Arbaclofen Placarbil, a Novel R-Baclofen Prodrug: Improved Absorption, Distribution, Metabolism, and Elimination Properties Compared with R-Baclofen

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ABSTRACT

Baclofen is a racemic GABA receptor agonist that has a number of significant pharmacokinetic limitations, including a narrow window of absorption in the upper small intestine and rapid clearance from the blood. Arbaclofen placarbil is a novel transported prodrug of the pharmacologically active R-isomer of baclofen designed to be absorbed throughout the intestine by both passive and active mechanisms via the monocarboxylate type 1 transporter. Arbaclofen placarbil is rapidly converted to R-baclofen in human and animal tissues in vitro. This conversion seems to be primarily catalyzed in human tissues by human carboxylesterase-2, a major carboxylesterase expressed at high levels in various tissues including human intestinal cells. Arbaclofen placarbil was efficiently absorbed and rapidly converted to R-baclofen after oral dosing in rats, dogs, and monkeys. Exposure to R-baclofen was proportional to arbaclofen placarbil dose, whereas exposure to intact prodrug was low. Arbaclofen placarbil demonstrated enhanced colonic absorption, i.e., 5-fold higher R-baclofen exposure in rats and 12-fold higher in monkeys compared with intracolonic administration of R-baclofen. Sustained release formulations of arbaclofen placarbil demonstrated sustained R-baclofen exposure in dogs with bioavailability up to 68%. In clinical use, arbaclofen placarbil may improve the treatment of patients with gastroesophageal reflux disease, spasticity, and numerous other conditions by prolonging exposure and decreasing the fluctuations in plasma levels of R-baclofen.

Baclofen (R,S-baclofen, also termed racemic baclofen) is a structural analog of GABA that has been used in the United States since 1977 for treatment of spasticity and other neurologic disorders (Novartis, 1977). The drug has also shown efficacy in various placebo-controlled trials in gastroesophageal reflux disease (GERD) (Vela et al., 2003) and acute back spasms (Dapas et al., 1985). The clinical pharmacokinetics of baclofen has been studied in healthy volunteers (Wuis et al., 1989) and patients with spasticity (Wuis et al., 1990).

Oral and intravenous administration of radiolabeled R,S-baclofen to rats, dogs, and humans demonstrate that R,S-baclofen is virtually completely absorbed from the gastrointestinal tract in all species examined (Faigle and Keberle, 1972; Faigle et al., 1980). In humans, baclofen is rapidly absorbed after oral administration (T<sub>max</sub> ~ 2 h) and the drug is eliminated largely unchanged via renal excretion (>80% of ingested dose).

Baclofen (R,S-baclofen, also termed racemic baclofen) is a structural analog of GABA that has been used in the United States since 1977 for treatment of spasticity and other neurologic disorders (Novartis, 1977). The drug has also shown efficacy in various placebo-controlled trials in gastroesophageal reflux disease (GERD) (Vela et al., 2003) and acute back spasms (Dapas et al., 1985). The clinical pharmacokinetics of baclofen has been studied in healthy volunteers (Wuis et al., 1989) and patients with spasticity (Wuis et al., 1990). Oral baclofen has a number of significant pharmacokinetic limitations. It is only absorbed in the upper small intestine by saturable active transport mechanisms. In addition, baclofen has a short half-life of 3 to 4 h and is rapidly cleared from the blood. As a result, baclofen needs to be administered frequently (three or four times per day) to maintain therapeutic effects (Novartis, 1977; Wuis et al., 1990; Schwarz

ABBREVIATIONS: GERD, gastroesophageal reflux disease; Caco-2, human colonic adenocarcinoma cell line; hCE-1 and hCE-2, human carboxylesterase-1 and -2; HPLC, high-performance liquid chromatography; LC/MS/MS, liquid chromatography-tandem mass spectrometry; LLC-PK1, renal epithelial cell line derived from porcine kidney cells; MCT-1, monocarboxylate transporter type 1; MDDCK, Madin-Darby canine kidney; MRM, multiple reaction monitoring; RB, R-baclofen; S9, 9000g supernatant; SN-38, 7-ethyl-10-hydroxy-20(S)-camptothecin; XP19986 (also known as arbaclofen placarbil), [(R)-4-chloro-3-[[[(2-methyl-1-(S)-(2-methyl-1-oxoproxy)propoxy]carbonyl]-amino]methyl]-benzenepropionic acid].
Pharma, 2003). Even with frequent dosing, there are fluctuations in circulating plasma drug levels. Frequent dosing is inconvenient and may lead to significant noncompliance. The most important dose-limiting adverse effects of baclofen therapy (e.g., somnolence, dizziness, motor weakness, and fatigue) are potentially related to peak drug concentrations, as indicated by their time course in preclinical studies with baclofen. The optimal exposure to \( R \)-baclofen for the treatment of spasticity or GERD may be a stable therapeutic plasma concentration. Because of limited absorption of baclofen in the large intestine, attempts to develop a sustained release formulation of the drug have not been successful (Merino et al., 1989).

Arbaclofen placarbil (also known as XP19986) is a novel transported prodrug of the pharmacologically active \( R \)-isomer of baclofen (Fig. 1) that is currently in clinical development for the treatment of GERSD, spasticity, and acute back spasms. Arbaclofen placarbil was designed to be efficiently absorbed by high-capacity transport pathways expressed throughout the gastrointestinal tract and rapidly metabolized to release \( R \)-baclofen after absorption. Unlike baclofen, arbaclofen placarbil was designed to be well absorbed from the colon, allowing the drug to be delivered in a sustained release formulation that may allow for less frequent dosing and reduced fluctuations in plasma exposure. In this turn may lead to potentially improved efficacy through a combination of greater duration of action, greater subject convenience, and an improved safety profile compared with baclofen.

The purpose of the current work was to evaluate the in vitro metabolism and transport properties of arbaclofen placarbil and the pharmacokinetics and distribution of \( R \)-baclofen after administration of the prodrug in preclinical species.

