecan (**b**), NPC (**c**), APC (**d**), *SN-38* (**e**), and *SN-38G* (**f**) during all four chemotherapy courses. The open and closed symbols describe the two courses with methimazole and the two courses without methimazole co-treatment, respectively



SN-38G, which facilitates excretion from the circulation [2]. In the intestines, *SN-38G* can be transformed back into *SN-38* by bacterial β -glucuronidase. The metabolism of irinotecan is complicated by several drug-transporting proteins involved in the elimination of the drug (i.e. ATP-binding cassette transporters) [3]. Besides genetic alterations in the *UGT1A* gene, also environmental factors are known to influence its metabolism [3–5]. For instance, cigarette

smoking may induce its metabolism, thereby decreasing the systemic exposure to *SN-38* [6].

Here, we report on a patient who used methimazole while being treated with irinotecan chemotherapy. We hypothesized that methimazole could seriously influence irinotecan metabolism, as pre-clinical data suggest that methimazole inhibits *CYP3A* [7] and induces certain *UGT1A* subtypes [8], both being crucial enzyme systems

involved in the elimination of irinotecan and its metabolites. By performing additional in vitro experiments, we tested our hypothesis.

Materials and methods

Our patient was a cigarette smoking 53-year-old male, with locally advanced colorectal cancer. Six months prior to the start of irinotecan treatment, he was treated for hyperthyroidism due to Graves' disease using a combination of methimazole and levothyroxine. Other daily medicines were acetaminophen, fentanyl, pantoprazole, carbasalate calcium, metoclopramide, and dexamethasone. During two 3-weekly courses of irinotecan, the patient took a daily dose of 30 mg methimazole. Two weeks after the second chemotherapy course, methimazole was stopped and the patient was treated with radioiodine (I-131) as a definitive treatment for Graves' hyperthyroidism. Without delay, the following courses of irinotecan were administered. After written informed consent, plasma pharmacokinetics of irinotecan and its metabolites were collected during a total of four courses. Patient-related factors (i.e. co-medication, smoking status), laboratory values and toxicities were closely monitored, *UGT1A1**28 genotype was determined, and active hormone 3,5,3'-triiodothyronine (T3), and thyroid stimulating hormone (TSH, thyrotropin) levels were determined to exclude possible confounding effects of varying thyroid status.

During and after the 90-min intravenous infusions of irinotecan (350 mg/m²), blood was drawn at specific time-points [6]. Plasma concentrations of irinotecan, NPC, APC, SN-38, and SN-38G were determined using validated chromatography methods [9, 10]. Individual plasma pharmacokinetics were estimated using non-compartmental analyses (WinNonLin 5.0, Pharsight, CA). At weekly outpatient visits, toxicities were scored.

Methods for the additional in vitro experiments are described in detail in the "Appendix" section.

Results

The area under the plasma concentration–time curve (AUC) of irinotecan did not differ between the courses with or without methimazole co-treatment (mean 16.1 $\mu\text{g} \times \text{h/mL}$; Fig. 1b; Table 1). However, plasma concentrations of both SN-38 and SN-38G were higher during the courses with methimazole (Fig. 1e, f). With methimazole, the mean SN-38 AUC was 14% higher than without methimazole (125 $\text{ng} \times \text{h/mL}$ vs. 110 $\text{ng} \times \text{h/mL}$). In the presence of methimazole, the mean SN-38G AUC was 67% higher (1,255 $\text{ng} \times \text{h/mL}$ vs. 753 $\text{ng} \times \text{h/mL}$). Consequently, a

Table 1 Baseline characteristics, pharmacokinetics, chemistry, and toxicities during four treatment courses with irinotecan

Irinotecan course	1	2	3	4
Methimazole	Yes	Yes	No	No
TSH (0.4–4.3 mU/L) ^a	0.0	2.6	0.0	0.0
T3 (1.4–2.5 nmol/L)	1.54	2.11	2.14	2.86
Dose irinotecan (mg)	660	660	660	660
AUC _(0–56 h) irinotecan ($\mu\text{g} \times \text{h/mL}$)	16.6	16.0	15.8	16.0
AUC _(0–56 h) APC ($\text{ng} \times \text{h/mL}$)	3,227	2,919	3,028	2,897
AUC _(0–8 h) NPC ($\text{ng} \times \text{h/mL}$)	31.9	32.4	32.2	32.5
AUC _(0–56 h) SN-38 ($\text{ng} \times \text{h/mL}$)	117	133	106	114
AUC _(0–56 h) SN-38G ($\text{ng} \times \text{h/mL}$)	1,301	1,209	728	777
REG	11.1	9.09	6.87	6.82
Bilirubin (0–16 U/L)	5	6	7	6
Alkaline phosphatase (0–119 U/L)	189	182	176	152
γ -Glutamyltransferase (0–49 U/L)	60	42	34	33
AST (0–36 U/L)	20	21	18	16
ALT (0–40 U/L)	24	23	24	18
Neutrophil nadir ($\times 10^9/\text{L}$)	4.7	4.1	4.1	4.0
Diarrhea (grade) ^b	1	0	0	0

