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Pharmacokinetics and absolute bioavailability of oral cefuroxime axetil in the rat

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Abstract

The objectives of this study were to determine the oral bioavailability of cefuroxime (C) and to evaluate the pharmacokinetic model that best describes the plasma concentration behaviour following single intravenous (IV), intraperitoneal (IP) and oral single doses. The same dose of C was administered by IV, IP and oral routes to three separate groups of rats (2.02 mg of cefuroxime axetil (CA) by the oral route or 1.78 mg of cefuroxime sodium (CNa) by IV and IP route). A two-compartment open model without lag time can predict the C disposition kinetics. The influence of the administration route on the pharmacokinetic parameters and AUC values was investigated by means of a one-way analysis of variance test. The results indicated that the first-pass effect in the intestine and liver reduce oral biovailability when the drug is admistered orally. Cefuroxime bioavailability after oral and IP administration estimated from the plasma levels was nearly 24 and 75%, respectively.

Keywords: Cefuroxime axetil; Pharmacokinetic model; Absolute bioavailability; Rat

1. Introduction

CA is an ester, prodrug of the cephalosporin C. Since C is not absorbed orally, the 1-acetyloxyethyl (axetil) ester of C was used to improve its gastrointestinal absorption. After oral administration, CA is absorbed and rapidly hydrolysed by esterases in the intestinal mucosa and portal blood to produce C (Powell et al., 1991). CA is used in the treatment of a wide range of infections, but it exhibits poor, variable bioavailability and it is difficult to establish the optimal oral dosage schedule (Ridgway et al., 1991). Accordingly, the pharmacological response of C shows great interindividual variability.

In clinical practice, chronic treatment in humans is established in an empirical way by modifying the dose of the prodrug and verifying the pharmacological response. The dosage schedule for C is 1 g twice a day intravenously, and CA is administered 250 mg twice a day orally, despite

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the fact that the prodrug shows quite variable absolute bioavailability, ranging from 30% in fasted to 50% in fed states (Finn et al., 1987).

The aims of the present study were to determine the pharmacokinetic model of C after IV administration and to determine the absolute bioavailability of C after IP administration of C and oral administration of CA. In this study the C plasma levels observed using different administration routes were compared in order to detect possible non-linear processes. The rat was used as the experimental model.

2. Materials and methods

2.1. Animals and surgical preparation

All the pharmacokinetic studies reported here adhere to the Principles of Laboratory Animal Care. Male Wistar rats weighing 250–300 g were used for all the experiments. Twenty-four hours before drug administration the rats were subjected to jugular vein cannulation with a 12-cm-long fragment of medical-grade silicon tubing (Silastic, Dow Corning Co.; inner diameter, 0.5 mm; outer diameter, 0.94 mm).

The anaesthesia solution administered prior to intervention was prepared by mixing 0.2 ml of a ketamine 50 mg/ml solution, 0.24 ml of a diazepan 5 mg/ml solution and 0.37 ml of an atropine 1 mg/ml solution. A total of 2.7 ml/kg of anaesthesia solution was administered by an IP injection. Under anaesthesia, 3.4 cm of the cannula was introduced into the jugular vein toward the heart and the free end of the cannula was subcutaneously conducted to the dorsal base of the neck, where it emerged; the exteriorised end was closed with a polyethylene plug. The cannula was permanently filled with heparinized (20 IU/ml) saline solution. After the surgery and until drug administration, the animals were kept fasted overnight with water free available.

2.2. Administration and sampling protocol

GLAXO Laboratories supplied the CA and CNa. The internal standard, cefoxitin, was purchased to Merck Sharp & Dhome.

A random experimental design was used. Animals were randomly assigned to one of the three groups (IP, IV and oral administration). In order to facilitate blood sampling and IV dosing to conscious rats, a 15-cm long silicon tube (bridge-tubing) was connected to the free end of the cannula. All the animals received a dose of 1.69 mg of C in a different way.

2.2.1. Oral administration

Seven rats were subjected to gastric intubation under light ether anaesthesia and received 2 ml of a solution containing CA (1.01 mg/ml) in 20% propylene glycol isotonic saline solution.

2.2.2. IV administration

Two millilitres of CNa (0.89 mg/ml) in isotonic saline solution was administered via the jugular cannula as a bolus to seven rats. The cannula was immediately rinsed with 2 ml of heparinized saline solution.