**Materials and Methods**

**Materials.** \( R \)-Baclofen (\( R \)-4-amino-3-(4-chlorophenyl)-butyric acid) was obtained from Excella Pharma Source (Feucht, Germany).

Arbaclofen placarbil (XP19986) and a potential \( \gamma \)-hydroxy metabolite of \( R \)-baclofen were synthesized by XenoPort, Inc. (Santa Clara, CA). \(^3\)H-Arbaclofen placarbil was synthesized from \(^3\)H-\( R \)-baclofen by XenoPort by similar methods. \(^{14} \)C-Lactate (162 mCi/mmol) was from GE Healthcare (Piscataway, NJ). Clopidogrel and SN-38 were purchased from ChemPacific (Baltimore, MD). Clopidogrel carboxylate was obtained from Toronto Research Chemicals Inc. (North York, ON, Canada) and irinotecan from Beta Pharma (New Haven, CT). All other chemicals were obtained from Sigma-Aldrich (St. Louis, MO). Monkey, dog, and rat tissue (liver, kidney, lung, and intestine) S9 (9000 ng supernatant) preparations and human liver and kidney S9 preparations were obtained from Xenotech LLC (Lenexa, KS). Human lung and intestinal S9 preparations were from In Vitro Technologies, Inc. (Baltimore, MD). Human plasma was from Tennessee Blood Services, Inc. (Memphis, TN). Rat plasma was from Pel-Freez Biologicals (Rogers, AR). Plasma was frozen and maintained at \(-80^\circ C\) before use. Rat colonic wash (pooled) was prepared by flushing dissected colon with modified Dulbecco's phosphate-buffered saline (without calcium chloride and magnesium chloride) pH 7.1–7.5; Sigma-Aldrich). Monkey colonic wash was prepared similarly and provided by Sierra Biochemical, Inc. (Sparks, NV). Caco-2 S9 was prepared from cultured Caco-2 cells grown in flasks over 21 days.

**Synthesis of Arbaclofen Placarbil**

**Step 1.** 1-Chloro-2-methylpropyl chloroformate was reacted with sodium methyliolate, resulting in the formation of \( O-(1\text{-chloroisobut oxy})\)-S-methyl thiocarbonate. This product was then reacted with tetrathymylammonium isobutyrate to produce \( O-(1\text{-isobutanyloxyisobutyroxy})\)-S-methyl thiocarbonate.

**Step 2.** \( (\text{-}\)-Dibenzoyl-tartaric acid was reacted with acetic anhydride, resulting in the formation of \( (3\text{-R,AR})\)-2,5-dioxo-3,4-dibenzoyloxoy-3,4-dihydrofuran. This product was then reacted with hydroxyamine to give 1-hydroxy-(\( 3\text{-R,AR})\)-2,5-dioxo-3,4-dibenzoyloxyppyrrolidine.

**Step 3.** The products from steps 1 and 2 were reacted with per-acetic acid to afford \( (1\text{-S})\)-1\(-(3\text{-R,AR})\)-2,5-dioxo-3,4-dibenzoyloxyppryrolidinyloxy carbonyl oxy)-2-methylpropyl-2-methylpropanoate.

**Step 4: Preparation of Arbaclofen Placarbil** (Fig. 1). \( R \)-Baclofen was reacted with \( (1\text{-S})\)-1\(-(3\text{-R,AR})\)-2,5-dioxo-3,4-dibenzoxypyrrolidinyloxy carbonyloxy)-2-methylpropyl-2-methylpropanoate, resulting in the desired product (2) (Fig. 1) as a white solid in 90% yield.

**In Vitro Metabolism Studies**

**Chemical Stability.** Buffers were prepared at pH 2.0 (0.1 M potassium phosphate and 0.5 M sodium chloride), pH 7.4 (0.1 M Tris-HCl and 0.5 M sodium chloride), and pH 8.0 (0.1 M Tris-HCl and 0.5 M sodium chloride). Compounds (5 \( \mu \)M) were incubated with buffers at 37°C for 1 h in a temperature-controlled HPLC autosampler. Samples were injected at zero and 1 h after addition and analyzed by LC/MS/MS as described below.

**Metabolic Stability.** Arbaclofen placarbil (5 \( \mu \)M) was incubated with the following matrices at 37°C for 1 h: 90% rat or human plasma; rat and human liver S9 preparations at 0.5 mg of protein/ml in the presence of 1 mM NADPH at pH 7.4; Caco-2 S9 preparation (0.5 mg of protein/ml) at pH 7.4; porcine pancreatic (10 mg/ml in pH 7.5 buffer); rat or monkey colonic wash.

For determination of the rate of conversion to \( R \)-baclofen (pmol/min/mg protein or pmol/min/ml plasma), arbaclofen placarbil (10 \( \mu \)M) was incubated with plasma, intestinal S9, lung S9, liver S9, and kidney S9 from rats, dogs, monkeys, and humans at 37°C. All preparations contained 1 mg of protein/ml. Samples were obtained at intervals over 1 h after addition and were immediately quenched with methanol to prevent further conversion. Quenched samples were frozen and maintained at \(-80^\circ C\) before analysis. Samples were analyzed by LC/MS/MS as described below. Potential formation of the \( \gamma \)-hydroxy metabolite of \( R \)-baclofen by deamination of arbaclofen placarbil was examined by incubating 50 \( \mu \)M arbaclofen placarbil at
Identification of Isobutyric Acid from Hydrolysis of Arbaclofen Placarbil. Verification of the hydrolysis of arbaclofen placarbil to release isobutyric acid was conducted by incubating arbaclofen placarbil at 1 mM with or without 0.25 mg/ml human intestinal S9 in 10 mM phosphate buffer, pH 7.4, for 1 h at 37°C, with use of human intestinal S9 without arbaclofen placarbil as a control. Similar experiments were also conducted with human liver S9. After incubation, the reactions were quenched with methanol and the resulting mixtures were centrifuged and filtered. The supernatant was evaporated to dryness, and the residue was reconstituted with methanol and injected into a gas chromatograph equipped with mass spectrometric detector as described in the section of analytical methods.