TSH Thyroid stimulating hormone, T3 active hormone 3,5,3'-triiodothyronine, AUC area under the plasma concentration versus time curve, SN-38 active metabolite of irinotecan; SN-38G detoxified metabolite of SN-38, REG relative extent of glucuronidation, AST aspartate aminotransferase, ALT alanine aminotransferase

^a Normal values between brackets. For TSH and T3, means of weekly values within a period of 3 weeks have been given

^b Grading according to National Cancer Institute—Common Terminology Criteria for Adverse Events version 3.0

mean 47% increased relative extent of glucuronidation, which is the ratio of SN-38G over SN-38 (mean, 10.1 vs. 6.85), was found during the combination treatment courses. The exposure to the CYP3A metabolites APC (mean 3,018 $\text{ng} \times \text{h/mL}$; Fig. 1d) and NPC (mean 32.3 $\text{ng} \times \text{h/mL}$; Fig. 1c) was not different between the courses with or without methimazole.

Except for methimazole, co-medication did not change during the studied courses and also smoking behavior of the patient (15–20 cigarettes per day) did not change. The patient appeared to be wild-type (*TA₆/TA₆*) for *UGT1A1**28, meaning that *UGT1A1* function was not lowered based on this familiar genetic polymorphism [3]. Thyroid hormone levels varied during the assessed courses (Table 1), with a transient but clear hyperthyroidism during the fourth course. Nevertheless, a correlation between thyroid function and systemic chemotherapy levels could not be established. Irinotecan-related toxicity was mild during all courses. The absolute neutrophil count nadir was similar in all courses (mean $4.2 \times 10^9/\text{L}$).

In the in vitro experiments, simultaneous incubation of human liver microsomes with irinotecan and methimazole

resulted in a slightly decreased formation of NPC and APC (both 16% reduced compared to incubation in the absence of methimazole; Appendix Fig. 2a). Control experiments in which irinotecan was combined with fluconazole, a known potent CYP3A-inhibitor, resulted in a strong inhibition of NPC and APC formation (78 and 74% inhibition, respectively, compared to experiments in the absence of fluconazole; Appendix Fig. 2a). No effect of methimazole on SN-38 formation was noticed. In addition, SN-38G formation did not decrease during the co-incubation of microsomes with methimazole and SN-38, while a reduction of 43% was observed during simultaneous incubation of SN-38 with the UGT1A1 inhibitor ketoconazole.

In order to determine whether methimazole is capable of inducing UGT1A1 expression, a HCT 116 colorectal carcinoma cell-line was cultured in the presence of various concentrations of methimazole (25–100 μM) for ~48 h after which UGT1A1 mRNA levels were measured by quantitative RT-PCR. Appendix Fig. 2b displays the results of the experiment showing a 15–18-fold induction of UGT1A1 mRNA levels by methimazole compared to untreated control cells. The lowest concentration of methimazole (25 μM) gave rise to the highest induction levels after 48 h, whereas the higher concentrations (50 and 100 μM) already showed strongly elevated UGT1A1 levels after 24 h that seem to return to normal in a concentration-dependent manner after a longer incubation period.

Our *in vitro* tests in which the transport of mitoxantrone by ABCG2 was studied showed that methimazole in concentrations up to 100 μM did not affect the efflux of mitoxantrone. In contrast, the known ABCG2 inhibitor Ko-143 reduced the efflux of mitoxantrone, thereby causing accumulation of the drug.

Discussion

In the current case, factors known to significantly alter irinotecan pharmacokinetics did not change over time, except for the use of methimazole. As a relationship between thyroid status and plasma concentrations of chemotherapy was not found, a possible influence of thyroid hormone on UGT1A activity is probably very limited in our case [11]. Therefore, we assume that the intra-patient differences in pharmacokinetics found over the courses are mainly attributable to methimazole.

