Human Pharmacokinetics and Disposition of Sarmoxicillin, a Lipophilic Amoxicillin Prodrug

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Sarmoxicillin, an amoxicillin prodrug, is the methoxymethyl ester of hemoximocillin. Esterification converted amoxicillin from an amphoteric compound and resulted in a 30- to 600-fold increase in lipid partitioning. Oral absorption studies in normal subjects demonstrated that sarmoxicillin was only partially hydrolyzed by nonenzymatic and gut or hepatic first-pass metabolism and that significant quantities of intact ester appeared in the systemic circulation. Sarmoxicillin was converted to amoxicillin in plasma by hydrolysis of the acetone penicinate and the methoxymethyl ester bonds. Significant amoxicillin levels were demonstrated in saliva after administration of sarmoxicillin, but not amoxicillin, over a 250- to 1,000-mg dose range. Differences in the absorption, distribution, or metabolism of amoxicillin were also evident in the lower plasma amoxicillin maximum concentration and area under the curve and longer half-life after sarmoxicillin administration. Differences in the distribution of this lipophilic ester could result in a significant increase in tissue penetration and subsequent therapeutic efficacy of amoxicillin when administered as sarmoxicillin.

Sarmoxicillin, the methoxymethyl ester of hemoximocillin (Fig. 1), has the same in vitro antimicrobial spectrum as amoxicillin (Bristol Laboratories, unpublished data). However, esterification of the carboxyl group results in a significant change in the physicochemical and tissue distribution characteristics of amoxicillin. Esterification converts amoxicillin from an amphoteric (18) (pK, 2.4, 7.4, 9.6) to a cationic (pK, 7.4, 9.6) compound with increased lipophilicity at physiological pH. Increased cerebrospinal and prostatic fluid concentrations of antibiotic activity have been demonstrated in dogs with the methoxymethyl ester of betacillin as compared with ampicillin (9, 10). Ampicillin ester prodrugs have also been prepared to improve bioavailability. Although the pivaloyloxymethyl (pivampicillin) (2), phthalidyl (salmampicillin) (7), and ethoxycarbonyloxymethyl (bacampicillin) (6) esters have at least twofold-greater oral bioavailability than ampicillin, these esters are almost completely hydrolyzed in the gastrointestinal mucosa and appear in the portal circulation as ampicillin. The methoxymethyl ester of ampicillin is only partially hydrolyzed by gut and hepatic first-pass metabolism and appears in the systemic circulation and tissues as intact ester (11).

The purpose of the present studies was to characterize the physicochemical properties, absorption, distribution in saliva, metabolism, and elimination of sarmoxicillin and amoxicillin in man.

MATERIALS AND METHODS

Formulations were as follows: formulation A, sarmoxicillin tablet, 250 mg of anhydrous amoxicillin-equivalent activity per tablet; formulation B, amoxicillin capsules, 250 mg of anhydrous amoxicillin-equivalent activity per capsule; formulation C, capsule containing ground sarmoxicillin tablet, 125 mg of anhydrous amoxicillin-equivalent activity sealed at capsule interface and polished to remove any surface contamination. Sarmoxicillin, hetamoxicillin, and amoxicillin trihydrate were used as supplied for analytical standards and in vitro studies. All bulk chemicals and formulations were synthesized and prepared at Bristol Laboratories in accordance with good manufacturing practices.

Partition coefficient. The partition coefficients of sarmoxicillin and amoxicillin between n-octanol or chloroform and 0.1 M KCl-HCl (pH 2), 0.1 M citrate (pH 3), and 0.1 M phosphate (pH 6, 7.4, and 8) buffers were determined with equal volumes of buffer and octanol at 25°C by conventional procedures (4). The compounds were dissolved in buffer at a concentration of 100 to 150 µg/ml, and concentrations were determined in the aqueous phase after partitioning by measuring absorbance at 270 nm.

Stability. The stability of sarmoxicillin and amoxicillin was determined in fresh human, rhesus monkey, dog, rabbit, and rat sera. 0.1 N HCl, and 0.1 M phos-
SARMOCILLIN (METHOXYMETHYL-6-[2,2,2-DIMETHYL-5-0XO-4-(4-HYDROXYPHENYL)-1-IMIDAZOLIDINYL]-3,3 DIMETHYL-7-0XO-4-THIA-L-AZABICYCLO (3.2.0) HEPTANE - 2 - CARBOXYLATE )

AMOXICILLIN - METHOXYMETHYL ESTER

AMOXICILLIN

Fig. 1. Hydrolysis of sarmoxicillin.

The study subjects were healthy adult males between the ages of 21 and 35 years weighing 70 to 90 kg. There were 24 subjects in phase I and 36 subjects in phase II. Informed consent was obtained from all subjects. Complete physical examinations were performed 1 week before and after the dosing period.

In phase I, two sarmoxicillin tablets (formulation A) or four capsules (formulation C) were administered to the 24 subjects in a balanced crossover design with a 1-day interval between doses. Blood and saliva samples were collected at zero time (immediately before dosing) and at 5, 10, 20, 30, 40, 60, and 75 min. A postdose mouth rinse was immediately collected. Details of dosing and sample collection are described below.