2.2.3. IP administration

Two millilitres of CNa (0.89 mg/ml) in isotonic saline solution was administered to seven rats by IP injection under light ether anaesthesia.

Blood samples (0.5 ml) were withdrawn into heparinized syringes from the jugular vein cannula at 15, 30, 45, 60, 90, 120, 150, 180 and 210 min. After each sampling the blood volume was replaced with the same volume of saline solution. The number of samples processed to obtain the curve of the plasma level of C was never larger than nine in a 15–210 min period, which corresponds approximately to four times the half-lives of the antibiotic. In these conditions the hematocrite value at the end of the experience had decreased about 19%. The plasma was immediately separated from erythrocytes by centrifugation (2000 rpm for 5 min) and stored at -30°C until analysis.

2.3. Analytical procedures

The plasma samples were assayed for C content by high-performance liquid chromatography (HPLC), which provided excellent separation and quantification of the antibiotic.

Previously C was extracted from plasma samples through BOND ELUT cartridges. The method used can be briefly summarised as follows: 200 μl plasma were mixed with 25 μl of cefoxitin (200 μg/ml) saline solution (pH 6.7), as internal standard. On the other hand, the cartridges were rinsed with 2 ml of hexane. One hundred microlitres of the sample prepared was immediately transferred to the cartridge. C and cefoxitin were eluted with 1 ml of methanol which contained 0.5% of ammonium acetate, and the elute was collected in a glass tube. The solution obtained was evaporated to dryness under low pressure and re-dissolved with 100 μl of mobile phase. After centrifugation, 20 μl of the aqueous supernatant was injected into the chromatograph. The mobile phase was a mixture of acetonitrile and aqueous 0.050 M ammonium acetate and 0.050 M acetic acid buffer (pH 4.5), 14:86 (vol./vol.). A flow rate of 2.0 ml/min was used. A reversed phase column (Spherisorb S-10 ODS-2, 250 × 4.6 mm) in conjunction with a C-130B precolumn (Tecknokroma C-18) was used. A Perkin-Elmer spectrophotometer, model LC 90 BIO, set at 273 nm, was used to monitor the column effluent.

Calibration curves covering the whole range of C concentrations in plasma samples were prepared in triplicate. The peak area ratio of C and the internal standard was measured in each sample and correlated with the C concentration. Excellent linear plots relating the peak area ratios and C concentrations were obtained, and the intercept was not significantly different from zero. The accuracy and precision of the method were established using six concentrations covering the range of the concentrations to be analysed. The accuracy and precision were evaluated by calculating the relative error and coefficient of variation, respectively, which were always less than 6.24 and 8.56%. The limit of quantification was 0.9 μg/ml. The results obtained were considered fully acceptable (Karnes and March, 1993).

2.4. Pharmacokinetic calculations and statistical analysis

The equations of the classic compartmental models were fitted to the experimental plasma concentrations of C versus time data obtained, using weighted least-squares non-linear regression by means of the PCNONLIN 3.0 program (Metzler, 1989). The weighting factor was $1/C_p^2$ (C_p is the experimental plasma concentration) (Gabrielsson and Weiner, 1996).

One and two-compartment open models were used for IV, IP and oral routes. For oral administration the models with and without lag time were fitted. In the case of the IP route, the IV two-compartment open model was fitted to the experimental data, because there is no absorption phase. Under these circumstances the absorption process is instantaneous and the possible lost of bioavailability is due to the hepatic first-pass.

All the pharmacokinetic parameters were obtained using two pharmacokinetic approaches, the individual approach (one-stage analysis) and the population approach (two-stage analysis). In the latter case naive average data on plasma levels (NAD) at each sampling time were used to each administration route, and the model parameters (V_c, k_{10}, k_{12} and k_{21}) were considered common for the three routes. For the IP and oral routes the bioavailability (F_{ip} and F_{oral}) and absorption rate constant (k_{01}) were estimated as model parameters.

To select the best model, the Akaike information criteria, AIC (Akaike, 1986) and the Snedecor F-test (Boxenbaum et al., 1974) ($\alpha = 0.05$) were applied.