Metabolism by CYP450 Isoforms. Studies were also performed to determine the role of specific CYP450 isozymes in the metabolism of arbaclofen placarbil by use of human liver S9 and standard inhibitors of each isozyme: furafylline (CYP1A2), sulfaphenazole (CYP2C9), tranilcypromine (CYP2C19), quinidine (CYP2D6), diethyldithiocarbamic acid (CYP2E1), and ketoconazole (CYP3A4). All experiments used 1 mM NADPH as the cofactor and were conducted in a 96-well format. Human liver S9 fractions (0.5 mg/ml) were preincubated with each inhibitor, and arbaclofen placarbil (5 μM) was added to initiate the experiment. The disappearance of arbaclofen placarbil was examined over the course of 10 min at 37°C. Samples were obtained at 0 and 10 min after addition and were immediately quenched with methanol to prevent further conversion. Samples were analyzed by LC/MS/MS as described below.

Metabolism by Human Carboxylesterase-1 and -2. hCE-1 or hCE-2 cDNA inserted into the pENTR2221 vector were obtained from Invitrogen (Carlsbad, CA) and subsequently subcloned into pTR-EX-DEST30 vector (Invitrogen). HEK cells conditionally expressing hCE-1 or hCE-2 were isolated by transfecting the hCE expression plasmid into T-REx-293 cells (Invitrogen) and selecting for G418-resistant clones and identifying clones with robust tetracycline-inducible expression according to the manufacturer’s instructions. Cells of the chosen clones were then scaled up, treated with or without tetracycline, and microsomal fractions were subsequently isolated from these cells.

The known hCE-1 substrate clopidogrel (60 μM) and the hCE-2 substrate irinotecan (3 μM) were each incubated with microsomes prepared from hCE-1, hCE-2, or nonexpressing cells at 37°C for 10 min. The reaction was quenched by addition of an equal volume of acetonitrile followed by centrifugation. The resulting supernatant was analyzed by LC/MS/MS to determine the formation of clopidogrel carboxylate and SN-38 from clopidogrel and irinotecan, respectively. A common substrate for both hCE-1 and hCE-2, phenylacetate (1 mM), was also incubated with the above-mentioned components of transport, respectively.

In Vivo Studies

Formulations. R-Baclofen hydrochloride was dissolved in water for intravenous, intracolonic, or oral administration. Arbaclofen placarbil free acid was dissolved in phosphate buffer saline, pH 7.4, for intravenous administration and suspended in 0.5% methyl cellulose/1% Tween 80 for oral and intracolonic administration.

Tablet formulations. One controlled release formulation (CR2) based on coated-bead technology (immediate release beads of arbaclofen placarbil overcoated with a pH-sensitive polymer filled into hydropropylmethyl cellulose capsules) and three sustained release tablet formulations (SR1, SR2, and SR3) based on polymer matrix technology were developed.

Animals. All studies were conducted in accordance with the Guide for the Care and Use of Laboratory Animals (National Re-
search Council Publication, National Academy Press, Washington, DC) and were approved by an Institutional Animal Care and Use Committee. Male Sprague-Dawley rats (-250 g) were obtained from Charles River Laboratories, Inc. (Wilmington, MA) with indwelling jugular vein cannulas. For colonic studies, rats were further cannulated in the proximal colon just distal to the cecum. All animals were acclimated for >48 h on site before study. The tissue distribution and recovery study was conducted in male and female Sprague-Dawley rats at MDS Pharma Services (Montreal, QC, Canada). The monkey study was conducted at MPI Research Corporation (Muttawann, MI) with use of male cynomolgus monkeys (mean body weight, -2.4 kg).

Two groups of male beagle dogs were used for the pharmacokinetic studies (mean body weight, -10.0 kg) conducted at MPI Research Corporation. All animals were fasted overnight and for the first 4 h of the study. Water was provided ad libitum.

Intravenous Pharmacokinetics. Two groups of male Sprague-Dawley rats (6–7 rats/group) received intravenous bolus injections of R-baclofen hydrochloride at 10 mg-equivalents of R-baclofen/kg (mg-Eq RB/kg) or arbaclofen placarbil free acid administered at 1 mg-Eq RB/kg via a tail vein. R-Baclofen hydrochloride was also administered intravenously to four male cynomolgus monkeys and to one group of four male beagle dogs at 1 mg-Eq RB/kg.

Colonic Absorption. R-Baclofen hydrochloride solution and arbaclofen placarbil suspension (10 mg-Eq RB/kg; 2.5 ml/kg) were each administered to groups of four to six male rats as a bolus injection directly into the colon via the indwelling cannula. Blood samples were obtained via the jugular cannula at intervals over 8 h. For intracolonic dosing in monkeys, a flexible French catheter was inserted into the rectum of each monkey and extended to the proximal colon (~16 inches) by use of fluoroscopy. Monkeys were lightly sedated by administration of Telazol/ketamine during dosing. R-Baclofen hydrochloride solution and arbaclofen placarbil suspension were each administered as a bolus injection directly into the colon of four monkeys via the colonic catheter at a dose of 5 mg-Eq RB/kg. Blood samples were obtained at intervals over 24 h after dosing. For intracolonic dosing in dogs, a Foley catheter was inserted into the rectum of each animal and extended to the proximal colon. Arbaclofen placarbil suspension was administered as a bolus injection directly into the colon of four dogs via the colonic catheter at a dose of 5 mg-Eq RB/kg (1 ml/kg). Blood samples were obtained at intervals over 12 h.

