0022-3565/04/3111-324–333$20.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
JPET 311:324–333, 2004

Vol. 311, No. 1
67959/1166481
Printed in U.S.A.

XP13512 [(±)-1-([(α-Isobutanoyloxyethoxy)carbonyl] aminomethyl)-1-cyclohexane Acetic Acid], A Novel Gabapentin Prodrug: II. Improved Oral Bioavailability, Dose Proportionality, and Colonic Absorption Compared with Gabapentin in Rats and Monkeys

Kenneth C. Cundy, Thamil Annamalai, Lin Bu, Josephine De Vera, Jenny Estrela, Wendy Luo, Payal Shirsat, Allan Torneros, Fenmei Yao, Joan Zou, Ronald W. Barrett, and Mark A. Gallop

XenoPort, Inc., Santa Clara, California

Received March 5, 2004; accepted May 14, 2004

ABSTRACT

The absorption of gabapentin (Neurontin) is dose-dependent and variable between patients. Rapid clearance of the drug necessitates dosing three or more times per day to maintain therapeutic levels. These deficiencies appear to result from the low capacity, limited intestinal distribution, and variable expression of the solute transporter responsible for gabapentin absorption. Saturation of this transporter at doses used clinically leads to unpredictable drug exposure and potentially ineffective therapy in some patients. XP13512 [(±)-1-([(α-isobutanoyloxyethoxy)carbonyl]aminomethyl)-1-cyclohexane acetic acid] is a novel prodrug of gabapentin designed to be absorbed by high-capacity nutrient transporters located throughout the intestine. XP13512 was efficiently absorbed and rapidly converted to gabapentin after oral dosing in rats and monkeys. Exposure to gabapentin was proportional to prodrug dose, whereas exposure to intact XP13512 was low. In rats, >95% of an oral dose of ^{14}C-XP13512 was excreted in urine in 24 h as gabapentin. In monkeys, oral bioavailability of gabapentin from XP13512 capsules was 84.2% compared with 25.4% after a similar oral Neurontin dose. Compared with intracolonic gabapentin, intracolonic XP13512 gave a 17-fold higher gabapentin exposure in rats and 34-fold higher in monkeys. XP13512 may therefore be incorporated into a sustained release formulation to provide extended gabapentin exposure. XP13512 demonstrated improved gabapentin bioavailability, increased dose proportionality, and enhanced colonic absorption. In clinical use, XP13512 may improve the treatment of neuropathic pain, epilepsy, and numerous other conditions by increasing efficacy, reducing interpatient variability, and decreasing frequency of dosing.

Gabapentin (Fig. 1) is a structural analog of GABA with demonstrated therapeutic utility in epilepsy (McLean, 1999), neuropathic pain (Backonja et al., 1998; Rowbotham et al., 1998; Rice and Maton, 2001), restless legs syndrome (Garcia-Borreguero et al., 2002), anxiety disorders (Pollack et al., 1998), hot flashes (Guttoso et al., 2003), and numerous other indications. The drug is currently marketed in the United States under the brand name Neurontin as an adjunctive therapy for partial seizures in adults with epilepsy and for management of postherpetic neuralgia. The mechanism of action of gabapentin in most indications remains undefined, but the drug does not directly interact with GABA receptors (Kelly, 1998). Its efficacy in neuropathic pain and epilepsy may involve binding of the drug to the $\alpha_2\delta$ subunit of a voltage-dependent calcium channel (Gee et al., 1996; Marais et al., 2001).

The clinical pharmacokinetics of gabapentin have been studied in healthy volunteers and patients with epilepsy (McLean, 1995; Gidal et al., 1998, 2000; Boyd et al., 1999). Gabapentin bioavailability is dose-dependent, decreasing from an average of about 60% at a 300-mg dose to about 35% or less at doses used to treat neuropathic pain. The underly-

Article, publication date, and citation information can be found at http://jpet.aspetjournals.org.
doi:10.1124/jpet.104.067959.

ABBREVIATIONS: XP13512, (±)-1-([(α-isobutanoyloxyethoxy)carbonyl]aminomethyl)-1-cyclohexane acetic acid; SMVT, sodium-dependent multivitamin transporter; MCT-1, monocarboxylate transporter type 1; HPLC, high-pressure liquid chromatography; GP, gabapentin; LC/MS/MS, liquid chromatography-tandem mass spectrometry; CSF, cerebrospinal fluid; $t_{1/2}$, elimination half-life; T_{max}, time to maximum concentration; $AUC_{(0\text{-inf})}$, area under the concentration versus time curve extrapolated to infinity; AUC, area under the curve.

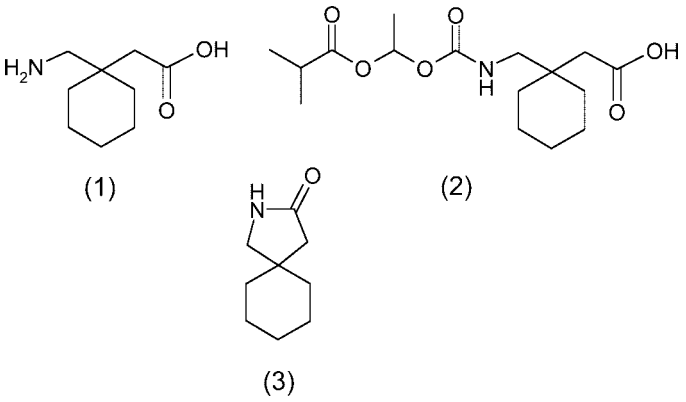

Fig. 1. The structures of gabapentin (1), XP13512 (2), and gabapentin lactam (3).

ing mechanism responsible for this dose dependence is believed to be saturable absorption of gabapentin from the intestine of humans and animals by a low-capacity, solute transporter localized in the upper small intestine (Stewart et al., 1993; Uchino et al., 2002).

This absorption pathway is apparently saturated at doses normally used to treat neuropathic pain. As a result, the plasma exposure to gabapentin in patients receiving Neurontin is not dose-proportional and therefore may not reach therapeutically useful levels in some patients (Gidal et al., 2000). Furthermore, intestinal expression of the gabapentin transporter may also vary significantly between individuals, leading to large interpatient variability in plasma exposure. There appears to be a subset of patients with limited ability to absorb gabapentin, possibly due to a lower abundance of the transporter in their intestines. This phenomenon may contribute to the high incidence of nonresponders to oral gabapentin therapy reported in clinical trials in epilepsy, postherpetic neuralgia, and diabetic neuropathy (McLean, 1995; Backonja et al., 1998; Rice and Maton, 2001).

Following oral absorption, gabapentin is excreted in the urine without significant metabolism (Radulovic et al., 1995). The plasma half-life of gabapentin in humans is relatively short (5–7 h), necessitating administration three or four times per day (McLean, 1995). It has been shown that dosing regimens requiring three or four doses per day can lead to significant noncompliance in patients with epilepsy (Richter et al., 2003). Patients who experience sleep interference from their underlying symptoms may be inadequately treated if the effect of a bedtime dose of gabapentin does not last through the night. A more prolonged, stable exposure to gabapentin may provide several clinical benefits, including greater efficacy, prolonged duration of action, and a reduced incidence of adverse effects related to peak drug levels. However, it has not been possible to achieve this with a sustained release formulation of gabapentin, due to the lack of significant absorption in the large intestine (Kriel et al., 1997).

XP13512 (Fig. 1) is a novel prodrug of gabapentin designed to overcome the pharmacokinetic limitations of gabapentin. In contrast to gabapentin, the prodrug was engineered to be absorbed from all regions of the intestine by high-capacity pathways. The enzymatic conversion of XP13512 to gabapentin and the transport of the prodrug by specific nutrient transporters are described in a companion paper (Cundy et al., 2004). The prodrug was chemically stable and was rapidly converted to gabapentin, presumably by nonspecific esterases present in tissues encountered following oral absorption. XP13512 showed pH dependent passive permeability and was taken up in vitro by cells expressing either the sodium-dependent multivitamin transporter (SMVT) or the monocarboxylate transporter type-1 (MCT-1). The prodrug also demonstrated a 5-fold apical to basolateral preference for permeation across cultured intestinal cell monolayers. SMVT and MCT-1 are broadly expressed along the intestinal tract of rats and humans (Said et al., 1998; Juel and Halestrap, 1999; Wang et al., 1999; K. Woodford and N. Zerangue, unpublished data). Therefore, the broad distribution of these transporters should lead to superior colonic absorption of XP13512 compared with gabapentin. Furthermore, the high transport capacity of MCT-1 and SMVT should allow higher prodrug doses to be absorbed without saturation of uptake, providing dose-proportional exposure to gabapentin. The purpose of the present work was to evaluate in preclinical models the effect of the improved transport properties of XP13512 on the resulting pharmacokinetics and distribution of gabapentin.