The total area under the plasma drug concentration versus time curve (AUC) was calculated using two methods: a compartmental method in which the values were obtained from the equations that used the pharmacokinetic parameters obtained in the fit (AUC_b); and a noncompartmental analysis in which the values were calculated using the linear trapezoidal rule with extrapolation to infinite (AUC_t). The area under the plasma concentration versus time curve from 0 to the last measured concentration ($AUC_{0\rightarrow t^*}$) was calculated by trapezoidal integration. The AUC from the last experimental time to infinity ($AUC_{t^*\rightarrow\infty}$) was calculated by dividing the last

measurable plasma concentration value by the elimination rate constant (K_{el}). The total $AUC_{0\rightarrow t^*}$ was calculated as the sume of $AUC_{0\rightarrow t^*} + AUC_{t^*\rightarrow\infty}$. K_{el} was calculated as the negative of the slope of the regression line of the terminal linear portion of the natural log serum concentration versus time curve (Wagner, 1983). The AUC and areas at the first moment of the concentration–time curves (AUMC) were calculated by the linear trapezoidal method using the PK fit program (Pk-fit, 1996).

Absolute bioavailability was obtained by the compartmental method as the ratio of the mean values of AUC_b and by the noncompartmental analysis as the ratio of the mean values of AUC_t. Moreover, the average individual values of F obtained by compartmental (F_{comp}) and noncompartment analysis ($F_{noncomp}$) allow to calculate the mean value of F, with its standard deviation, coefficient of variation and a 90 per cent confidence interval.

For each animal, the IV mean residence time (MRT_{iv}) was obtained by applying Eq. (1). The global oral mean residence time (MRT_{oral}) was obtained by means of Eq. (2). The oral mean residence time value includes the average IV residence time (MRT_{iv}) and the mean absorption time (MAT), Eq. (3).

$$MRT_{iv} = AUMC_{iv}/AUC_{iv} \quad (1)$$

$$MRT_{oral} = AUMC_{oral}/AUC_{oral} \quad (2)$$

$$MRT_{oral} = MRT_{iv} + MAT \quad (3)$$

Clearance using noncompartmental analysis (CL) was obtained using Eq. (4) and (5), for IV and oral routes, respectively.

$$CL = D/AUC_{iv} \quad (4)$$

$$CL/F = D/AUC_{oral} \quad (5)$$

One-way analysis of variance (ANOVA or Kruskal–Wallis test) was applied to compare the pharmacokinetic parameters obtained for these routes of administration, and differences were considered significant at $P < 0.05$.

3. Results

Table 1 shows the average pharmacokinetic parameters of C ($n = 7$) calculated after IP and oral administration by fitting the two-compartment model to the individual experimental values: volumen of central compartment (V_c), absorption rate constant (k_{01}), terminal disposition half-life ($t_{1/2\beta}$), forward partition rate constant between blood and tissue (k_{12}), backward partition rate constant between blood and tissue (k_{21}), apparent volume of distribution at steady state (Vd_{ss}), alpha disposition constant (α), beta disposition constant (β), clearance (CL), area under the curve concentration-time calculated using the parameters obtained with the two-compartment open model fit (AUC_b), bioavailability after oral administration (F_{oral}) and bioavailability after IP administration (F_{ip}). The pharmacokinetic parameters obtained using simultaneously all the individual data (NAD), $n = 21$, are also shown in Table 1.

The one-way ANOVA test of pharmacokinetic parameters showed statistically significant differences among IV, IP and oral administration for the parameters V_c, CL, AUC_b, k_{21}, k_{12} and α of C ($P < 0.005$ for all parameters).

The average pharmacokinetic parameters of C calculated after IV, IP and oral administration by noncompartmental analysis of the experimental data are given in Table 2. Statistical comparison of the pharmacokinetic parameters as a function of the administration route (oral, IV or IP) was performed using a one-way ANOVA test for MRT, CL, AUC_t and Vd_{ss} values. The results clearly indicate the existence of significant differences ($P < 10^{-4}$ for all parameters).

Table 3 gives the mean values of individual F with their standard deviations and 90% confidence interval, following oral administration of CA and IP administration of the C ($n = 49$). Mean values of the relative bioavailability of C obtained through compartmental and noncompartmental analysis are also listed.