Oral Bioavailability. Additional groups of male rats (7 rats/group) received the following treatments by oral gavage: R-baclofen hydrochloride at 1, 5, 10, or 25 mg-Eq RB/kg; arbaclofen placarbil free acid at 1, 5, 10, or 25 mg-Eq RB/kg. Blood samples were obtained at intervals over 24 h after dosing. In monkeys, the same animals each received two sequential treatments by oral gavage as follows: R-baclofen hydrochloride solution and arbaclofen placarbil free acid suspension at 5 mg-Eq RB/kg with a 5- to 7-day washout between treatments. In dogs, the same animals each received two sequential treatments by oral gavage as follows: R-baclofen hydrochloride solution and arbaclofen placarbil free acid suspension at 5 mg-Eq RB/kg with a 5- to 7-day washout between treatments. A second set of four male beagle dogs each received consecutive oral treatments by gavage as follows: CR2 capsules, SR1, SR2, and SR3 tablets at 10 mg with a 5- to 7-day washout between treatments. Blood samples were obtained from all animals at intervals over 48 h after dosing.

Tissue Distribution and Recovery. Male and female rats (12/sex) received a single oral dose of 3H-R-baclofen or 3H-arbaclofen placarbil (labeled at the carbon atom adjacent to the amino group) (~1 mg-Eq RB/kg; 280 μCi/kg) as a solution in phosphate-buffered saline, pH 7.4. Urine and feces were collected at intervals over 168 h. A panel of 22 different tissues was excised from three animals per sex at each of 0.5, 6, and 24 h after dosing. Concentrations of radioactivity were determined by standard liquid scintillation methodods after homogenization and dissolution. Urine samples were subjected to further analysis for potential metabolites with use of HPLC with radioactive flow detection (Flo-One Beta, PerkinElmer Life and Analytical Sciences, Waltham, MA).

Analytical Methods

In Vitro Studies. The γ-hydroxy metabolite of R-baclofen was monitored in negative ion mode with MRM transition of 212.9 and 151.1 with limit of detection of approximately 0.25 μM. The analytical methods for arbaclofen placarbil, R-baclofen lactam, and R-baclofen were essentially the same as in vivo studies described below. Similar analytical methods were used for clopidogrel carboxylate, SN-38, except that 4000 QTRAP instrument (Applied Biosystems, Foster City, CA) was used, and the MRM transitions (amu) were 308.0 and 198.2 for clopidogrel carboxylate and 393.2 and 349.3 for SN-38. The ranges for quantification were 0.05 to 10 μM for clopidogrel carboxylate and 0.5 to 50 nM for SN-38.

To demonstrate the formation of isobutyric acid released from arbaclofen placarbil, an analytical procedure with gas chromatogram/mass spectrometry method for isobutyric acid was developed. Samples (1 μl) were directly injected into a CP-3800 gas chromatograph equipped with a Saturn 2200 ion trap mass spectrometry detector from Varian (Palo Alto, CA). A CP-Wax 52 CB fused silica column (30 m × 0.25 mm i.d., 0.25 μm film thickness; Varian) is preceded by a 5 m × 0.25 mm uncoated ( deactivated, intermediate-polarity) guard column from Restek (Bellefonte, PA). Helium was used as the carrier gas at the flow rate of 1 ml/min. The oven temperature was programmed at 40°C for 4 min, increased to 220°C at 8°C/min, and finally held at this temperature for 4 min. The temperature in the injection port was held at 220°C. The temperatures of MS transfer line and ionization chamber were set at 270°C and 150°C, respectively, and the trap emission current of 10 μA was used. The full-scan mode (40–200 m/z mass range) was recorded during the run, and the filament was turned on at 5 min. The retention time of isobutyric acid was approximately 16 min. The gas chromatography/mass spectrometry method for isobutyric acid was linear over the concentration range from 0.1 to 1 mM. The limit of quantification for isobutyric acid was 100 μM.

In Vivo Studies. To minimize the potential for postsampling conversion of prodrug to R-baclofen, blood samples were directly quenched with methanol on collection. Samples were analyzed by a sensitive and specific LC/MS/MS method for simultaneous determination of prodrug and R-baclofen. Quenched samples were injected on a Phenomenex Synergy Hydro-RP column (4 μm; 50 × 4.6 mm) (Phenomenex, Torrance, 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 1200 μl/min (200 μl/min to the detector). The gradient was 5% B for 0.5 min, rising to 95% B over 1.3 min, remaining at 95% for another 1.2 min, then returning to 5% B. The detector was an API 2000 LC/MS/MS (Applied Biosystems), and the MRM transitions (amu) were 400/240 for arbaclofen placarbil, 196/144 for R-baclofen lactam, and 214/151 for R-baclofen. The injection volume was 20 μl. The method was linear for arbaclofen placarbil, R-baclofen lactam, and R-baclofen over the concentration range of 0.004 to 10 μg/ml. The limit of quantitation for all three analytes was 0.004 μg/ml.

Pharmacokinetic Analysis. Concentration data for prodrug and R-baclofen in blood were analyzed by noncompartmental methods by use of WinNonlin (Pharsight Corp., Mountain View, CA). The maximum concentration (C(max)) and time to C(max) (T(max)) were observed by observation. After intravenous administration, an initial concentration (C0) was estimated by backextrapolating to time 0 by use of a log-linear regression of the first two concentration values. The apparent elimination half-life (t1/2) 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-inf)) was obtained by the linear trapezoidal method. The bioavailability (F) of R-baclofen after oral or intracolonic dosing of R-baclofen or prodrug was calculated by comparison of dose-normalized AUC values to data for intravenous R-baclofen.
Results

In Vitro Metabolism

Chemical and Metabolic Stability of Arbaclofen Placarbil. Arbaclofen placarbil was chemically stable for 1 h at 37°C over the pH range 2 to 8. Table 1 shows the extent of conversion of arbaclofen placarbil to R-baclofen after incubation with various buffers and tissue preparations. Hydrolysis of arbaclofen placarbil to R-baclofen was slow in human plasma, pancreatin, monkey or rat colonic wash, but rapid in Caco-2 cell S9 fraction, rat plasma, and human and rat liver S9 fraction. Release of R-baclofen was quantitative and no R-baclofen lactam (3) (Fig. 1), was detected in any of the incubations (limit of detection 1%).