Irinotecan drug-concentrations assessed in the courses without methimazole are within the low-normal range of literature data [6, 12, 13], possibly due to patients' smoking behavior. As SN-38 levels are only moderately increased, while SN-38G concentrations are much higher in the presence of methimazole, our clinical data support the pre-clinical literature describing combined effects of CYP3A-

inhibition and UGT1A-induction by methimazole [7, 8]. However, inhibition of CYP3A was not confirmed by lower systemic concentrations of NPC and APC in the courses with methimazole. In addition, our *in vitro* experiments could not determine an important effect of methimazole on CYP3A activity. Therefore, we have to conclude that the involvement of CYP3A is probably limited in the observed pharmacokinetic alterations during methimazole exposed courses.

UGT1A induction in turn will lead to increased SN-38G levels, catalyzing SN-38 transformation into SN-38G. This is expressed by the higher glucuronidation rate during the combination treatment. Although the exact mechanism of irinotecan-induced delayed-onset diarrhea is unclear, there is consensus that intestinal toxicity is caused by local reactivation of SN-38 from SN-38G by β -glucuronidase-producing bacteria in the gut [14, 15]. Therefore, higher SN-38G levels as a result of methimazole co-treatment could potentially lead to more intestinal toxicity, since higher systemic SN-38G concentrations could cause increased intestinal SN-38 levels when SN-38G is excreted in the gut and is de-glucuronidated by intestinal bacteria. This was also shown in a population-pharmacokinetic model of irinotecan, in which the AUC of SN-38G was correlated with diarrhea scores ($P < 0.005$) [16]. In addition, it was shown that co-treatment with the antibiotic neomycin reduces the fecal β -glucuronidase activity and fecal SN-38G/SN-38 ratio, thereby reducing the incidence of diarrhea [17].

In our view, it is plausible that the effect of higher SN-38G levels in our patient did not result in more diarrhea because this patient already had a low pharmacokinetic and toxicity profile, most likely because of his smoking behavior and wild-type *UGT1A1**28 genotype [6]. However, in patients who are more prone to toxicity, higher SN-38G levels as a result of concomitant methimazole use, could potentially lead to severe diarrhea.

One cannot formally rule out the possibility that additional mechanisms contribute to the observed clinical phenotype. For instance, methimazole might interfere with ABC-transporters involved in the efflux of the irinotecan metabolites, leading to accumulation of SN-38 and SN-38G. However, there is no literature available indicating that methimazole is a substrate or inhibitor of ABC-transporters. Moreover, our experiments confirmed that therapeutic concentrations of methimazole do not affect ABCG2-mediated transport.

Conclusions

Although the exact explanation for our findings is subject for further study, the combination of irinotecan and methimazole might potentially lead to increased toxicity

due to higher systemic SN-38 and SN-38G concentrations. Reactivation of high concentrations SN-38G by bacterial enzymes in the bowel is potentially dangerous in that respect and could lead to local toxicity. We therefore advise physicians to be careful in combining methimazole with regular irinotecan doses, especially in patients who are prone to irinotecan toxicity.

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Conflicts of interest We have no conflicts of interest or disclosures. There was also no financial support to perform the in vitro experiments.

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Appendix

Methods of in vitro experiments

In vitro experiments were performed to study the effects of methimazole on the metabolism of irinotecan and SN-38. Pooled human liver microsomes were incubated for 30 min with irinotecan (10 μ M) in the presence or absence of methimazole (37.5 μ M) or fluconazole (25 μ M; CYP3A inhibitor) based on the method described by Slatter et al. [18]. The experiment was performed on 4 separate occasions. In each experiment, microsomal proteins (1 mg/mL) were incubated in triplicate. In addition, pooled human liver microsomes were incubated for 30 min with SN-38 (5 μ M) in the presence or absence of methimazole (37.5 μ M) or ketoconazole (25 μ M; UGT1A inhibitor) based on the method described by Yong et al. [19]. This experiment was performed on separate occasions, during which microsomal proteins (0.8 mg/mL) were incubated in triplicate. Experiments were terminated by the addition of a perchloric acid/methanol solution. Irinotecan and metabolite concentrations from these experiments were measured, using the methods mentioned earlier (Fig. 2).