Materials and Methods

Materials. Gabapentin [(1-aminomethyl)-cyclohexaneacetic acid] was obtained from Teva Pharmaceuticals U.S.A. (North Wales, PA). Gabapentin hydrochloride salt and gabapentin lactam were synthesized from commercial gabapentin at XenoPort, Inc. The gabapentin prodrug XP13512 and its sodium salt were synthesized by XenoPort, Inc. as described elsewhere (Cundy et al., 2004). XP13512 was further separated into its two enantiomers by preparative chiral HPLC. [1-Aminomethyl-^{14}C]gabapentin was obtained from PerkinElmer Life and Analytical Sciences (Boston, MA). ^{14}C-XP13512 was synthesized from ^{14}C-gabapentin by XenoPort, Inc. using similar methods. Gabapentin HCl salt and XP13512 sodium salt were dissolved in water for oral administration. XP13512 was formulated as a suspension in 0.5% or 1% methylcellulose/0.1% (v/v) Tween 80 in water. Addition of Tween 80 was necessary to achieve homogeneity at the highest dose levels. XP13512 and its sodium salt were also formulated as neat drug substance hand-filled into size 0 HPMC capsules (Shionogi, Osaka, Japan). All other chemicals were obtained from Sigma-Aldrich (St. Louis, MO).

Animals. All studies were conducted in accordance with the Guide for the Care and Use of Laboratory Animals (National Research Council Publication, National Academy Press, Washington, DC) and were approved by an Institutional Animal Care and Use Committee. Male Sprague-Dawley rats (approximately 250 g) were obtained from Charles River (Hollister, CA and Raleigh, NC) with indwelling jugular vein cannulas. For colonic studies, rats were further cannulated in the proximal colon just distal to the cecum. For CSF penetration studies, rats were cannulated in the cisterna magna. All animals were allowed 48 h to recover prior to shipping and were acclimated for >48 h on site prior to study. Rats were fasted overnight and for the first 4 h of the study. Water was provided ad lib. The tissue distribution and recovery study was conducted in male and female Sprague-Dawley rats at MDS Pharma Services (Montreal, QC, Canada). Two groups of male cynomolgus monkeys were used for the pharmacokinetic studies (mean body weight approximately 6 and 2.4 kg, respectively). The animals were housed at TherImmune Research Corporation (Gaithersburg, MD). Monkeys were fasted overnight and for the first 4 h of the study. Water was provided ad lib. Monkeys were lightly sedated by administration of Telazol/ketamine during dosing. A 5- to 7-day washout was allowed between treatments. For the repeated dose toxicity and toxicokinetic study, four male and four female cynomolgus monkeys were housed at Covance Laboratories (Madison, WI).

Intravenous Pharmacokinetics. Two groups of male Sprague-Dawley rats (six rats/group) received intravenous bolus injections of gabapentin HCl salt or XP13512 sodium salt administered at 25 mg-Eq gabapentin/kg via a tail vein. For intravenous administration, gabapentin HCl was dissolved in water, and XP13512 was dissolved in 0.1 M phosphate buffer, pH 7.4. Gabapentin HCl salt was also administered intravenously to two groups of four male cynomolgus monkeys at 10 mg-Eq GP/kg.

Oral Bioavailability. Additional groups of male rats (five–six rats/group) received the following treatments by oral gavage: gabapentin HCl salt at 25, 50, 100, or 200 mg-Eq GP/kg; XP13512 sodium salt at 100, 200, and 2000 mg-Eq GP/kg; or free acid (XP13512) at 2480 mg-Eq GP/kg (5 g/kg). The separated isomers of XP13512 were each administered to six male rats by oral gavage at 25 mg-Eq GP/kg. Blood samples were obtained at intervals over 24-h postdosing. Gabapentin HCl was administered to four male cynomolgus monkeys by intravenous bolus injection into the saphenous vein at a dose of 10 mg/kg. The same animals each received four subsequent treatments by oral gavage as follows: gabapentin HCl salt at 10 and 75 mg/kg and XP13512 sodium salt at 10 and 75 mg-Eq GP/kg. Animals were allowed a 5- to 7-day washout between treatments. A second group of four male cynomolgus monkeys each received consecutive oral treatments by gavage as follows: commercial gabapentin capsules (Neurontin) (2 × 100-mg capsules; 81 mg GP/kg) and XP13512-free acid in HPMC capsules (91 mg-Eq GP/kg). Animals were allowed a 5- to 7-day washout between treatments. Blood samples were obtained from all animals at intervals over 48-h postdosing. Blood was processed immediately for plasma at 4°C. All plasma samples were subsequently analyzed for intact prodrug (XP13512), gabapentin, and gabapentin lactam using LC/MS/MS.

Steady-State Pharmacokinetics. XP13512 was formulated as a suspension in 0.5% methylcellulose/0.1% Tween 80 in water and administered to cynomolgus monkeys ($n = 3$ per sex) by oral gavage at doses of 0 (vehicle control), 250, 750, and 2000 mg/kg/day for 14 days in a toxicity and toxicokinetic study. Blood samples were obtained at intervals over 24 h following the first and last doses of the study. Samples were quenched by addition of methanol and stored at −80°C until analyzed by LC/MS/MS. Clinical pathology and electrocardiographic telemetry were assessed prior to study initiation and during week 2 of the study. Full histopathology examinations were conducted following necropsy on day 15 of the study.

Colonic Absorption. Gabapentin HCl salt solution and gabapentin prodrug suspension (25 mg-Eq GP/kg; 2.5 ml/kg) were each administered to groups of five to seven male rats as a bolus injection directly into the colon via the indwelling cannula. Blood samples (0.5 ml) were obtained via the jugular cannula at intervals over 8 h and were immediately quenched by addition of 0.3 ml of acetonitrile/methanol (1:1) and 20 μl of internal standard. For intracolonic dosing in monkeys, a flexible French catheter was inserted into the rectum of each monkey and extended to the proximal colon (approximately 16 inches) using fluoroscopy. Monkeys were lightly sedated by administration of Telazol/ketamine during dosing. Gabapentin HCl salt solution and XP13512 suspension were each administered as a bolus injection directly into the colon of four monkeys via the colonic catheter at a dose of 10 mg-Eq GP/kg (0.25 ml/kg). A washout period of at least 5 to 7 days was allowed between treatments. Following dosing, blood samples were obtained at intervals over 24 h and were immediately processed for plasma at 4°C.

CSF Penetration. Gabapentin and XP13512 sodium salt were each administered to groups of six male rats by intravenous bolus injection (1.0 ml/kg) or oral gavage (2.5 ml/kg) at a dose of 200 mg-Eq GP/kg. CSF samples were obtained via the cisterna magna cannula at 2 and 4 h postdosing. Blood samples were obtained at 4 h and were immediately processed for plasma at 4°C.

Tissue Distribution and Recovery. Male and female rats (12/sex) received a single oral dose of ^{14}C-XP13512 (labeled in the aminomethyl moiety) (50 mg-Eq GP/kg; 250 μCi/kg; 5 ml/kg) as a solution in 0.1 M phosphate buffer, pH 7.4. Urine and feces were collected at intervals over 72 h. A panel of 22 different tissues were excised from three animals/sex at each of 2, 6, and 24 h postdose. Concentrations of radioactivity were determined by standard liquid scintillation methods after homogenization and dissolution. Urine samples were subjected to further analysis for potential metabolites using HPLC with radioactive flow detection (Flo-One Beta; PerkinElmer Life and Analytical Sciences).