Metabolic Stability of Arbaclofen Placarbil in Tissue Preparations from Various Species. Similar rates of hydrolysis of arbaclofen placarbil to R-baclofen were seen in liver and plasma from four different species (Table 2), except that rate of hydrolysis was higher in rat plasma. The rates of conversion in kidney and lung S9 fractions were in the rank order of monkey > dog > rat > human. In intestinal S9 fractions, the rate of conversion of arbaclofen placarbil to R-baclofen followed the rank order of monkey > rat > dog > human. In addition, the potential γ-hydroxy metabolite of R-baclofen (4) (Fig. 1) was not detected after incubation of arbaclofen placarbil with rat and human liver S9 fractions in the presence of NADPH.

Formation of Isobutyric Acid from Hydrolysis of Arbaclofen Placarbil. After incubation of arbaclofen placarbil with human intestinal S9 in phosphate buffer, isobutyric acid was released, as based on coelution of the primary metabolite peak with isobutyric acid standard on the gas chromatogram. No isobutyric acid peak was detected in S9 blank extract. The mass spectrum of the metabolite peak formed from arbaclofen placarbil in the presence of human intestinal S9 was also identical to that of the isobutyric acid standard. Similar results were also obtained in the experiments with human liver S9.

CYP450 Metabolism Studies. Arbaclofen placarbil was not a substrate for CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 in human liver S9.

TABLE 1
Stability of arbaclofen placarbil in buffers and tissue preparations
All incubations were for 1 h at 37°C. The initial arbaclofen placarbil concentration was 5 μM. R-Baclofen lactam was not detected in any of the incubations (<1% release).

<table>
<thead>
<tr>
<th>Tissue Preparation</th>
<th>Arbaclofen Placarbil Remaining</th>
<th>R-Baclofen Released</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buffer, pH 2.0</td>
<td>100</td>
<td>ND</td>
</tr>
<tr>
<td>Buffer, pH 7.4</td>
<td>100</td>
<td>ND</td>
</tr>
<tr>
<td>Buffer, pH 8.0</td>
<td>100</td>
<td>ND</td>
</tr>
<tr>
<td>Pancreatin</td>
<td>90</td>
<td>6</td>
</tr>
<tr>
<td>Caco-2 S9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>17</td>
<td>83</td>
</tr>
<tr>
<td>Rat plasma, 90%</td>
<td>14</td>
<td>85</td>
</tr>
<tr>
<td>Human plasma, 90%</td>
<td>98</td>
<td>2</td>
</tr>
<tr>
<td>Rat liver S9</td>
<td>3</td>
<td>97</td>
</tr>
<tr>
<td>Human liver S9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3</td>
<td>97</td>
</tr>
<tr>
<td>Rat colonic wash</td>
<td>93</td>
<td>7</td>
</tr>
<tr>
<td>Monkey colonic wash</td>
<td>98</td>
<td>2</td>
</tr>
</tbody>
</table>

ND, not detected (<1%).

<sup>a</sup>Porcine pancreatin was 10 mg/ml in pH 7.5 buffer.
<sup>b</sup>Caco-2 S9 was 0.5 mg/ml protein at pH 7.4.
<sup>c</sup>Liver S9 contained 0.5 mg/ml protein and 1 mM NADPH at pH 7.4.

Carboxylesterase Metabolism Studies. Clopidogrel and irinotecan, selective substrates of hCE-1 and hCE-2 (Humerickhouse et al., 2000; Tang et al., 2006), respectively, were used to verify the level of expression of these enzymes in the microsomal preparations from conditionally expressing cells. Table 3 shows that the formation of clopidogrel carboxylate from clopidogrel was 35-fold higher with microsomes expressing hCE-1 than its control microsomes, and no increased activity was observed with hCE-2 enzymes. The formation of SN-38 from irinotecan was 29-fold higher with microsomes expressing hCE-2 than its control microsomes, and no increased activity was observed with hCE-1 enzymes. Therefore, the substrate selectivity of the microsomal preparations was consistent with the literature (Humerickhouse et al., 2000; Tang et al., 2006). The relative level of expression of hCE-1 and hCE-2 in microsomes was assessed with use of p-nitrophenylacetate, a common substrate for these two enzymes (Xie et al., 2002). As shown in Table 3, hydrolysis rates of p-nitrophenylacetate were increased with microsomes expressing hCE-1 or hCE-2 compared with their respective controls, and the activities for hCE-1 and hCE-2 were comparable (1.4 versus 1.7 μmol/min, respectively). The results of incubation of arbaclofen placarbil with microsomes expressing hCE-1 or hCE-2 are presented in Table 3. These data show that R-baclofen formation from arbaclofen placarbil was increased by 3-fold and 19-fold with expressed hCE-1 and hCE-2 enzymes, respectively, compared with their respective control microsomes. The specific activity of hCE-2 for hydrolysis of arbaclofen placarbil was approximately 29-fold greater than that of hCE-1 after correcting for the relative expression of these two enzymes in the microsomal preparations based on the data for the hydrolysis of p-nitrophenylacetate. These data indicate that hydrolysis by hCE-2 is the major pathway of arbaclofen placarbil metabolism, whereas conversion by hCE-1 is only a minor pathway.

In Vitro Transport Studies

Transport Across Polarized Cell and Artificial Lipid Membranes. Table 4 compares the epithelial cell permeability of R-baclofen and arbaclofen placarbil determined in Caco-2 and MDCK cell monolayers (P<sub>app</sub>), and the passive permeability (P<sub>app</sub>) of these compounds determined in the parallel artificial membrane permeability assay. Data were compared with control compounds with high (propranolol and diltiazem) and medium (metoprolol) passive permeability properties. The calculated apparent permeability constants (P<sub>app</sub> for R<sub>app</sub> and P<sub>app</sub>) for R-baclofen were low in both mammalian cell types and in the artificial membrane system, consistent with poor passive absorption. Transport of arbaclofen placarbil across the artificial membrane was significantly higher than the permeability of R-baclofen itself. In addition, the permeability was affected by pH with P<sub>app</sub> values 20-fold higher at pH 6.0 than at 7.4, suggesting that the prodrug has higher passive permeability properties in its uncharged state. Arbaclofen placarbil was partially hydrolyzed during transit through the mammalian cells. The P<sub>app</sub> value for arbaclofen placarbil, determined from the sum of the prodrug and released R-baclofen appearing in the receiving chamber, was greater than 5 × 10⁻⁵ cm/s in both cell types, suggesting that the prodrug will be efficiently absorbed in vivo (Stewart et al., 1995). In addition, transport of the prodrug in the apical-to-basolateral direction was ap-
proximately 3-fold greater than in the basolateral-to-apical direction.

