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Phenytoin Prodrugs VI: *In Vivo* Evaluation of a Phosphate Ester Prodrug of Phenytoin after Parenteral Administration to Rats

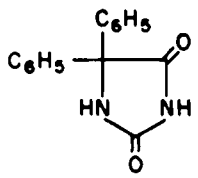
S. A. VARIA * and V. J. STELLA ˣ

Received December 22, 1982, from the *Department of Pharmaceutical Chemistry, School of Pharmacy, The University of Kansas, Lawrence, Kansas 66045.* Accepted for publication September 6, 1983. *Present address: Squibb Institute for Medical Research, New Brunswick, NJ 08903.

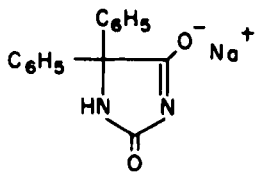
Abstract □ Tissue damage caused by subcutaneous and intramuscular administration of three phenytoin prodrugs to rats was assessed. Since two of the prodrugs caused significant irritation, only 3-(hydroxymethyl)-5,5-diphenylhydantoin disodium phosphate ester might be useful as a nonirritant phenytoin prodrug suitable for parenteral administration. To confirm the release of phenytoin from this prodrug, phenytoin availability after intramuscular and intravenous administrations of the phosphate prodrug was evaluated in rats and compared with sodium phenytoin. The prodrug quantitatively released phenytoin after intravenous administration, and phenytoin levels from intramuscular administration of the prodrug were far superior to those generated from similarly administered sodium phenytoin. Based on this and earlier studies, it was concluded that this prodrug should be further assessed as a parenteral form of phenytoin.

Keyphrases □ Phenytoin—phosphate prodrug, parenteral administration, rats □ Prodrugs—phenytoin, phosphate ester, parenteral administration, rats □ Anticonvulsants—phenytoin, phosphate prodrug, parenteral administration, rats

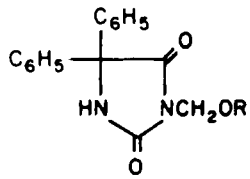
The parenteral form of the anticonvulsant drug phenytoin (I), *i.e.*, sodium phenytoin (Ia) dissolved in a vehicle consisting of 40% propylene glycol and 10% alcohol at pH ~12, is hazardous if too rapidly injected intravenously (1, 2); intramuscular injection results in delayed release of phenytoin from the precipitated phenytoin acid at the injection site (3–8). We recently evaluated the potential usefulness of a series of phenytoin prodrugs (9–11). Based on those studies, II–IV were thought to be possible parenteral forms of phenytoin because of their superior solubility properties compared with phenytoin (9). In a dog study, these prodrugs quantitatively released phenytoin after intravenous injection (11), although III was observed to cause significant acute toxicity in the dog and II had only marginal chemical stability (10). It was concluded that IV would be the best candidate among prodrugs II–IV (11) for parenteral administration.



I



Ia



II: R = $-COCH_2\overset{+}{N}H(CH_3)_2\ CH_3SO_3^-$
III: R = $-CO_2(CH_2)_2\overset{+}{N}H(CH_3)_2\ CH_3SO_3^-$
IV: R = $-PO_3^{2-}\ Na_2^+$

Presented here are two further studies, designed to evaluate the possible utility of II–IV as parenteral forms of phenytoin. First, an evaluation of the tissue damage after subcutaneous and intramuscular injection of prodrugs II–IV to rats was initiated. Based on these findings (significant irritation seen with both II and III but not IV) a second study, the intravenous and intramuscular availability of phenytoin from IV in rats, was addressed. The results of the two studies are presented in this paper.

EXPERIMENTAL SECTION

Evaluation of the Tissue Damage Caused by Subcutaneous and Intramuscular Administration of II–IV—Male Sprague-Dawley rats[1], weighing between 250–275 g, were used; twelve rats were used for each ester studied. Fresh aqueous solutions of esters II–IV (9), 25 mg/kg (phenytoin equivalents), were prepared, and each of six groups of six rats received an ester injected intramuscularly in the thigh muscle or an ester injected subcutaneously under the thigh skin. The injection volume did not exceed 200 μL. After administration, the rats were placed in metabolism cages with access to food and water. At 24 h postdose, three rats administered drug intramuscularly and three rats administered drug subcutaneously for each ester were sacrificed, and the extent of tissue damage was evaluated. The extent of tissue damage in the remaining six rats was evaluated after 7 d postdose. Visual observations were made to determine the extent of tissue damage. The rats were observed externally to check for any skin damage after the subcutaneous injection. The animals were then checked for internal damage by exposing the thigh muscle (intramuscular administration) or the muscles underlying the skin at the injection site (subcutaneous injection).