Fig. 1 graphically shows the mean plasma levels of C obtained as a function of time after IV and IP dosing of C (1.78 mg) and after oral administration of CA (2.02 mg). The population fit to the two-compartment was also plotted.

4. Discussion

The analytical procedure used here made it possible to quantify the C in plasma samples with excellent precision and accuracy. The recoveries of C and cefoxitin from standard plasma solutions in the range of concentrations assayed after the clean up step were consistently in the range of 95.72–109.05% (Ruiz-Carretero et al., 2000). The lower limit for quantitative analysis was 0.90 μg/ml and the concentrations which appeared later than 210 min after administration were lower than this value. Therefore, plasma sample collection was not continued after this period.

Compartmental analysis was done to obtain the pharmacokinetic parameters of C in the rat. In the compartmental fit the weighting factor chosen was the inverse of the square dependent variable ($1/C_p^2$) because the residual variances of the C_p were heterogeneous. The results obtained using as weighting factors the inverse of the dependent variable, the inverse of the variance, or the inverse of the square predicted concentrations were similar.

The two-compartment open model gave the best parameters according to statistical criteria (AIC and Snedecor F-test). However, most of the parameters were estimated in each animal with a high standard error, particularly after oral administration.

The one-way ANOVA test of the pharmacokinetic parameters obtained as a function of the administration route showed significant differences ($P < 10^{-4}$) for all of them except the beta disposition constant. A subsequent Scheffé multiple comparison test showed that the pharmacokinetic parameters obtained by the oral route are significantly different from those obtained by IV and IP routes, whereas the pharmacokinetic parameters obtained by the IV and IP routes showed no significant differences. These results can be explained by the fact that after oral administration absorption and disposition phases overlap. Therefore, the values of the pharmacokinetic parameters obtained from oral administration were considered unreliable.

In order to avoid the drawback observed after individual fits, a population fit was done assuming

Table 1
Pharmacokinetic parameters of cefuroxime in rats obtained after individual and population fit to compartmental models

Parameter	Individual fit			Population fit[b]
	IV ($n = 7$)[a]	IP ($n = 7$)[a]	Oral ($n = 7$)[a]	IV-IP-ORAL ($n = 21$)
V_c (l)	0.040 (0.017)	0.044 (0.014)	–	0.045 (0.007)
V_c/F (l)	–	–	0.278 (0.001)	–
k_{01} (per h)	–	–	3.12 (0.55)	2.79 (0.38)
k_{10} (per h)	1.27 (1.40)	1.24 (1.04)	0.52 (0.07)	0.67 (0.11)
k_{12} (per h)	3.10 (3.16)	2.60 (1.97)	0.49 (0.11)	0.99 (0.57)
k_{21} (per h)	3.44 (2.56)	1.96 (0.37)	1.06 (0.90)	1.78 (0.62)
Vd_{ss} (l)	0.069 (0.016)	–	–	0.070 (0.005)
Vd_{ss}/F (l)	–	0.092 (0.012)	–	–
α (per h)	7.42 (4.53)	5.40 (2.86)	1.84 (0.86)	3.05 (1.21)
β (per h)	0.44 (0.08)	0.40 (0.07)	0.27 (0.08)	0.39 (0.04)
$t_{1/2\beta}$ (h)	1.64 (0.32)	1.77 (0.29)	2.72 (0.69)	1.78 (0.19)
CL (l/h)	0.034 (0.004)	–	–	–
CL/F (l/h)	–	0.042 (0.009)	0.143 (0.028)	0.030 (0.001)
AUC_b (mg·h/l)	32.02 (3.71)	24.78 (6.28)	7.43 (0.93)	–
F_{ip} (%)	–	73.38	–	74.70 (26.89)
F_{oral} (%)	–	–	23.09	23.96 (0.90)
F_{abs} (%)	–	–	29.84	–

[a] Average parameters with standard deviation (mean ± SD).
[b] Parameters with standard error (value ± SE).