Analytical Methods. To minimize the potential for postsampling conversion of prodrug to gabapentin, initial studies involved preparation of plasma samples at low temperature without chemical quenching. The stability of XP13512 in rat blood was significantly increased by addition of 2 mM diisopropyl fluorophosphate, suggesting that cleavage of the prodrug was mediated by nonspecific esterases. However, due to the safety issues in handling diisopropyl fluorophosphate, subsequent studies involved directly quenching whole blood using methanol. Concentrations of gabapentin in quenched whole blood were generally within 10% of the corresponding levels determined in plasma. Quenched blood, plasma, or CSF samples were frozen and stored at −80°C prior to analysis. Samples were analyzed by a sensitive and specific LC/MS/MS method for simultaneous determination of prodrug, gabapentin, and gabapentin lactam. The system comprised two model LC10Advp pumps and a model SCL10Avp controller (Shimadzu Scientific Instruments, Inc., Columbia, MD) with a Model HTS-PAL autosampler with cooling stack (Leap Technologies, Carrboro, NC). The column was a Zorbax XDB C8 (5 μm; 150 × 4.6 mm) (Agilent Technologies, Palo Alto, CA). The mobile phase was A, 0.1% formic acid in water; and B, 0.1% formic acid in acetonitrile, with a flow rate of 800 μl/min (200 μl/min to the detector) and a linear gradient from 5% B to 98% B over 3.5 min. The detector was an API 2000 LC/MS/MS (Applied Biosystems, Foster City, CA), and the multiple reaction monitoring transitions (atomic mass units) were 330.10 and 197.97 for XP13512, 172.10 and 137.20 for gabapentin, and 154.00 and 95.00 for gabapentin lactam. The injection volume was 10 μl. The method was linear for XP13512 and gabapentin lactam over the concentration range 0.004 to 2.5 μg/ml and for gabapentin over the range 0.004 to 10 μg/ml. The limit of quantitation for all three analytes was 0.004 μg/ml. Intraday precision (% CV) was <17% for all three analytes; intraday accuracy (% deviation) was <12%. Similar sensitivity and linearity was observed in quenched blood or CSF.

Concentrations of biotin in plasma were determined by LC/MS/MS using the same separation method. The limit of quantitation for biotin in plasma was 0.02 μg/ml.

Pharmacokinetic Analysis. Concentration data for prodrug and gabapentin in plasma or blood were analyzed by noncompartmental methods using WinNonlin version 4.0.1 (Pharsight, Mountain View, CA). C_{max} and time to C_{max} (T_{max}) were obtained by observation. The apparent elimination half-life ($t_{1/2}$) was obtained by linear regression of three or more log-transformed data points. The area under the concentration versus time curve extrapolated to infinity [$AUC_{(0\text{-inf})}$] was obtained by the linear trapezoidal method. The bioavailability (F) of gabapentin after oral or intracolonic dosing of gabapentin or prodrug was calculated by comparison of dose-normalized AUC values with data for intravenous gabapentin. For monkey studies, two groups of animals were used. Bioavailability values were therefore determined by comparison with intravenous data within the same animal.

Results

Intravenous Pharmacokinetics in Rats. Following intravenous bolus administration to rats, gabapentin was cleared with an apparent plasma half-life of 1.8 h (Table 1). In contrast, intravenous XP13512 was rapidly converted to gabapentin with a half-life of approximately 5 min (Table 2). Conversion to gabapentin was essentially complete (99.2 ± 6.4%) based on comparison of AUC values with intravenous

TABLE 1
Pharmacokinetic parameters for gabapentin in plasma following administration of gabapentin to rats or monkeys
Values are expressed as mean ± S.D. Concentrations were determined in whole blood after intracolonic dosing.

Species	Route	Form	Dose	N	Analyte	C_0/C_{max}	T_{max}	$t_{1/2}$	$AUC_{(0\text{-inf})}$	F^a
			mg-Eq GP/kg			*μg/ml*	*h*		*μg·h/ml*	%
Rat	i.v.	Solution	25	6	Gabapentin	30.1 ± 2.95	N/A	1.8 ± 0.1	39.2 ± 4.16	100
	p.o.	Solution	25	6	Gabapentin	6.85 ± 0.72	1.8 ± 0.4	1.9 ± 0.9	32.8 ± 3.94	83.8 ± 10.1
	p.o.	Solution	50	6	Gabapentin	13.8 ± 2.44	1.8 ± 0.4	2.4 ± 0.5	76.9 ± 7.40	98.2 ± 9.44
	p.o.	Solution	100	6	Gabapentin	22.7 ± 1.12	2.7 ± 1.0	2.0 ± 0.5	125 ± 18.5	80.0 ± 11.8
	p.o.	Solution	200	6	Gabapentin	27.0 ± 3.09	2.0 ± 1.1	2.6 ± 1.7	148 ± 24.2	47.5 ± 7.72
	i.c.	Solution	25	6	Gabapentin	0.55 ± 0.27	0.5 ± 0.2	1.5 ± 0.4	1.30 ± 0.63	3.38 ± 1.60
Monkey	i.v.	Solution	10	4	Gabapentin	11.5 ± 1.04	N/A	4.0 ± 0.7	59.6 ± 5.3	100
	p.o.	Solution	10	3	Gabapentin	3.67 ± 1.63	2.3 ± 1.5	5.5 ± 1.9	32.1 ± 10.4	53.9 ± 17.3
	p.o.	Solution	75	3	Gabapentin	15.1 ± 5.71	2.0 ± 0.0	3.7 ± 0.9	113 ± 22.7	26.3 ± 5.31
	p.o.	Capsule[b]	39	4	Gabapentin	7.33 ± 3.45	2.5 ± 1.0	4.6 ± 0.7	57.5 ± 16.0	25.4 ± 4.85
	i.c.	Solution	10	3	Gabapentin	0.16 ± 0.27	0.5 ± 0.0	5.6[c]	1.06[c]	1.77[c]

N/A, not applicable.
[a] *F* is calculated relative to intravenous gabapentin at 25 mg/kg for rats (separate group) and 10 mg/kg for monkeys (within the same animal).
[b] Commercial Neurontin capsules (2 × 100 mg).
[c] Data for one animal with a defined terminal phase.

TABLE 2
Pharmacokinetic parameters for gabapentin and XP13512 in plasma following administration of XP13512 to rats
Values are expressed as mean ± S.D. Concentrations were determined in whole blood after intracolonic dosing.

Compound	Route	Form	Dose	N	Analyte	C_0/C_{max}	T_{max}	$t_{1/2}$	$AUC_{(0\text{-inf})}$	F^a
			mg-Eq GP/kg			*μg/ml*	*h*		*μg·h/ml*	%
XP13512	i.v.	Solution	10	6	Gabapentin	9.45 ± 1.10	0.1 ± 0.0	1.2 ± 0.1	15.6 ± 1.01	99.2 ± 6.44
					XP13512	33.6 ± 17.3	N/A	0.1 ± 0.0	1.75 ± 0.80	N/A
XP13512 sodium salt	p.o.	Solution	100	6	Gabapentin	22.5 ± 10.1	0.8 ± 0.6	8.6 ± 7.3	102 ± 9.16	64.9 ± 5.85
					XP13512	0.19 ± 0.15	0.5 ± 0.0	1.4 ± 0.5	0.50 ± 0.31	N/A
	p.o.	Solution	200	6	Gabapentin	34.1 ± 6.65	1.2 ± 0.7	4.5 ± 2.5	190 ± 15.6	60.6 ± 4.98
					XP13512	0.18 ± 0.16	1.3 ± 1.4	5.9 ± 1.8	0.95 ± 0.10	N/A
	p.o.	Solution	2000	6	Gabapentin	155 ± 41.6	1.4 ± 0.8	6.4 ± 3.5	2230 ± 357	71.2 ± 11.4
					XP13512	10.4 ± 3.32	1.5 ± 1.5	4.6 ± 2.4	63.8 ± 18.7	N/A
XP13512	p.o.	Suspension	2480	6	Gabapentin	177 ± 34.1	1.4 ± 0.5	3.2 ± 0.7	2230 ± 385	57.5 ± 9.93
					XP13512	11.6 ± 7.80	1.1 ± 0.8	6.3 ± 3.4	59.6 ± 30.7	N/A
(*S*)-isomer	p.o.	Solution	25	5	Gabapentin	4.77 ± 1.79	0.7 ± 0.3	2.5 ± 0.8	22.5 ± 7.10	57.7 ± 18.1
					XP13512	0.18 ± 0.10	0.8 ± 0.3	2.2 ± 0.3	0.47 ± 0.25	N/A
(*R*)-isomer	p.o.	Solution	25	5	Gabapentin	3.94 ± 1.46	0.7 ± 0.3	2.8 ± 0.4	19.3 ± 4.28	49.3 ± 10.9
					XP13512	0.15 ± 0.09	0.6 ± 0.2	6.2 ± 3.2	0.82 ± 0.57	N/A
XP13512	i.c.	Suspension	25	5	Gabapentin	9.17 ± 0.87	0.3 ± 0.1	1.1 ± 0.2	19.1 ± 1.60	48.7 ± 4.07
					XP13512	1.34 ± 0.75	0.3 ± 0.0	0.7 ± 0.3	0.73 ± 0.30	N/A

N/A, not applicable.
[a] *F* is calculated relative to intravenous gabapentin at 25 mg/kg.

gabapentin. The steady-state volume of distribution of XP13512 (364 ± 269 ml/kg) was 25% of that of gabapentin (1380 ± 85.0 ml/kg). Plasma clearance of XP13512 was 13.0 ± 6.20 l/h/kg compared with 0.64 ± 0.07 l/h/kg for gabapentin. The corresponding mean residence time values were 0.03 ± 0.01 and 2.2 ± 0.3 h, respectively.