***In Vivo* Evaluation of IV as a Prodrug of Phenytoin in Rats**—The availability of phenytoin after intramuscular administration of IV was studied in

[1] Harlan Sprague-Dawley, Madison, Wis.

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Table I—Extent of Tissue Damage[a] Observed at the End of 1 and 7 d after Subcutaneous and Intramuscular Injections of II–IV to Rats[a]

Compound	Observations after Subcutaneous Administration	Observations after Intramuscular Administration
II	Externally, a white patch at the injection site Severe tissue damage and necrosis of the skin	Slight necrosis with inflammation at site of injection
III	Build up of scar tissue and severe skin necrosis	Inflammation at injection site
IV[a]	No visible damage	No visible damage

[a] Doses were 25 mg/kg (phenytoin equivalents). [b] It is realized that more elaborate studies including histopathology would be needed if considerations were given to testing IV clinically. However, these clear-cut findings probably eliminate further evaluation of II and III clinically.

the rat model. Specifically, three different types of crossover studies were carried out on male Sprague–Dawley rats in an effort to evaluate the quantitative nature of the conversion of IV to phenytoin after intravenous and intramuscular dosing. The crossover studies comprised of: (*a*) three rats which received phenytoin-equivalent doses of 7 mg/kg im of IV[2] and 10 mg/kg im of sodium phenytoin; (*b*) three rats which received 7 mg/kg im of IV[2] and 10 mg/kg iv of sodium phenytoin, and a second group of three rats which received 10 mg/kg im of IV and 10 mg/kg iv of sodium phenytoin; and (c) two rats which received 10 mg/kg iv of IV and 10 mg/kg iv of sodium phenytoin. The rats weighed between 250–300 g. Each rat was used for only one crossover study, at the end of which it was sacrificed. The rats were rested for at least 1 week between doses and were fed standard laboratory diet and water *ad libitum*.

Prior to a study, the rats were weighed and anesthetized with 60 mg/kg ip of sodium pentobarbital. The animals were kept on a heated surgical table (38°C) to maintain their normal body temperature. The rats were kept unconscious throughout the experiment by administering smaller doses of sodium pentobarbital (30 mg/kg) whenever the animal showed signs of regaining consciousness.

The jugular vein was exposed by means of a small incision on the ventral side of the neck region. The right jugular vein was used to administer aqueous solutions of IV and also to obtain blood samples at various time intervals. At the end of the experiment the area of incision was cleaned with ethanol, and the incision was closed using a nonabsorbable, sterile, surgical silk suture[3].

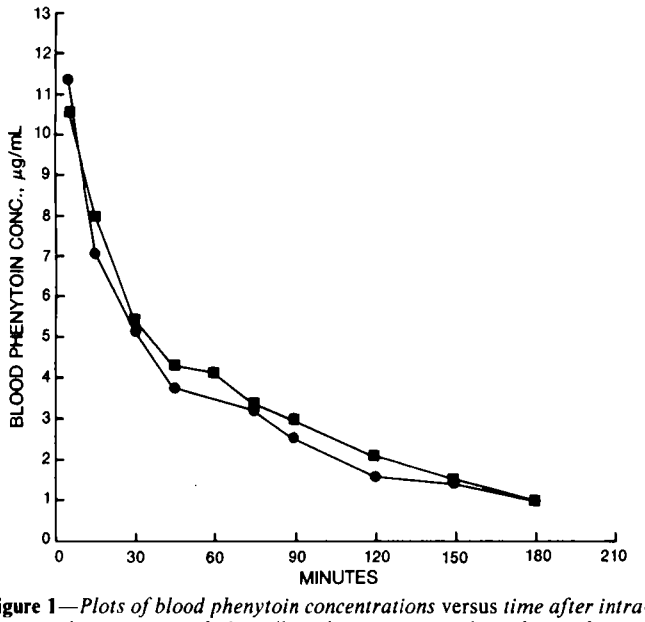

Figure 1—*Plots of blood phenytoin concentrations* versus *time after intravenous administration of 10-mg/kg (phenytoin equivalent) doses of Ia (●) and IV (■) to the same rat.*