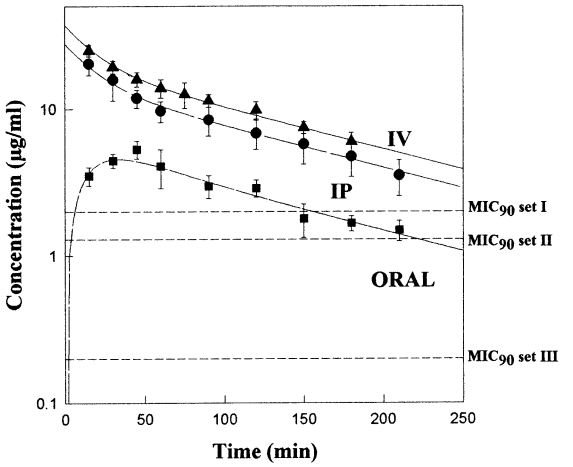

Fig. 1. Plasma levels of cefuroxime (mean with standard deviation) obtained after IV administration of cefuroxime sodium (1.78 mg) ($n = 7$) (▲), IP administration of cefuroxime sodium (1.78 mg) (●) and oral administration of cefuroxime axetil (2.02 mg) ($n = 7$) (■). The minimal inhibitory concentration for 90% of the microorganism population (MIC_{90}) are marked with dashed lines. Set I refers to common respiratory, skin and skin structure pathogens considered resistant, set II for those considered moderately susceptible and set III for susceptible microorganisms.

Table 2
Pharmacokinetic parameters of cefuroxime in rats obtained by means of noncompartmental analysis[a]

Parameter	IV ($n = 7$)	IP ($n = 7$)	Oral ($n = 7$)
MRT (h)	1.97 (0.18)	1.98 (0.18)	2.37 (0.23)
MAT (h)	–	–	0.46 (0.18)
CL (l/h)	0.036 (0.005)	–	–
CL/F (1/h)	–	0.044 (0.009)	0.148 (0.028)
Vd_{ss} (l)	0.072 (0.007)	–	–
Vd_{ss}/F (l)	–	0.088 (0.002)	0.343 (0.053)
$t_{1/2}$ (h)	1.25 (0.31)	1.37 (0.13)	1.56 (0.20)
AUC_t (mg·h/l)	29.20 (2.66)	23.49 (4.59)	7.58 (1.33)
F_{ip} (%)	–	80.64	–
F_{oral} (%)	–	–	25.75
F_{abs} (%)	–	–	31.93

[a] Values with standard deviation (value(SD)).

common disposition parameters for the three administration routes. The estimated standard errors were lower than those obtained after individual fits (see Table 1). More complex models in which the parameter values depend on the administration route did not improve the fit. In the population fit, F_{ip} and F_{oral} were obtained as model parameters.

A noncompartmental analysis was also done (Table 2). The one-way ANOVA test of the MRT obtained by the IV (MRT_{iv}), IP (MRT_{ip}) and oral (MRT_{oral}) routes showed significant differences ($P < 10^{-4}$). The Scheffé multiple comparison test revealed that the oral route was different from the others. The MRT calculated by the oral route (MRT_{oral}) includes the MRT_{iv} and the mean absorption time (MAT). For this reason, the oral MRT, calculated is higher than the IV and IP MRT (Table 2). The inverse of the mean absorption time (MAT) represents the absorption rate constant ($1/MAT = k_{01}$). The absorption rate constant calculated by noncompartmental analysis is 2.68 (0.74) per h. This value is similar to the one obtained by compartmental analysis, 3.12 (0.55) per h. With respect to Vd_{ss} and CL, the compartmental and noncompartmental values are very similar, as can be observed in the Tables 1 and 2.

Tables 1 and 2 show the AUC values obtained using compartmental and noncompartmental analysis. The two methods provide similar AUC values. The differences between AUC values ($n = 21$) obtained after IV, IP and oral administration revealed by the ANOVA test indicate that the bioavailability of C is incomplete. Table 3 shows the mean values of the absolute and relative bioavailability. These values are similar to those obtained by the ratio of the average value of AUC.

In all approaches (compartmental individual and population fit, and noncompartmental analysis) the value of F_{ip} obtained indicates that bioavailability after IP administration of the drug is less than 100%. Therefore, it seems that after IP administration of the drug to normal rats, hepatic extraction of the antibiotic occurs.

The product $F_{ip} \cdot F_{abs}$ (where F_{abs} is the absorpbed fraction) gives the magnitude of oral bioavailability (F_{oral}). When CA is administered by the oral route, F_{abs} of C is about 32% of the

administered dose (Tables 1–3). In others words, only 32% of the oral dose administered is available for absorption from the intestinal tract.