**MCT-1-Mediated Transport.** Both arbaclofen placarbil and \( R \)-baclofen were tested for their ability to compete with uptake of \(^{14}C\)-lactate, a natural substrate for MCT-1, in LLC-PK1-derived cells expressing high levels of MCT-1 (Fig. 2). The prodrug inhibited the uptake of lactate with an IC\(_{50}\) of 1.1 mM, whereas \( R \)-baclofen did not significantly interact with MCT-1. The direct uptake of arbaclofen placarbil into MCT-1-expressing oocytes was greater than into nonexpressing oocytes (Fig. 3), as measured by LC/MS/MS, and no detectable uptake of \( R \)-baclofen was measured in these oocytes incubated with \( R \)-baclofen alone. Uptake of arbaclofen placarbil into nonexpressing oocytes may have been the result of passive diffusion or transport by an endogenous monocarboxylate transporter reported to be expressed in *Xenopus* oocytes (Tosco et al., 2000).

### In Vivo Studies

**Intravenous Pharmacokinetics.** After intravenous bolus administration of \( R \)-baclofen to rats, dogs, and monkeys, \( R \)-baclofen was cleared with an apparent blood half-life ranging from 1.6 to 3.4 h (Table 5). Total blood clearance was 0.51 ± 0.11 l/h/kg in rats, monkeys, and dogs, respectively. The corresponding steady-state volume of distribution was 0.11 ± 0.01 l/kg in rats, monkeys, and dogs, respectively. The corresponding steady-state volume of distribution was 967 ± 718 ml/kg at ASPET Journals on May 18, 2017 jpet.aspetjournals.org Downloaded from
pressed as picomoles per second per oocyte (mean ± S.E.) were determined by LC/MS/MS. Intracellular concentrations of the prodrug (3H-arbaclofen) were determined by LC/MS/MS with the ion trap mass spectrometer (Fig. 3). The bioavailability, determined as released R-baclofen, from intracolonic dosing of arbaclofen placarbil suspension was 37 ± 9% in rats and 37 ± 15% in monkeys (Table 5), representing an increase of approximately 5-fold and 12-fold, respectively, compared with intracolonic R-baclofen (Table 5). Bioavailability of R-baclofen in dogs after intracolonic dosing of arbaclofen placarbil was also high (77 ± 23%) (Table 8).

Concentrations of intact prodrug in blood after intracolonic dosing of arbaclofen placarbil were low. The exposure to arbaclofen placarbil (based on AUC) in blood was approximately 190-fold, 60-fold, and 200-fold, respectively, lower than the corresponding R-baclofen AUC.

The formation of R-baclofen lactam, a potential metabolite of arbaclofen placarbil from the prodrug was not significant after oral dosing in preclinical species. At the highest prodrug dose, R-baclofen lactam C_max was approximately 100-fold lower than the corresponding R-baclofen C_max in rats and monkeys and approximately 15-fold lower in dogs (data on file).

**Colonic Absorption.** Bioavailability of R-baclofen after intracolonic dosing of R-baclofen was low, 7 ± 3% in rats and 3 ± 2% in monkeys (Table 5), consistent with the lack of significant colonic expression of the solute transport pathway normally responsible for absorption of R-baclofen. In contrast, intracolonic administration of arbaclofen placarbil produced a substantial increase in blood R-baclofen levels at an equimolar dose (Fig. 4). The bioavailability, determined as released R-baclofen, from intracolonic dosing of arbaclofen placarbil suspension was 37 ± 9% in rats (Table 6) and 37 ± 15% in monkeys (Table 7), representing an increase of approximately 5-fold and 12-fold, respectively, compared with intracolonic R-baclofen (Table 5). Bioavailability of R-baclofen in dogs after intracolonic dosing of arbaclofen placarbil was also high (77 ± 23%) (Table 8).

Concentrations of intact prodrug in blood after intracolonic dosing of arbaclofen placarbil were low. The exposure to arbaclofen placarbil (based on AUC) in blood was approximately 6-fold, 40-fold, and 30-fold lower than the corresponding R-baclofen AAC in rats, monkeys, and dogs, respectively.

Concentrations of R-baclofen lactam in blood after intracolonic dosing of arbaclofen placarbil were also low; the maximum concentration of R-baclofen lactam in blood was 60-fold less than the corresponding C_max of R-baclofen in rats and monkeys and 6-fold lower in dogs (data on file).

**Formulation Evaluation.** Various solid oral dosage formulations of arbaclofen placarbil were developed and evaluated in dogs in an effort to identify a suitable sustained/controlled release formulation for twice-daily dosing in clinical studies (Fig. 5). Bioavailability of R-baclofen after oral dosing of the controlled release formulation (CR2) of arbaclofen placarbil was 46 ± 28% (Table 8). The resulting T_max of R-baclofen was 3.5 h.

The bioavailability as released R-baclofen in dogs after dosing sustained release formulations of arbaclofen placarbil was: 68 ± 6% (SR1), 62 ± 8% (SR2), and 27 ± 19% (SR3) (Table 8). The corresponding T_max values of R-baclofen in blood were 3.6 h, 3.0 h, and 6.5 h, respectively.