[2] After having carried out these two partial studies, it was found that one particular batch of IV (prepared just before this *in vivo* study) was only 70% pure as confirmed by GC and TLC (9). The impurity was determined to be inorganic in nature. Hence, instead of administering 10 mg/kg (phenytoin equivalents) of IV, rats in study a and the first study b received a 7-mg/kg (phenytoin equivalent) dose of IV. This was the only batch of IV that was so contaminated. Earlier batches reported (9–11) were pure.

[3] Sutupak, SA-63H; Etgicon, Inc., Somerville, N.J.

Table II—Area under the Blood Phenytoin Concentration *versus* Time Curves for Ia and IV after Intramuscular Administration of 10 and 7 mg/kg[a]

Compound	AUC_0^{210}, μg·min/mL[b] Rat 1	Rat 2	Rat 3	Mean ± *SD*
Ia	30	189	75	97.8 ± 82.0
IV	348	343	329	339.8 ± 9.7

[a] Doses expressed as phenytoin equivalents. [b] Calculated *via* the trapezoidal method.

The rats were then placed in metabolism cages with access to food and water.

Administration of sodium phenytoin intravenously and intramuscularly leads to precipitation of phenytoin at the injection site. If blood samples were obtained after intravenous administration of sodium phenytoin from the same vein where sodium phenytoin had been administered, it may show erroneous blood levels of the drug. To overcome this problem, sodium phenytoin was administered intravenously through the exposed femoral vein and blood samples were obtained from the left jugular vein.

The various routes of administration of sodium phenytoin and IV were as follows.

1. For IV, fresh aqueous solutions were intravenously administered into the right jugular vein, with blood samples from the same vein; intramuscular administration was into the thigh muscle, with blood sampling also from the right jugular vein.

2. For sodium phenytoin, the drug was dissolved in a solvent of propylene glycol–alcohol–water (4:1:5) with the pH adjusted to 11.5–12 with sodium hydroxide. This was administered intravenously into a femoral vein, and blood was sampled from the left jugular vein. Intramuscular administration was into the thigh muscle, with blood sampling also from the left jugular vein. The volume administered did not exceed 250 μL. Intravenous injections of sodium phenytoin and IV were infused slowly over a 1-min period.

Blood samples obtained from the jugular vein were transferred to containers[4] containing 3 mg of EDTA and were immersed in an ice bath. A measured quantity (usually 100–200 μL) of blood was extracted into 2 mL of toluene containing the internal standard. The GC procedure described earlier (12) for the determination of phenytoin was then followed. No effort was made to determine the presence of the prodrug, as earlier studies had indicated rapid conversion of IV to phenytoin in rat tissues (9).

RESULTS AND DISCUSSION

Compound IV has been shown to have physicochemical properties that are ideal for a prodrug of phenytoin for parenteral use (9–11). Although prodrugs II and III had been projected as possible oral delivery forms of phenytoin (9, 10), they may also be potentially useful parenteral prodrugs.

Emergency use of parenteral phenytoin, *e.g.*, in cases of controlling seizures in patients with head injuries, may require the administration of the prodrug intramuscularly. A study was undertaken, therefore, to qualitatively assess the extent of the localized tissue damage caused by prodrugs II–IV after intramuscular and subcutaneous administration to rats.

To be clinically acceptable, intramuscular administration of a drug should cause minimal tissue damage at the injection site. Intramuscular administration of sodium phenytoin has been reported to be painful, probably due to the precipitation of phenytoin (7). It has also been shown to cause hemorrhage, hematoma, and necrosis at the injection site in cats and rabbits (3, 8).