The first-pass metabolism (intestinal and hepatic) and the loss of absorbability have a significant effect on drug bioavailability when the drug is given by the oral route. Following oral administration, CA is rapidly hydrolysed to C by nonspecific esterases in the intestinal mucosa and blood. The axetil moiety is metabolised to acetaldehyde and acetic acid. While C is not metabolised and it is excreted unchanged, principally in urine by both glomerular filtration and tubular secretion (McEvoy, 1996; konishi et al., 1993). In addition, the variability of the bioavailability obtained can be justified by the existence of interindividual variability in the enzymatic activity of the intestinal esterase responsible for the hydrolysis of the prodrug, i.e. the greater the hydrolysed fraction, the smaller the absorbable fraction. On the other hand, hepatic extraction, which can be attributed to hepatic metabolism or billiary excretion, equals about 25% of the dose, which can be considered a significant contribution to the global elimination of C. Moreover, the existence of a non-linear absorption process (Ruiz-Balaguer et al., 1997) could also be one of the reasons for the poor oral bioavailability.

However, as shown in Fig. 1, in spite of the poor oral bioavailability of CA (24%), when the same dose level (1.69 mg) is administered IV and orally, the plasma levels in both cases are higher than the minimal inhibitory concentration for 90% of microorganism population (MIC_{90}) for most common respiratory pathogens, including β-lactamase-positive and -negative strains, i.e. *P. mirabilis* ($MIC_{90} = 1.3$ μg/ml) (Ridgway et al., 1991). The levels are maintained long enough to ensure effective in vivo antibacterial concentrations (from 0.15 to 3 h after dosing). In these conditions, the oral route seems to be the most convenient alternative. Nevertheless, in the treatment of diseases caused by resistant pathogens, i.e. *E. coli* ($MIC_{90} = 5$ μg/ml) only IV administration provides an effective plasma level of C (oral dosing does not guarantee plasma levels above MIC_{90}).

In the rat the biological half-life obtained is 1.78 (0.19) h, and the reference value in humans is 1.2–1.6 h (McEvoy, 1996; Konishi et al., 1993). In both cases the drug is eliminated from the body in a short period of time. Considering that in humans the regimen schedule for CA is 250 mg twice a day, and the biological half-life of C is about 1.4 h there is no accumulation of the drug in the body between doses. Therefore, the results obtained in rat ($t_{1/2} = 1.78$ h) after one dose can be considered as representative of the multiple dose schedule in humans.

It is important to emphasise that the variability of the bioavailability obtained in this study is lower than the one obtained by others authors in humans (Williams and Harding, 1984). This high degree of reproducibility could be attributed to the high homogeneity of the assayed group, i.e. all the rats were grown in standard conditions. However, the reported results let to establish some recommendations in order to improve the oral bioavailability of CA in man. Thus, the structure of the produg should be modified to increase its stability in the intestine and ensure that most of the prodrug is released before leaving the absorption site. Bioavailability could also be improved if

Table 3
Absolute and relative bioavailability (F) estimated by compartmental and noncompartmental analysis[a]

		F_{comp} (mean)			$F_{noncomp}$ (mean)		
		Mean value (%)	CV (%)	IC_{90} (%)	Mean value (%)	CV (%)	IC_{90} (%)
Absolute	AUC_{oral}/AUC_{iv}	23.44 (3.64)	15.53	22.57-24.31	26.14 (4.80)	18.36	24.99–27.29
	AUC_{ip}/AUC_{iv}	77.95 (19.98)	25.63	73.16-82.73	80.92 (16.15)	19.96	77.05–84.78
Relative	AUC_{oral}/AUC_{ip}	32.05 (9.98)	31.14	29.65-34.44	33.55 (8.99)	26.80	31.39–34.68

[a] Mean value ($n = 49$) with its standard deviation, coefficient of variation (CV) and 90 per cent confidence interval (IC_{90}).

the prodrug were administered together a specific innocuous inhibitor of intestinal esterases, i.e. a lipid rich diet, preferably with middle-chain triglycerides (Jiménez-Torres, 1988) which are hydrolysed by the intestinal esterases and would compete with the prodrug.

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