Oral Bioavailability in Rats. The oral bioavailability of gabapentin HCl in rats was 83.8 ± 10.1% at low dose (25 mg/kg) but decreased significantly to 47.5 ± 7.72% at 200 mg/kg (Table 1). This is consistent with saturation of the active transport pathway responsible for absorption of gabapentin. In contrast, oral bioavailability of gabapentin from the XP13512 sodium salt was consistently high across a wide dose range (64.9 ± 5.85% at 25 mg-Eq GP/kg and 71.2 ± 11.4% at 2000 mg-Eq GP/kg) (Table 2). Oral bioavailability of XP13512 administered as a suspension at 2480 mg-Eq GP /kg was 57.5 ± 9.93%. The 2480 mg-Eq/kg dose is a dose of 5000 mg/kg prodrug as a suspension and represents the practical limit for oral dosing in rats. The highest anticipated human doses are in the range of 40 mg/kg. Systemic exposure to the intact XP13512 was low after oral dosing of the prodrug in rats. The maximum XP13512 concentration observed in plasma after a prodrug dose of 2000 mg-Eq GP/kg was approximately 15-fold lower than the corresponding gabapentin C_{max}. The formation of gabapentin lactam, a potential metabolite of XP13512, from the prodrug was not significant after oral dosing in rats. At the highest prodrug dose, gabapentin lactam concentrations were >20-fold lower than the corresponding gabapentin levels. A low level of gabapentin lactam was also observed after oral dosing of gabapentin HCl salt.

Intravenous Pharmacokinetics in Monkeys. Following intravenous administration of gabapentin to monkeys, the drug was eliminated from plasma with a terminal half-life of 4.0 h (Table 1). Total plasma clearance was 0.178 ± 0.015 l/h/kg, and steady-state volume of distribution was 972 ± 98.6 ml/kg.

Oral Bioavailability in Monkeys. Fig. 2 compares the time courses of gabapentin concentrations in plasma after oral administration of gabapentin HCl or XP13512 sodium salt to monkeys. Oral dosing of gabapentin resulted in dose-dependent pharmacokinetics; oral bioavailability was 53.9 ± 17.3% at low dose (10 mg/kg) but decreased significantly to 26.3 ± 5.31% at 75 mg/kg (Table 1). This again is consistent with saturation of the active transport pathway responsible for intestinal absorption of gabapentin. In contrast, oral bio-

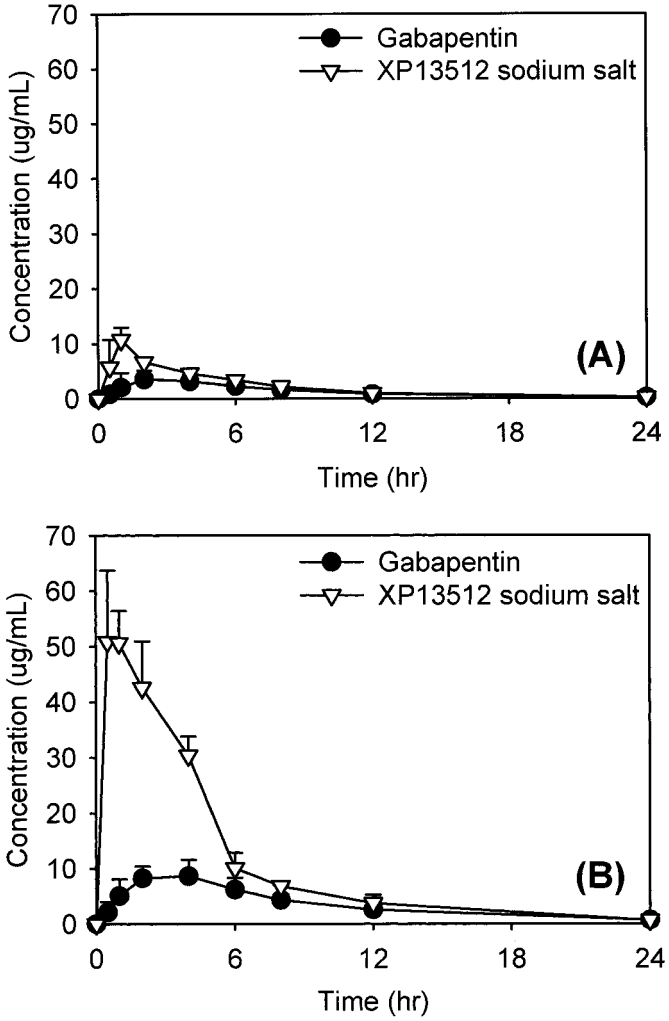

Fig. 2. Concentrations of gabapentin in plasma of monkeys following oral administration of gabapentin (closed circles) or XP13512 sodium salt (open triangles). Compounds were administered at equimolar doses of: A, 10 mg-Eq GP/kg; and B, 75 mg-Eq GP/kg. Data are the mean ± S.D. for three animals.

availability of gabapentin from XP13512 sodium salt was consistently high at both equivalent dose levels (93.5 ± 8.43% at 10 mg-Eq GP/kg and 60.1 ± 10.6% at 75 mg-Eq GP/kg) (Table 3). These data indicate that oral XP13512 was rapidly absorbed and converted to gabapentin in monkeys and was not subject to saturation at doses where gabapentin absorption is limited (Fig. 2). Exposure to prodrug in these animals was minimal; prodrug C_{max} was 50-fold lower than the corresponding gabapentin C_{max} at the high dose. Bioavailability of the commercial Neurontin capsules (2 × 100 mg) in monkeys was 25.4 ± 4.85%, whereas oral bioavailability of gabapentin from a near equimolar dose of XP13512 in HPMC capsules was significantly higher (84.2 ± 7.24%) (Fig. 3). Similar high bioavailability of gabapentin was also seen for oral XP13512 sodium salt in capsules (78.9 ± 13.5%). Exposure to intact prodrug after dosing XP13512 capsules was low; prodrug C_{max} in plasma was approximately 30-fold lower than the corresponding C_{max} of gabapentin, and the prodrug was only detected in plasma for the first 4 to 6 h after dosing.

Exposure to the potential metabolite gabapentin lactam was negligible after oral dosing of either Neurontin or XP13512 capsules. The C_{max} of gabapentin lactam in plasma was >1500-fold less than the corresponding C_{max} of gabapentin. These data indicate that no significant conversion of XP13512 to lactam occurred after dosing in monkeys.

XP13512 was well tolerated in monkeys after 14 days of repeated oral dosing at doses up to 2000 mg/kg/day (1040 mg-Eq GP/kg/day). There were no significant clinical observations, macroscopic or microscopic pathological findings, behavioral effects, or electrocardiographic effects at any of the doses tested. The steady-state pharmacokinetics of XP13512 and gabapentin in blood following 14 days of repeated daily oral dosing of XP13512 are presented in Table 4. Steady-state AUC of gabapentin in blood of these animals was approximately proportional to dose (Fig. 4). The reported daily gabapentin exposure achieved in monkeys given oral doses of gabapentin up to 1000 mg/kg/day are shown in the same plot for comparison (Neurontin Summary Basis of Approval, NDA 20-235, U.S. Food and Drug Administration). At the highest prodrug dose (2000 mg/kg/day; approximately 1040 mg-Eq gabapentin/kg/day), the daily gabapentin AUC (4190 μg/h/ml) was 8.7-fold higher than the highest exposure previously achieved in monkeys given 1000 mg/kg/day gabapentin.

Pharmacokinetics of XP13512 Isomers. The two separated isomers of XP13512 gave similar concentration profiles of gabapentin in plasma after oral administration to rats (Fig. 5). Bioavailability as gabapentin was 57.7 ± 18.1% for the *S*-isomer and 49.3 ± 10.9% for the *R*-isomer. Concentrations of intact prodrug observed in plasma were low. These data demonstrate that there was no apparent stereoselectivity in the in vivo absorption and cleavage of the isomers of XP13512 in rats.

TABLE 3
Pharmacokinetic parameters for gabapentin and XP13512 in plasma following administration of the prodrug to monkeys
Values are expressed as mean ± S.D.