Table I summarizes the extent of tissue damage observed after subcutaneous and intramuscular administration of II–IV to rats. There were only some minor qualitative differences between the 1- and 7-d observations; the results were, therefore, summarized together. Esters II and III cause tissue damage after subcutaneous as well as intramuscular administration. The tissue damage may have been caused by the ester or the products formed on hydrolysis of the ester. Recently, Adachi *et al.* (13) have shown that aged solutions of cephalothin caused pain when administered intraperitoneally to mice, which was attributed to the acetic acid produced on hydrolysis of cephalothin. The possibility of irritation and tissue damage caused by the acids produced on hydrolysis of the esters cannot be ruled out. Another possibility for the cause of the tissue damage was the methanesulfonate anion of II and III. Administration of the hydrochloride salt of 3-(hydroxymethyl)-5,5-diphenylhydantoin *N*,*N*-dimethylglycine ester was found to cause tissue damage comparable to that caused by II[5]. Many parenteral dosage forms of amine drugs for intramuscular use are administered as their hydrochloride salts and have

[4] Vacutainers, No. 6496; Becton, Dickinson and Co., Rutherford, N.J.

[5] The hydrochloride salt was not extensively evaluated with respect to its physicochemical properties because of its hygroscopic properties. It was prepared in a small quantity specifically for this test.

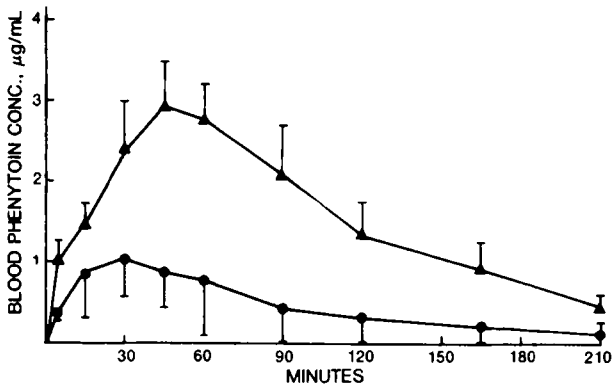

Figure 2—*Blood concentrations of phenytoin in rats* (n = 3) *following intramuscular administration of Ia* (●) *and IV* (▲). *Doses (phenytoin equivalents) were 10 mg/kg of Ia and 7 mg/kg of IV; Bars represent* SD.

not been reported to cause any specific tissue damage due to the choice of the hydrochloride salt. Thus, it seems that the counter anion of II and III does not cause the observed tissue damage.

Ester IV did not exhibit any tissue damage after subcutaneous or intramuscular administration. Thus, IV could be a suitable prodrug candidate for intramuscular delivery of phenytoin, providing that the ester is well absorbed from the site of injection and is quantitatively converted to phenytoin *in vivo*.

The bioavailability of phenytoin after intramuscular and intravenous injections of IV to rats was studied. The specific aims of this study were to (*a*) determine whether IV was quantitatively converted to phenytoin *in vivo* after its intravenous administration, (*b*) compare the levels of phenytoin obtained after intramuscular administration of IV with those obtained after intramuscular administration of sodium phenytoin (Ia), and (*c*) determine the absolute bioavailability of IV after intramuscular administration. All the studies carried out in rats were crossover studies, as described in the *Experimental Section*. Crossover studies were used instead of a single treatment per rat in order to minimize the effects of differences in the elimination half-lives of phenytoin due to variations in the extent of protein binding of phenytoin among rats (14).

Gerber *et al.* (15), Ashley and Levy (16, 17) and Vicuna *et al.* (18) have shown that phenytoin displays dose-dependent or nonlinear kinetics in rats. The apparent half-lives of phenytoin after intravenous administrations of 10-, 25-, and 40-mg/kg doses of phenytoin to rats increased from 0.6 to 1.2 to 2.5 h, respectively (15). There is considerable controversy as to whether the dose dependency exhibited by phenytoin in rats is due to saturation of the enzyme system responsible for metabolism of phenytoin to 5-(*p*-hydroxyphenyl)-5-phenylhydantoin (*p*-HPPH) or to product inhibition in which *p*-HPPH can have an inhibitory effect on the biotransformation of phenytoin. However, it has been reported by a number of workers (15-18) that the pharmacokinetics of phenytoin approaches linear elimination kinetics in rats after a 10-mg/kg iv dose of phenytoin. Thus, for the present study, doses of 10 mg/kg (administration equivalent) of IV and Ia were used, and the data was evaluated assuming linear phenytoin elimination kinetics.