HCT116 colorectal carcinoma cells were cultured in Glutamax™ containing Hepes-buffered RPMI 1640 medium supplemented with 10% fetal calf serum (Gibco BRL, Paisley, UK), 100 U/mL penicillin and 100 μ g/mL streptomycin at 37°C in a humidified atmosphere containing 5% CO₂. HCT116 cultures of 60% confluence were cultured in the presence of methimazole (25, 50, and 100 μ M) or 0.1% (v/v) MeOH as a solute control. After 5, 24 or 48 h, total RNA was extracted using RNA-Bee (Tel-TEST Temco, Inc. Friendswood, TX). Relative UGT1A1 mRNA

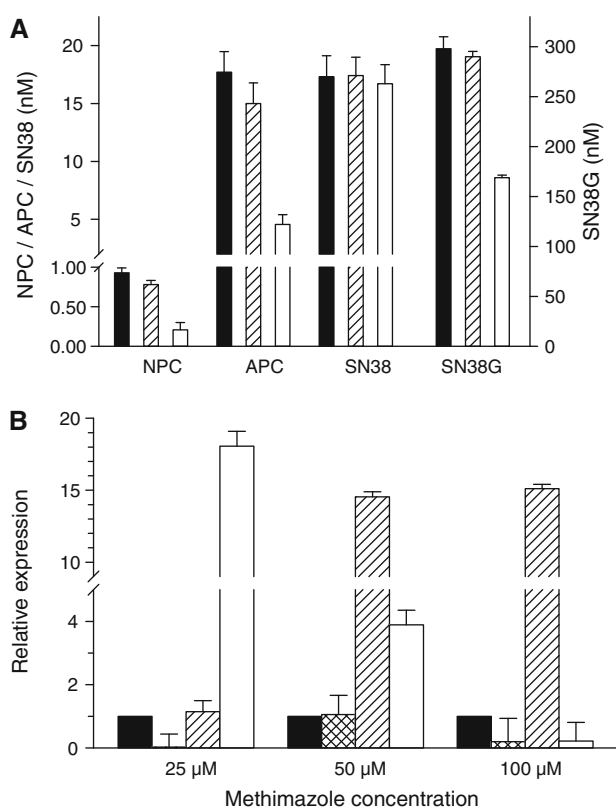


Fig. 2 In vitro experiments. **a** Effects of methimazole (striped bars) and fluconazole (open bars) on the formation of NPC, APC, and SN-38 during co-incubation with irinotecan, and effects of methimazole (striped bars) and ketoconazole (open bars) on the formation of SN38G during co-incubation with SN-38. The black bars represent the formation of irinotecan metabolites in the absence of any (potential) inhibitor. **b** Methimazole induces UGT1A1 mRNA levels. HCT116 cells were cultured in the presence or absence (control) of various concentrations of methimazole. At 5 (cross-hatched bar), 24 (hatched bar) and 48 (white bar) hours total RNA was isolated and used to measure UGT1A1 mRNA levels by quantitative RT-PCR (Taqman™). Depicted is the expression of UGT1A1 compared to the control UGT1A1 levels (black bar), which are arbitrarily set at 1. Error bars indicate 2 \times standard deviation ($n = 3$)

expression levels were measured by real-time RT-PCR using the Taqman Universal Master mix and Assay-On-Demand products from Applied Biosystems (UGT1A1 assay ID: Hs02511055-s1). The human glyceraldehyde-3-phosphate dehydrogenase (GAPDH assay ID: 4310884E; VIC/TAMRA) was used for normalization. Reactions were run on an ABI PRISM 7900 sequence detector system (Applied Biosystems, Foster City, CA) using the following cycling conditions: 50°C for 2 min, 95°C for 10 min followed by 40 cycles of 95°C for 15 s, and 60°C for 1 min.

Hek293 cells transfected with pcDNA3 (HEK293/neo) or wild-type BCRP/ABCG2-R482R (HEK293/R) were cultured under similar conditions as HCT116. To investigate whether ABCG2 activity is affected by methimazole, we analyzed the intracellular accumulation of mitoxantrone

(a well known ABCG2 substrate) in the presence of methimazole. A cell suspension of 10^6 cells of HEK293/neo or HEK293/R in RPMI1640 medium without further supplements was incubated in the presence of 3 μM mitoxantrone at 37°C for 90 min with or without the addition of 10, 25, 50, 100 μM methimazole or 200 nM of the fumitremorgin C analog Ko-143. The mitoxantrone accumulation (fluorescence intensity) was determined by flow cytometry as described previously [20].

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