Compound	Route	Form	Dose	*N*	Analyte	C_{max}	T_{max}	$t_{1/2}$	$AUC_{(0\text{-inf})}$	*F*[a]
			mg-Eq GP/kg			*μg/ml*	*h*		*μg·h/ml*	*%*
XP13512 sodium salt	p.o.	Solution	10	3	Gabapentin	11.3 ± 2.06	0.8 ± 0.3	3.9 ± 0.7	53.4 ± 4.92	93.5 ± 8.43
					XP13512	1.09 ± 0.86	0.7 ± 0.3	0.2 ± 0.0	0.75 ± 0.56	N/A
	p.o.	Solution	75	3	Gabapentin	54.8 ± 9.13	0.8 ± 0.3	3.8 ± 0.3	256 ± 35.8	60.1 ± 10.6
					XP13512	1.29 ± 0.83	1.0 ± 0.0	0.6 ± 0.2	2.10 ± 0.91	N/A
XP13512	p.o.	Capsule[b]	36	4	Gabapentin	27.3 ± 3.24	2.8 ± 1.5	4.1 ± 0.4	171 ± 17.7	84.2 ± 7.24
					XP13512	0.97 ± 0.64	1.5 ± 0.6	1.6 ± 0.5	2.10 ± 0.33	N/A
	i.c.	Suspension	10	4	Gabapentin	7.59 ± 2.88	1.5 ± 1.7	3.1 ± 0.9	34.6 ± 12.2	60.6 ± 21.4
					XP13512	1.09 ± 0.59	1.0 ± 0.7	1.4 ± 0.6	2.10 ± 2.31	N/A

N/A, not applicable.
[a] *F* is calculated relative to intravenous gabapentin at 10 mg/kg within the same animal.
[b] Clinical capsules containing 350 mg of XP13512.

TABLE 4
Steady-state pharmacokinetic parameters for gabapentin and XP13512 in blood following repeated oral administration of XP13512 to cynomolgus monkeys in a 14-day toxicity and toxicokinetic study
Values are expressed as mean ± S.D.

Compound	Route	Form	Dose	*N*	Analyte	C_{max}	T_{max}	$t_{1/2}$	$AUC_{(0-24)}$
			mg/kg			*μg/ml*	*h*		*μg·h/ml*
XP13512	p.o.	Suspension	250	3/sex	Gabapentin	117 ± 23.9	1.7 ± 0.3	4.1 ± 0.5	679 ± 174
					XP13512	9.05 ± 7.50	0.6 ± 0.2	0.8 ± 0.4	9.77 ± 7.13
	p.o.	Suspension	750	3/sex	Gabapentin	183 ± 30.3	2.6 ± 1.1	4.5 ± 0.7	1470 ± 315
					XP13512	12.3 ± 5.90	0.8 ± 0.4	2.9 ± 1.6	22.5 ± 7.58
	p.o.	Suspension	2000	3/sex	Gabapentin	445 ± 63.9	3.7 ± 0.8	5.1 ± 0.9	4190 ± 553
					XP13512	39.4 ± 12.6	1.6 ± 0.7	2.6 ± 0.8	141 ± 51.4

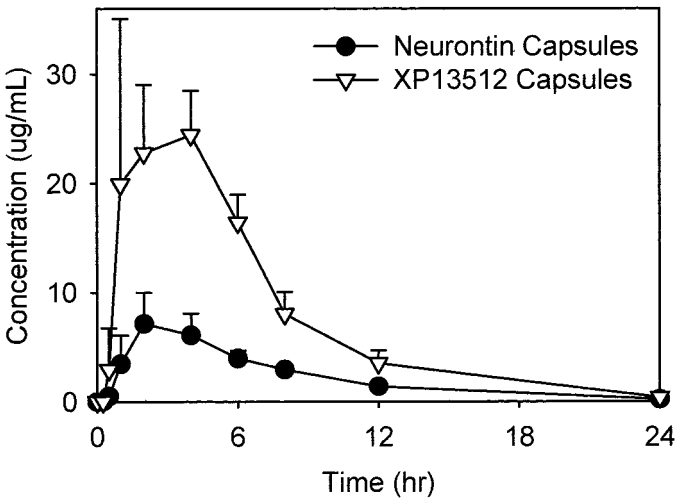

Fig. 3. Dose-normalized concentrations of gabapentin in plasma of monkeys following oral administration of Neurontin capsules (2 × 100 mg) (closed circles) or XP13512 capsules (1 × 350 mg; 182 mg-Eq GP) (open triangles). Data are the mean ± S.D. for four monkeys normalized to a 36 mg-Eq GP/kg dose.

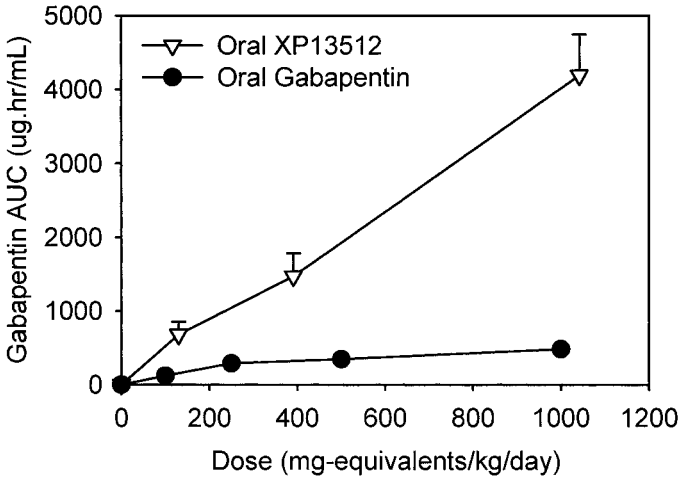

Fig. 4. Effect of prodrug dose on steady-state AUC of gabapentin in blood of monkeys after 14 days of repeated daily oral administration of XP13512 (open triangles). Data are the mean ± S.D. for three monkeys per sex. Steady-state AUC data for repeated oral dosing of gabapentin over the same dose range are shown for comparison (closed circles) (publicly available data from Neurontin NDA 20-235, Summary Basis of Approval, Federal Drug Administration).

CSF Penetration. Concentrations of gabapentin in CSF at 2 h after oral dosing of gabapentin HCl salt in rats were less than proportional to dose, increasing only 3-fold over the dose range 25 to 200 mg/kg (Fig. 6). In contrast, concentrations of gabapentin in CSF at 2 h after oral administration of equimolar doses of XP13512 sodium salt were approximately dose-proportional. At the highest dose level (200 mg-Eq GP/kg), CSF levels of gabapentin at 2 h after dosing were 2.3-fold greater for oral prodrug compared with oral gabapentin. The CSF to plasma ratio of gabapentin concentrations was independent of dose and similar for both treatments (0.13 ± 0.02 for oral gabapentin versus 0.12 ± 0.04 for oral XP13512 sodium salt at equimolar 200 mg-Eq gabapentin/kg doses). Concentrations of intact prodrug in CSF following oral administration of XP13512 sodium salt were below quantifiable levels at the 25 and 100 mg-Eq gabapentin/kg dose levels. At the highest dose level (200 mg-Eq gabapentin/kg), the concentration of XP13512 in CSF was 0.03 ± 0.12 μg/ml, or approximately 125-fold lower than the corresponding concentration of gabapentin in CSF.

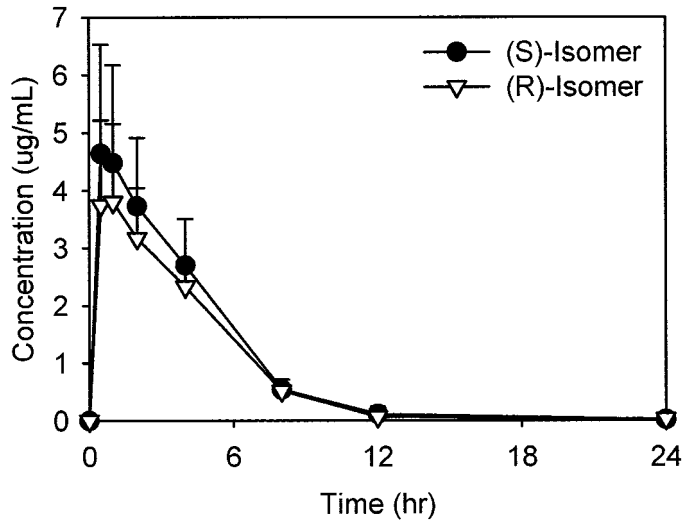

Fig. 5. Concentrations of gabapentin in plasma of rats after oral administration of the separated isomers of XP13512 at 25 mg-Eq GP/kg. Data are the mean ± S.D. for five rats.