To determine whether IV reverted quantitatively to phenytoin *in vivo*, a crossover study in which each rat received either a 10-mg/kg (phenytoin equivalent) dose of IV or a 10-mg/kg (phenytoin equivalent) dose of Ia intravenously was undertaken. Figure 1 is a linear plot of blood phenytoin concentrations as a function of time in one rat after intravenous administrations of Ia and IV. Semilogarithmic plots of blood phenytoin *versus* time after intravenous administrations of IV and Ia showed that phenytoin exhibited two-compartmental pharmacokinetics in the rat, which is consistent with the results obtained by other workers (14, 16, 17). Compound IV produced plasma phenytoin levels similar to those obtained after the intravenous administration of an equivalent dose of Ia. The percentage ratios of the areas under the plasma concentration *versus* time profiles from 0 to 180 min after intravenous administrations of IV and Ia were 109.7 and 91.2% in the two rats studied. This suggests that IV was completely hydrolyzed to phenytoin in these rats.

The evaluation of IV as an intramuscular form for the delivery of phenytoin required the determination of blood levels of phenytoin after intramuscular administration of the prodrug and Ia. Figure 2 shows a plot of the mean blood concentrations of phenytoin *versus* time obtained after intramuscular administrations of IV and Ia at doses of 7 and 10 mg/kg (phenytoin equivalents), respectively, to three rats. Table II summarizes the area under the blood phenytoin concentration *versus* time curves from 0 to 210 min obtained in each rat after intramuscular administrations of IV and Ia. Statistical analysis of the mean phenytoin blood level data using the paired *t* test showed that the

Table III—Area under the Blood Phenytoin Concentration *versus* Time Curve Obtained in Rats after Administration of IV Intramuscularly and Ia Intravenously [a]

Rat	Intramuscular Administered IV AUC_0^∞, μg·min/mL[b]	Intravenous Administered Ia AUC_0^∞, μg·min/mL[c]	F[d]
4	522	723	1.0
5	527	786	1.0
6	330	578	0.8
7	837	763	1.1
8	2209	2695	0.8
9	552	467	1.2

[a] Rats 4-6 received 7 mg/kg of IV intramuscularly; rats 7-9 received 10 mg/kg of IV intramuscularly. Compound Ia was administered at a dose of 10 mg/kg. All doses were phenytoin equivalents. [b] AUC_0^∞ was calculated using the trapezoidal method. [c] AUC_0^∞ was calculated using $(A/\alpha) + (B/\beta)$. [d] Calculated by AUC_0^∞/Dose (intramuscular) ÷ AUC_0^∞/Dose (intravenous).

blood levels of phenytoin at 5, 30, 45, and 60 min after intramuscular administrations of IV and Ia were significantly different ($p < 0.05$). The one-way ANOVA showed the mean area under the blood phenytoin concentration *versus* time curve from 0 to 210 min was significantly different ($p < 0.01$).

To determine the absolute bioavailability of intramuscularly administered IV, a crossover study was initiated in which the rats received an intramuscular injection of IV followed 1 week later by an intravenous dose of Ia. The same order of administration of IV and Ia was maintained in all the rats (see *Experimental Section* for explanation). The results are reported in two groups of three rats each. The first group of rats received 7 mg/kg (phenytoin equivalents) of IV intramuscularly and the second group of rats received 10 mg/kg (phenytoin equivalents) of IV. The division into two groups occurred as the first group was administered an impure batch of IV[2]; *i.e.*, the ester was only 70% pure, with the other 30% of the dose as inorganic impurities. Thus, instead of administering a 10-mg/kg (phenytoin equivalent) dose of IV, the rats in group 1 were inadvertently administered a 7-mg/kg (phenytoin equivalent) dose of IV. Both the groups received 10-mg/kg (phenytoin equivalent) dose of Ia intravenously. The blood phenytoin concentration *versus* time profiles for a rat in group 2 is shown in Fig. 3. Table III summarizes the areas under the blood phenytoin concentration *versus* time curves (AUC_0^∞) obtained after intramuscular injection of IV, calculated using the trapezoidal method (19). The blood phenytoin concentration (C) *versus* time profile after intravenous administration of Ia was computer-fitted to Eq. 1 using the AUTOAN-NONLIN library program (20, 21):