**Tissue Distribution and Recovery.** There were no significant differences in the tissue distribution, excretion, and metabolite profiles of R-baclofen after oral dosing of either 3H-R-baclofen or 3H-arbaclofen placarbil in rats. After oral administration of 3H-arbaclofen placarbil to rats, radioactivity was relatively widely distributed throughout the body. Highest tissue concentrations were observed in the kidneys (16–18 μg-Eq/g) and liver (2–3 μg-Eq/g). Concentrations of radioactivity in most tissues were below 1 μg-Eq/g after 24 h. Between 84 and 88% of the radioactive dose was recovered in urine in 24 h. Less than 1% of the radioactive dose was recovered in feces. R-Baclofen accounted for approximately 97% of the radioactivity recovered in urine based on HPLC analysis using radioactive flow detection. Intact prodrug and
R-baclofen lactam were not detected in urine. The γ-hydroxy metabolite accounted for 1.9 to 3.2% of radioactivity recovered in urine.

**Discussion**

Arbaclofen placarbil is a transported prodrug of the pharmacologically active R-isomer of baclofen, a GABA_\text{A} agonist, that was designed to be absorbed throughout the gastrointestinal tract by high-capacity nutrient transporters. Reversible modification of either the amine or carboxylate functionalities of R-baclofen yields compounds that are monoanionic or monocarboxylic at physiological pH. Derivatization of the carboxylic acid group of R-baclofen as a simple ester prodrug proved impractical, however, because such compounds readily cyclize to yield R-baclofen lactam. Reversible masking of the amine group of R-baclofen with an acetyloxalkyl carbamoyl promoiety (as in arbaclofen placarbil) provided anionic compounds that were potential substrates for monocarboxylate transporters expressed apically along the length of the intestine, including the colon. It is noteworthy that arbaclofen placarbil does not undergo cyclization to the lactam in vitro or in vivo.

MCT-1 is a member of a family of at least nine gene products that function as proton-coupled transporters of simple organic carboxylates, such as lactate, pyruvate, and short-chain fatty acids, and certain monocarboxylate drugs (e.g., pravastatin, valproate, carindacilin) (Halestrap and Price, 1999; Enerson and Drewes, 2003). MCT-1 is highly expressed within small and large intestinal tissue, and contributes to the high-capacity (grams per day) uptake into
colonocytes of butyrate produced by microbial fermentation of carbohydrates.

Arbaclofen placarbil combines properties required for recognition by MCT-1 with nontoxic breakdown products. Arbaclofen placarbil is an acyloxyalkyl carbamate prodrug of R-baclofen, and prodrugs of this class are known to undergo esterase-mediated hydrolysis to release the parent amine (i.e., R-baclofen), and components of the promoiety (an acid, an aldehyde, and carbon dioxide) (Gallop et al., 2005). Therefore, arbaclofen placarbil is expected to undergo enzymatic hydrolysis to form R-baclofen, and equimolar amounts of isobutyric acid, isobutyraldehyde, and carbon dioxide. The formation of isobutyric acid was confirmed in vitro with use of gas chromatography and mass spectrometry. Although isobutyraldehyde and carbon dioxide are expected to be side products as well, they present difficulties for measurement because of the volatile nature of these compounds.

Arbaclofen placarbil had 1 mM affinity for MCT-1 in competition studies with transporter-expressing cultured cells based on inhibition of uptake of natural substrates. Because affinity alone is not a definitive proof of transport, direct uptake of arbaclofen placarbil by MCT-1 was also demonstrated. Transport of arbaclofen placarbil was confirmed by demonstrating uptake into *Xenopus laevis* oocytes expressing human MCT-1 to a significantly greater extent than nonexpressing oocytes.

Transcellular flux of arbaclofen placarbil across Caco-2 cell monolayers was 3-fold greater in the apical to basolateral direction than in the basolateral to apical direction, suggesting that the prodrug interacts with one or more apically expressed intestinal transporters. MCT-1 is expressed at high levels in Caco-2 cells (Stein et al., 2000). The high apparent permeability of arbaclofen placarbil observed in this assay (2.3–6.2 × 10⁻⁵ cm/s) suggests that the compound

<table>
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<tr>
<th>Route</th>
<th>Form</th>
<th>Dose</th>
<th>n</th>
<th>Analyte</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (µg/ml)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</th>
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<tr>
<td>p.o.</td>
<td>Suspension</td>
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<td>3</td>
<td>R-Baclofen</td>
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<td>3.6 ± 0.4</td>
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<td>Prodrug</td>
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<tr>
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<td>4</td>
<td>R-Baclofen</td>
<td>0.09 ± 0.07</td>
<td>3.5 ± 1.9</td>
<td>5.0 ± 1.3</td>
<td>0.78 ± 0.53</td>
<td>46 ± 26</td>
</tr>
<tr>
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<td>SR1</td>
<td>10 mg&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4</td>
<td>R-Baclofen</td>
<td>0.10 ± 0.03</td>
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NA, not applicable.

<sup>a</sup> F is calculated relative to R-baclofen at 1 mg/kg i.v. (mean data).

<sup>b</sup> Arbaclofen placarbil dose.

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**Fig. 4.** Concentrations of R-baclofen in blood after intracolonic administration of equimolar doses of R-baclofen (○) or arbaclofen placarbil (△) in rats at 10 mg-Eq RB/kg (A) and monkeys at 5 mg-Eq RB/kg (B). Data are the mean ± S.D. for six rats or four monkeys.

**Fig. 5.** Concentrations of R-baclofen in blood of dogs after oral administration of arbaclofen placarbil sustained release formulations at 10 mg and suspension formulation at 0.2 mg-Eq RB/kg. Note: R-Baclofen concentrations for suspension formulation were dose-normalized from 5 mg-Eq RB/kg to 0.2 mg-Eq RB/kg. Data are the mean ± S.D. for three to four dogs.
should be well absorbed in vivo after oral administration. Similar evidence of active transport was observed with use of MDCK cell monolayers. The flux of arbaclofen placarbil in the parallel artificial membrane permeability suggests that the prodrug should have some ability to passively diffuse across cells depending on local pH. The pKₐ of arbaclofen placarbil is 4.4, and therefore passive diffusion of the unionized form probably is a minor component of the extensive absorption seen after colonic dosing.