Colonic Absorption in Rats. Bioavailability of gabapentin after intracolonic dosing of gabapentin in rats was low (3.38 ± 1.60%) (Table 1), consistent with the lack of significant colonic expression of the solute transport pathway normally responsible for absorption of gabapentin. In contrast, intracolonic administration of XP13512 produced a substantial increase in blood gabapentin levels at an equimolar dose (Fig. 7A). Intracolonic bioavailability for XP13512 suspension was 48.7 ± 4.07%, representing an increase of approximately 14-fold in the gabapentin C_{max} and AUC compared with intracolonic gabapentin (Table 2). Concentrations of intact prodrug in blood after intracolonic dosing of XP13512 were low and transient.

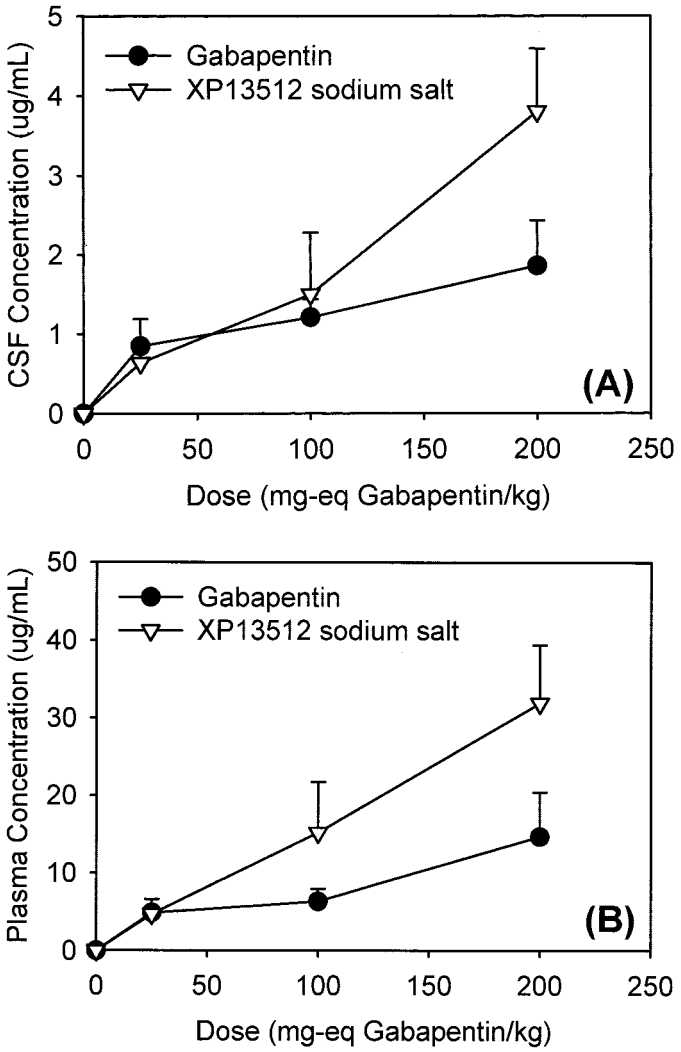

Fig. 6. Effect of dose on concentrations of gabapentin in: A, CSF; and B, plasma of rats at 2 h after oral administration of gabapentin (closed circles) or XP13512 sodium salt (open triangles). Data are the mean ± S.D. for three to six rats per data point.

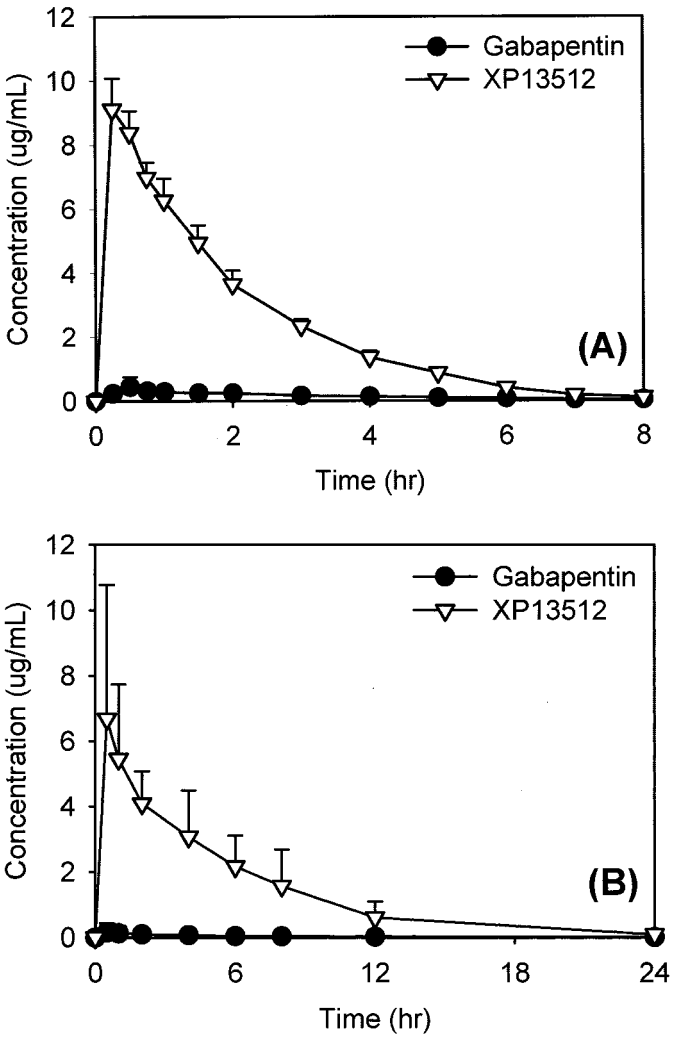

Fig. 7. Concentrations of gabapentin in plasma following intracolonic administration of equimolar doses of gabapentin (closed circles) or XP13512 (open triangles) in: A, rats at 25 mg-Eq GP/kg; and B, monkeys at 10 mg-Eq GP/kg. Data are the mean ± S.D. for six rats or three monkeys.

Colonic Absorption in Monkeys. Bioavailability of gabapentin in monkeys after intracolonic dosing of gabapentin was low (1.77%) (Table 1). In contrast, XP13512 gave a substantial increase in plasma gabapentin levels after intracolonic dosing at an equimolar dose (Fig. 7B). Bioavailability of gabapentin after intracolonic dosing of XP13512 was 60.6 ± 21.4% (Table 3). This represents a 34-fold increase in absorption compared with intracolonic gabapentin. Exposure to intact prodrug in these animals was low and variable. Gabapentin lactam was not detected in plasma of monkeys following intracolonic dosing of gabapentin HCl salt. Concentrations of lactam observed in monkey plasma after intracolonic dosing of XP13512 were negligible; the maximum concentration of gabapentin lactam in plasma was 230-fold less than the corresponding C_{max} of gabapentin. This is consistent with a low level of lactam present in the drug substance used in this study and suggests that no significant further conversion of prodrug to lactam occurred following absorption in monkeys.

Tissue Distribution and Recovery. Following oral administration of ^{14}C-labeled XP13512 to rats, radioactivity was distributed into most tissues. Highest tissue concentrations were observed in the pancreas (96.5–99.9 μg Eq/g) and kidney (57.3–64.2 μg Eq/g). Concentrations of radioactivity in most tissues were at or below 1 μg Eq/g after 24 h. More than 95% of the radioactive dose was recovered in urine in 24 h. Less than 1% was recovered in feces. Gabapentin accounted for >99% of the radioactivity recovered in urine based on HPLC analysis using radioactive flow detection. Intact XP13512 was not detected in urine. Gabapentin lactam (0.02–0.36%) and a minor polar metabolite (0.16–1.14%) were also detected in urine. Previous studies of oral ^{14}C-gabapentin in rats have reported a similar minor polar metabolite in urine accounting for <2% of total radioactivity (Radulovic et al., 1995).

SMVT Capacity Study. To assess the absorption capacity of the SMVT transporter in rat intestine, the bioavailability of biotin, an endogenous SMVT substrate, was determined after oral administration. Two groups of four male rats received single doses of biotin as a solution in polyethylene glycol 400 by intravenous injection (10 mg/kg) or oral gavage (50 mg/kg) routes. The absolute oral bioavailability of biotin

in rats at a 50 mg/kg dose was 82.6 ± 16.6% (n = 4), indicating that this transport pathway has sufficient capacity to contribute significantly to XP13512 absorption.