$$C = Ae^{-\alpha t} + Be^{-\beta} \qquad \text{(Eq. 1)}$$

Equation 1 describes a two-compartment open model. The parameters A, α, B, and β were then used to calculate AUC_0^∞ using:

$$AUC_0^\infty = \frac{A}{\alpha} + \frac{B}{\beta} \qquad \text{(Eq. 2)}$$

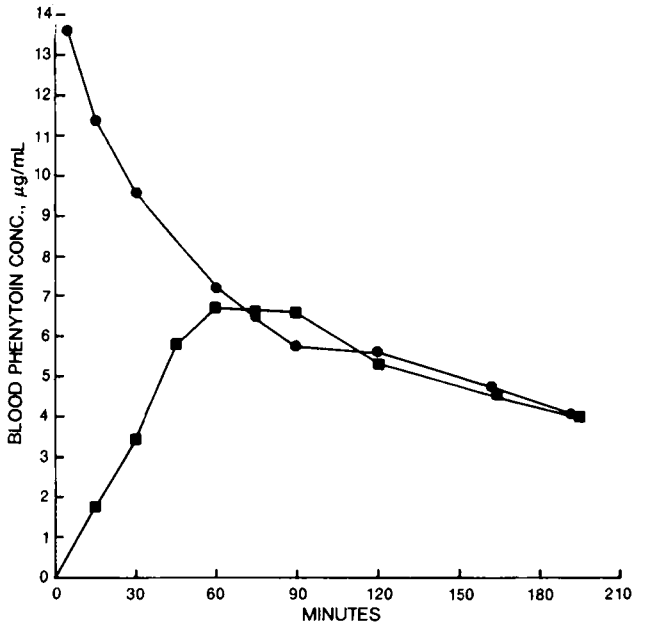

Figure 3—*Plots of the blood phenytoin concentrations* versus *time following administration of 10-mg/kg doses of IV intramuscularly* (■) *and of Ia intravenously* (●) *to rat 8. Doses are in phenytoin equivalents.*

The absolute bioavailability was determined by dividing the AUC_0^∞ values obtained after intramuscular administration of IV by those obtained after intravenous administration of Ia, corrected for dose.

Compound IV was rapidly and quantitatively hydrolyzed following intravenous administration to rats, producing blood levels of phenytoin similar to those obtained after intravenous administration of an equivalent dose of Ia. This is consistent with the rapid and quantitative hydrolysis of IV observed in an *in vitro* rat liver homogenate study (9). Thus, IV must be metabolized catalytically by phosphatase enzymes at a rate faster than the rate at which the ester would be eliminated by other mechanisms. Intramuscular administration of IV showed a higher area under the blood phenytoin concentration *versus* time profile compared with that obtained after intramuscular administration of Ia. The large standard deviation in the AUC_0^{240} value observed after intramuscular administration of Ia reflects the erratic and unpredictable absorption of phenytoin from Ia. This has been attributed to the precipitation of phenytoin at the site of injection. It has been shown that the intramuscular administration of Ia is much less effective, and doses of ~2–3 times higher than the oral dose may be necessary to achieve comparable plasma concentrations on single dose administration (5, 6). Intramuscular administration of IV produced higher blood phenytoin levels, which peaked within 45–60 min; this showed that IV was rapidly cleared from the site of injection. The mean absolute bioavailability of intramuscular administered ester IV was determined, assuming linear pharmacokinetics, to be 98.4%. This suggested that the administered dose of IV was completely absorbed from the site and was quantitatively converted to phenytoin *in vivo*. This is consistent with the quantitative conversion of IV observed after intravenous administration of this prodrug.

Based on rat data presented in this paper, earlier physicochemical studies (9, 10), and an *in vivo* evaluation in dogs (11), it can be concluded that IV would be an ideal prodrug for the parenteral delivery of phenytoin provided it is quantitatively hydrolyzed to phenytoin in humans. Compound IV could be administered intravenously or intramuscularly as an aqueous solution in emergency cases to control seizures. The use of IV as a parenteral delivery form would overcome the problems of precipitation of phenytoin associated with intravenous and intramuscular administration (3, 4, 8) of sodium phenytoin (Ia). It should also be free of the toxic cardiac effects seen after rapid intravenous injections of sodium phenytoin and the tissue damage reported to occur after intramuscular administration of sodium phenytoin.

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