The relative contributions of active transport and passive absorption to the total absorption of arbaclofen placarbil in humans depend on multiple factors, including the specific region of the intestine involved, the relative expression of MCT-1 within that region, the transit time, surface area, and the local pH. In the absence of specific animal or human models with deletion mutations for MCT-1, it is not possible to definitively determine the relative contributions of these processes in vivo. MCT-1 is a high-capacity transporter, and therefore, competition from endogenous ligands is unlikely to affect the absorption of arbaclofen placarbil. Likewise, at the doses contemplated for clinical use, oral administration of the prodrug is unlikely to affect absorption of endogenous ligands. The potential for uptake of arbaclofen placarbil by additional transporters such as the bicarbonate/small-chain fatty acid anion exchangers present in the human colon has not been studied.

Arbaclofen placarbil was chemically stable at physiological pH but was rapidly hydrolyzed to R-baclofen in S9 fractions of Caco-2 cells and rat or human liver. No other metabolites were observed. R-Baclofen lactam (3) (Fig. 1) and the γ-hydroxy metabolite of R-baclofen (4) (Fig. 1) were both considered as potential metabolites of arbaclofen placarbil, although neither was detected in the in vitro incubations. These results suggest that the prodrug would have sufficient luminal stability to be absorbed and would subsequently undergo extensive first-pass conversion to R-baclofen.

In preclinical species, arbaclofen placarbil produced dose-proportional exposure to R-baclofen after single and multiple oral dosing, with limited systemic exposure to the intact prodrug. Oral administration of arbaclofen placarbil in animals resulted in 44 to 94% bioavailability as R-baclofen, and bioavailability of R-baclofen after intracolonic dosing of arbaclofen placarbil was 5- to 12-fold greater than that from an equimolar intracolonlic dose of R-baclofen. These data led to the development of sustained release formulations of arbaclofen placarbil that would potentially deliver the prodrug throughout the gastrointestinal tract, thereby providing prolonged R-baclofen exposure in the systemic circulation.

Concentrations of intact prodrug in blood after oral dosing of arbaclofen placarbil in rats, dogs, and monkeys were low compared with the corresponding R-baclofen concentrations. Because the in vitro conversion of arbaclofen placarbil to R-baclofen is similar in tissues from rats, dogs, monkeys, and humans, these data suggest that minimal exposure to intact prodrug is likely to be observed in humans at clinically efficacious doses.

The tissue distribution and recovery of radioactivity in rats after dosing of 3H-labeled R-baclofen or arbaclofen placarbil indicated that the prodrug was extensively absorbed after oral dosing and almost completely converted to R-baclofen. Very low amounts of R-baclofen lactam and a minor polar metabolite were detected in urine; no other significant metabolites of arbaclofen placarbil were observed. Tissue distribution was essentially identical for both treatments. There was no evidence of significant accumulation in any of the tissues examined. The prodrug also did not alter the penetration of R-baclofen into cerebrospinal fluid (data on file).

Poor colonic absorption of R-baclofen was confirmed in both rats and monkeys in the present study. In contrast, arbaclofen placarbil was well absorbed from the colon of rats, dogs, and monkeys, consistent with uptake by alternative pathways present in all segments of the intestinal tract. The greatly enhanced colonic absorption of the prodrug has enabled incorporation of arbaclofen placarbil into sustained release formulations. The sustained release formulations of arbaclofen placarbil based on coated bead or polymer matrix technology demonstrated extended release up to 18 h in vitro dissolution tests. The dissolution rates of arbaclofen placarbil in these formulations ranked in the order (fastest to slowest) of CR2 > SR2 > SR1 > SR3 formulations (data on file). The in vivo absorption profiles, determined as released R-baclofen, were very consistent with in vitro dissolution behavior. All sustained release formulations delayed the peak R-baclofen concentration to 3 to 6.5 h compared with 0.3 h in the suspension formulation (Fig. 5) and provided sustained R-baclofen exposure in dogs with oral bioavailability ranging from 27 to 68% (Table 8). These results suggest that sustained therapeutic levels of R-baclofen may be achieved with once- or twice-daily dosing of arbaclofen placarbil. This may potentially reduce the incidence and severity of adverse effects (such as dizziness and somnolence) related to peak R-baclofen blood levels.

Arbaclofen placarbil was shown to have no significant interaction with the major CYP450 isozymes in vitro as a substrate, an inhibitor (data on file) or an inducer (data on file). The conversion of arbaclofen placarbil to R-baclofen appears to be catalyzed by human carboxylesterase-2, a major carboxylesterase expressed at high levels in various tissues including human intestinal cells (Imai, 2006). Therefore, the likelihood of significant drug-drug interactions after administration of arbaclofen placarbil in the clinic is considered to be low. Drug interactions as a result of competition for active transport pathways are also considered to be unlikely, based on the high capacity of the transporters targeted for arbaclofen placarbil absorption.

In summary, arbaclofen placarbil is a novel prodrug of R-baclofen that overcomes the pharmacokinetic limitations of R-baclofen. The prodrug is efficiently absorbed and rapidly converted to R-baclofen by nonspecific esterases. In rats, oral dosing of arbaclofen placarbil produced dose-proportional exposure to R-baclofen with limited exposure to intact prodrug. In dogs and monkeys, arbaclofen placarbil provided greater R-baclofen bioavailability than oral dosing of R-baclofen. Unlike R-baclofen, arbaclofen placarbil is well absorbed throughout the intestine, allowing it to be successfully incorporated into a sustained release formulation. Prototype sustained release formulations of arbaclofen placarbil have demonstrated sustained delivery of R-baclofen in dogs. In clinical use, arbaclofen placarbil may be expected to improve the treatment of patients with GERD, spasticity, and numerous other conditions by decreasing frequency of dosing, decreasing the fluctuations in plasma exposure, and potentially reducing incidence of side effects.
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Novartis (1977) Lioresal® NDA 17-851 and Summary Basis of Approval, Novartis, Basel, Switzerland.


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