Discussion

The oral bioavailability of gabapentin was confirmed to be dose-dependent in both rats and monkeys, consistent with saturation of the solute transporter believed to be responsible for absorption of gabapentin from the intestine. Saturation occurred at lower gabapentin doses in monkeys (<75 mg/kg) than in rats (>100 mg/kg), possibly indicating a higher abundance of the transporter in rodent species. Although the transporter responsible for gabapentin absorption was originally thought to be an L-type amino acid transporter, it is now known that LAT1 is not significantly expressed in human intestine (Prasad et al., 1999). Furthermore, we have shown that gabapentin is also not a substrate for the intestinal amino acid transporters B0,+, ATB0,+, or LAT2 in transfected oocytes, whereas it is a substrate for the organic anion transporter OCTN2 (N. Zerangue, unpublished data). The widespread intestinal expression of OCTN2 in both the small and large intestines (Slitt et al., 2002) does not explain the lack of significant absorption of gabapentin from the colon (Kriel et al., 1997). Although OCTN2 may contribute to apical uptake of gabapentin in the intestine, an understanding of the basolateral transport of gabapentin is necessary to explain localized absorption of the drug in the upper gastrointestinal tract.

Saturation of gabapentin absorption in humans occurs at clinically relevant doses between 300 and 1600 mg (approximately 4.3–23 mg/kg) (Gidal et al., 1998). It has been reported recently that exposure to gabapentin at high oral doses increased in a linear manner (Berry et al., 2003). However, this study was based on limited data from less than 10 subjects, only four of which reached the highest dose of 4800 mg/day. Several larger clinical studies have clearly demonstrated the lack of dose proportionality for oral gabapentin (Gidal et al., 1998; Neurontin Summary Basis of Approval, NDA 20-235, U.S. Food And Drug Administration). The exact dose at which saturation occurs for a given patient is presumably a function of the level of expression of the gabapentin transport system in the intestine. For drugs that are exclusively absorbed in a narrow window of the small intestine, large interpatient variability in the rate of transit through the small intestine leads to additional variability in the extent of absorption (Birkebaek et al., 1990; Riley et al., 1992).

XP13512 was designed to utilize alternative uptake pathways with higher capacity and broader distribution than the gabapentin transporter. It was hypothesized that increased transport capacity should avoid saturation of uptake at doses used clinically, allowing for absorption of higher gabapentin doses and greater dose proportionality. Higher capacity should also reduce variability related to interpatient differences in transporter expression levels. Broader distribution should permit longer durations of absorption for sustained release formulations and reduce variability related to interpatient differences in GI transit.

The pharmacokinetic properties of XP13512 were anticipated to be superior to those of gabapentin on the basis of our in vitro studies of metabolism and transport (Cundy et al., 2004). XP13512 was rapidly hydrolyzed to gabapentin by nonspecific esterases in intestinal and liver tissues. The prodrug was also a substrate for both MCT-1 and SMVT, high-capacity transporters with broad distribution in the intestinal tract. Furthermore, XP13512 displayed pH dependent passive permeability across artificial membranes. As predicted, XP13512 was rapidly absorbed after oral administration to rats and monkeys and extensively converted to gabapentin. In contrast to oral gabapentin, absorption of the prodrug showed no evidence of saturation in either species, and exposure to gabapentin was approximately dose proportional over a wide dose range (up to 5000 mg/kg in rats and 2000 mg/kg in monkeys). The maximum concentration of gabapentin achieved in blood of monkeys dosed orally with XP13512 at 2000 mg/kg (1040 mg-Eq GP/kg) was 445 μg/ml, more than 9-fold higher than previously attainable in this species by administration of oral gabapentin at similar doses (46.9 μg/ml at a dose of 1000 mg/kg/day) (Neurontin Summary Basis of Approval, NDA 20-235, U.S. Food and Drug Administration).

Initial bioavailability studies were conducted with suspensions of XP13512. In monkeys, oral administration of a simple capsule formulation of XP13512 without any additional excipients produced a 3.2-fold higher gabapentin bioavailability than seen for commercial Neurontin capsules at an almost equivalent molar dose. This indicates that dissolution of the prodrug in vivo does not limit its absorption. XP13512 demonstrates pH dependent solubility. Solubility of the free acid is 1 mg/ml at pH 5.0, and this increases significantly at higher pH. The highest dose of XP13512 administered to rats as a suspension (5 g/kg) represents the practical limit for oral dosing in this species. The maximum human dose is anticipated to be 40 mg/kg. The fact that bioavailability remained relatively high even at the highest suspension doses in rats suggests that dissolution limitations should not be clinically significant.

Concentrations of intact prodrug in plasma or blood following oral dosing of XP13512 in rats and monkeys were low in comparison with the corresponding gabapentin concentrations. Since the in vitro conversion of XP13512 to gabapentin is similar in tissues from rats, monkeys, and humans (Cundy et al., 2004), these data suggest that minimal exposure to intact prodrug will be observed in humans at clinical doses. Repeated oral dosing of XP13512 in monkeys for 14 days was well tolerated, and no significant toxicological findings were reported at doses as high as 2000 mg/kg/day (1040 mg-Eq GP/kg/day). Therefore, the no observable adverse effect level in this study was considered to be >2000 mg/kg/day. Toxicokinetic data showed linear pharmacokinetics for gabapentin exposure at steady state after 14 days of repeated dosing in monkeys. There was no evidence of accumulation of the drug. The exposure to gabapentin at the highest XP13512 dose tested was 26-fold higher than that produced clinically by a standard regimen of 600 mg of Neurontin given three times per day (Neurontin Summary Basis of Approval, NDA 20-235, U.S. Food and Drug Administration).

The two isomers of XP13512 exhibited equivalent in vivo bioavailability as gabapentin after oral dosing in rats, indicating a lack of stereoselectivity in the absorption and cleavage of the prodrug. Previous in vitro studies also showed that the two isomers were hydrolyzed at similar rates in human tissues (Cundy et al., 2004). Furthermore, both isomers of XP13512 release the same active drug and the same achiral

promoiety fragments. In view of these facts, subsequent preclinical studies and the clinical development of XP13512 have employed the racemic compound. A similar approach has been employed in the past for the development of prodrugs possessing chiral promoieties that are lost on hydrolysis, such as candesartan cilexetil (Gleiter and Morike, 2002).

The tissue distribution and recovery of radiolabeled XP13512 in rats indicated that the prodrug was extensively absorbed after oral dosing and almost completely converted to gabapentin. Very low amounts of gabapentin lactam and a minor polar metabolite were detected in urine; no other significant metabolites of XP13512 were observed. Distribution of radioactivity into pancreas and kidney was consistent with the previously reported distribution of ^{14}C-gabapentin in rats (Radulovic et al., 1995). There was no evidence of significant accumulation in any of the tissues examined.

In other studies, increasing oral doses of gabapentin produced a nonlinear increase in CSF gabapentin concentrations of rats, whereas oral administration of the prodrug gave approximately dose-proportional CSF gabapentin exposure. The CSF levels for both treatments were proportional to plasma levels and showed a similar CSF to plasma ratio at all doses. This suggests that CNS uptake of gabapentin was not saturated in the dose range examined, and supports the hypothesis that saturation of intestinal absorption of oral gabapentin at higher doses gave rise to a less than proportional increase in CSF exposure to the drug. The improved intestinal absorption of oral XP13512 sodium salt gave rise to greater plasma exposure and hence greater CSF exposure to gabapentin. Our data appear to contradict a previous report that concentrations of gabapentin in brain ECF of rats determined by microdialysis after intravenous dosing of gabapentin indicate saturable uptake at doses between 7.5 and 60 mg/kg (Luer et al., 1999). Data on human CSF levels for gabapentin (Ben-Menachem et al., 1992, 1995) suggest poor correlation between gabapentin and CSF levels in a limited number of subjects at doses between 600 and 1200 mg/day. The CSF to plasma ratio observed for gabapentin in these studies was similar to that of other amino acids. There are insufficient data available to conclude a species difference between rat and human. Notably, concentrations of gabapentin within brain tissue of rats appear to correlate well with plasma levels (Vollmer et al., 1986).

Sustained release formulations of gabapentin have not been successfully developed to date due to the lack of significant colonic absorption of the drug (Kriel et al., 1997). Poor colonic absorption of gabapentin was confirmed in both rats and monkeys in the present study. Similar results have also been reported following direct administration of gabapentin into the colon of dogs (Stevenson et al., 1997). In contrast to gabapentin, XP13512 was well absorbed from the colon of both rats and monkeys, consistent with uptake by alternative pathways present in all segments of the intestinal tract. The greatly enhanced colonic absorption of the prodrug suggests that XP13512 is suitable for incorporation into a controlled release formulation. Such a formulation should slowly release prodrug into the large intestine, where it will be efficiently absorbed and cleaved, thereby delivering a sustained level of gabapentin in the blood. A longer duration of absorption would support less frequent dosing, leading to improved patient compliance and potentially reduced incidence of treatment failure. The sustained gabapentin levels may also reduce the severity of side effects (dizziness and somnolence) that are potentially related to peak gabapentin blood levels.

In summary, XP13512 is a novel prodrug of gabapentin that overcomes the pharmacokinetic limitations of gabapentin. The prodrug is chemically stable and is rapidly converted to gabapentin presumably by nonspecific esterases following oral absorption. In rats and monkeys, XP13512 provides improved gabapentin bioavailability and increased dose proportionality compared with oral gabapentin. Unlike gabapentin, XP13512 is well absorbed throughout the intestine, suggesting that it may be successfully incorporated into a controlled release formulation. In clinical use, XP13512 may be expected to improve the treatment of neuropathic pain, epilepsy, and numerous other conditions by providing increased gabapentin exposure, reduced interpatient variability, decreased dosing frequency, and reduced incidence of side effects.

Acknowledgments

We thank Tono Estrada, Mark Gao, Adam Mann, Cristina Pulido, Stephen P. Raillard, Tiffany Winburn, Quincey Q. Wu, Jia-Ning Xiang, and Hui Yan (XenoPort, Inc.) for additional contributions.

References

Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, LaMoreaux L, and Garofalo E (1998) Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *J Am Med Assoc* **280:**1831–1836.

Ben-Menachem E, Persson LI, and Hedner T (1992) Selected CSF biochemistry and gabapentin concentrations in the CSF and plasma in patients with partial seizures after a single oral dose of gabapentin. *Epilepsy Res* **11:**45–49.

Ben-Menachem E, Soderfelt B, Hamberger A, Hedner T, and Persson LI (1995) Seizure frequency and CSF parameters in a double-blind placebo controlled trial of gabapentin in patients with intractable complex partial seizures. *Epilepsy Res* **21:**231–236.

Berry DJ, Beran RG, Plunkett MJ, Clarke LA, and Hung WT (2003) The absorption of gabapentin following high dose escalation. *Seizure* **12:**28–36.

Birkebaek NH, Memmert K, Mortensen J, Dirksen H, and Christensen MF (1990) Fractional gastrointestinal transit time: intra- and interindividual variation. *Nucl Med Commun* **11:**247–252.

Boyd RA, Turck D, Abel RB, Sedman AJ, and Bockbrader HN (1999) Effects of age and gender on single-dose pharmacokinetics of gabapentin. *Epilepsia* **40:**474–479.

Cundy KC, Branch R, Chernov-Rogan T, Dias T, Estrada T, Hold K, Koller K, Liu X, Mann A, Panuwat M, et al. (2004) XP13512, a novel gabapentin prodrug: I. design, synthesis, enzymatic conversion to gabapentin, and transport by intestinal solute transporters. *J Pharmacol Exp Ther* **311:**315–323.

Garcia-Borreguero D, Larrosa O, de la Llave Y, Verger K, Masramon X, and Hernandez G (2002) Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. *Neurology* **59:**1573–1579.

Gee NS, Brown JP, Dissanayake VU, Offord J, Thurlow R, and Woodruff GN (1996) The novel anticonvulsant drug, gabapentin (Neurontin), binds to the alpha2delta subunit of a calcium channel. *J Biol Chem* **271:**5768–5776.

Gidal BE, DeCerce J, Bockbrader HN, Gonzalez J, Kruger S, Pitterle ME, Rutecki P, and Ramsay RE (1998) Gabapentin bioavailability: effect of dose and frequency of administration in adult patients with epilepsy. *Epilepsy Res* **31:**91–99.

Gidal BE, Radulovic LL, Kruger S, Rutecki P, Pitterle M, and Bockbrader HN (2000) Inter- and intra-subject variability in gabapentin absorption and absolute bioavailability. *Epilepsy Res* **40:**123–127.

Gleiter CH and Morike KE (2002) Clinical pharmacokinetics of candesartan. *Clin Pharmacokinet* **41:**7–17.

Guttuso T Jr, Kurlan R, McDermott MP, and Kieburtz K (2003) Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. *Obstet Gynecol* **101:**337–345.

Juel C and Halestrap AP (1999) Lactate transport in skeletal muscle: role and regulation of the monocarboxylate transporter. *J Physiol* **517:**633–642.

Kelly KM (1998) Gabapentin: antiepileptic mechanism of action. *Neuropsychobiology* **38:**139–144.

Kriel RL, Birnbaum AK, Cloyd JC, Ricker BJ, Jones Saete C, and Caruso KJ (1997) Failure of absorption of gabapentin after rectal administration. *Epilepsia* **38:**1242–1244.

Luer MS, Hamani C, Dujovny M, Gidal B, Cwik M, Deyo K, and Fischer JH (1999) Saturable transport of gabapentin at the blood-brain barrier. *Neurol Res* **21:**559–562.

Marais E, Klugbauer N, and Hofmann F (2001) Calcium channel alpha(2)delta subunits-structure and gabapentin binding. *Mol Pharmacol* **59:**1243–1248.

McLean MJ (1995) Gabapentin. *Epilepsia* **36 (Suppl 2):**S73–S86.

McLean MJ (1999) Gabapentin in the management of convulsive disorders. *Epilepsia* **40 (Suppl 6):**S39–S50.

Pollack MH, Matthews J, and Scott EL (1998) Gabapentin as a potential treatment for anxiety disorders. *Am J Psychiatry* **155:**992–993.

Prasad PD, Wang H, Huang W, Kekuda R, Rajan DP, Leibach FH, and Ganapathy

V (1999) Human LAT1, a subunit of system L amino acid transporter: molecular cloning and transport function. *Biochem Biophys Res Commun* **16:**283–288.
Radulovic L, Turck D, Von Hodenberg A, Vollmer K, McNally W, Dehart P, Hanson B, Bockbrader H, and Chang T (1995) Disposition of gabapentin (Neurontin) in mice, rats, dogs and monkeys. *Drug Metab Dispos* **23:**441–448.
Rice AS and Maton S (2001) Postherpetic Neuralgia Study Group: gabapentin in postherpetic neuralgia: a randomised, double blind, placebo controlled study. *Pain* **94:**215–224.
Richter A, Anton SE, Koch P, and Dennett SL (2003) The impact of reducing dose frequency on health outcomes. *Clin Ther* **25:**2307–2335.
Riley SA, Sutcliffe F, Kim M, Kapas M, Rowland M, and Turnberg LA (1992) The influence of gastrointestinal transit on drug absorption in healthy volunteers. *Br J Clin Pharmacol* **34:**32–39.
Rowbotham M, Harden N, Stacey B, Bernstein P, and Magnus-Miller L (1998) Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *J Am Med Assoc* **280:**1837–1842.
Said HM, Ortiz A, McCloud E, Dyer D, Moyer MP, and Rubin S (1998) Biotin uptake by human colonic epithelial NCM460 cells: a carrier-mediated process shared with pantothenic acid. *Am J Physiol* **275:**C1365–C1371.
Slitt AL, Cherrington NJ, Hartley DP, Leazer TM, and Klassen CD (2002) Tissue distribution and renal developmental changes in rat organic cation transporter mRNA levels. *Drug Metab Dispos* **30:**212–219.
Stevenson CM, Kim J, and Fleisher D (1997) Colonic absorption of antiepileptic agents. *Epilepsia* **38:**63–67.
Stewart BH, Kugler AR, Thompson PR, and Bockbrader HN (1993) A saturable transport mechanism in the intestinal absorption of gabapentin is the underlying cause of the lack of proportionality between increasing dose and drug levels in plasma. *Pharm Res (NY)* **10:**276–281.
Uchino H, Kanai Y, Kim do K, Wempe MF, Chairoungdua A, Morimoto E, Anders MW, and Endou H (2002) Transport of amino acid-related compounds mediated by L-type amino acid transporter 1 (LAT1): insights into the mechanisms of substrate recognition. *Mol Pharmacol* **61:**729–737.
Vollmer KO, von Hodenberg A, and Kolle EU (1986) Pharmacokinetics and metabolism of gabapentin in rat, dog and man. *Arzneim-Forsch* **36:**830–839.
Wang H, Huang W, Fei YJ, Xia H, Yang-Feng TL, Leibach FH, Devoe LD, Ganapathy V, and Prasad PD (1999) Human placental Na^+-dependent multivitamin transporter: cloning, functional expression, gene structure and chromosomal localization. *J Biol Chem* **274:**14875–14883.

Address correspondence to: Dr. Kenneth C. Cundy, XenoPort, Inc., 3410 Central Expressway, Santa Clara, CA 95051. E-mail: kcundy@xenoport.com