In phase II, the 36 subjects were administered sar- moxicillin tablets (formulation A) and amoxicillin capsules (formulation B). They were divided into three groups of 12 subjects each. Each group received sarmoxicillin and amoxicillin at one of the three dose levels (250, 500, and 1,000 mg) with a complete crossover in order of formulation administration. There was a 3-day interval between successive doses in any given subject. Saliva and blood samples were collected just before dosing (zero time) and at 5, 10, 20, 30, and 40 min and 1, 1.25, 1.5, 2, 3, 4, 6, and 8 h. Urine collections were made just before dosing (zero time) and over the intervals of 0 to 2, 2 to 4, 4 to 8, 8 to 12, and 12 to 24 h. The interval between doses proved to be sufficient since no detectable activity was ever found in any subject’s zero time plasma samples.

The subjects were fasted from midnight of each study day but could have water ad libitum. They were instructed to swallow the individual tablets or capsules without rolling them around in their mouths. Each capsule or tablet was swallowed singly with 50 ml of water. The total dosing volume was 200 ml; subjects receiving the 250-mg dose swallowed an additional 150 ml of water, and subjects receiving the 500-mg dose swallowed an additional 100 ml of water. Each subject then rinsed his mouth with an additional 200 ml of water in small portions, which were then expectorated into a sink, followed by another mouth rinse with 20 ml of water, 10 ml of which was saved for bioassay. This entire dosing and rinsing procedure was scheduled to occupy a 1-min interval.

Blood samples were collected in 15-ml heparinized Vacutainer tubes. The blood was cooled in iced ice for 3 to 5 min and centrifuged for 5 min at 3,000 rpm at 5°C. Two samples of plasma, one containing a minimum of 2 ml and the other containing a minimum of 4 ml, were transferred to polypropylene tubes.

Each subject drank 200 ml of water at 2 and 4 h after dosing to assure adequate urine output. Total urine output over a collection interval was voided into a separate clean plastic bottle which was kept refrigerated. The volume and pH of the urine sample were then recorded, and two 10-ml urine samples were then transferred to polypropylene tubes.

The subjects were instructed to place glass marbles in their mouths and roll them around for 3 min before and 3 min after each scheduled saliva collection time to induce saliva secretion. A minimum of 3 ml of saliva was collected and placed in polypropylene tubes.

Immediately after transfer to the polypropylene
tubes, all samples were flash-frozen in an ethanol-dry ice bath and maintained at or below -20°C until thawed for assay. All samples were assayed within 1 month.

(ii) Study 2. The objective of study 2 was to determine the multiple-dose pharmacokinetics and safety of sarmoxicillin and amoxicillin. Twenty healthy adult male subjects between the ages of 18 and 38 years weighing 70 to 90 kg participated in this study. Informed consent was obtained and physical examinations were performed as described for study 1. Ten subjects received sarmoxicillin tablets, and 10 subjects received amoxicillin capsules at a dose of 250 mg every 8 h on study days 1 through 3 and 500 mg every 8 h on study days 4 through 10.

Plasma, urine, and saliva samples were collected, stored and analyzed on study days 1, 3, 4, and 10 as previously described for study 1.

Sample analysis. Total amoxicillin equivalent activity (ester plus true amoxicillin) in plasma, saliva, and urine was determined by standard cup plate bioassay procedures (5) using Sarcina lutea ATCC 9341 as the bioassay organism and amoxicillin trihydrate as the reference standard.

Sarmoxicillin (ester) was separated from amoxicillin in biological fluids by adding 1.0 ml of 0.1 M phosphate buffer (pH 7) and 2.0 ml of chloroform to one ml of plasma (or saliva), shaking for 5 min, and centrifuging to isolate the organic phase. The chloroform extract was then applied to 0.25-in. (ca. 6.25-mm) paper disks (no. 740E, Schleicher & Schuell Co.) and assayed by a disk procedure (5) with S. lutea ATCC 9341 as the bioassay organism and sarmoxicillin as the analytical standard. Prepared plasma and urine standards containing known concentrations of sarmoxicillin or amoxicillin were assayed for ester and amoxicillin activity to determine specificity, stability, and recovery through the preparation, shipping, storage, and bioassay procedures. Sarmoxicillin and amoxicillin were stable in plasma, urine, and saliva under these storage conditions (-20°C, 1 month).

Amoxicillin was not chloroform extractable and did not interfere with the sarmoxicillin assay. The total antibiotic concentration was equivalent to true amoxicillin plus sarmoxicillin derived from in vitro hydrolysis of sarmoxicillin on the assay plate. The recovery of amoxicillin and sarmoxicillin from plasma standards was >90%.

The lower limits of detection for the assay procedures were 0.02 µg/ml for the total amoxicillin-equivalent activity cup plate assay and 0.1 µg/ml for the sarmoxicillin (ester) disk assay. True amoxicillin concentrations were determined by subtracting ester concentrations from total amoxicillin activity concentrations. All concentrations, including those for ester, are reported as anhydrous amoxicillin-equivalent concentrations. The linear range for the amoxicillin assay was 0.02 to 0.1 µg/ml and for the sarmoxicillin (ester) assay was 0.1 to 1.0 µg/ml of diluted biological fluid. The precision of the assay for amoxicillin and sarmoxicillin as determined on replicate samples within and between days was 10% (coefficient of variation).

Pharmacokinetic analysis. The time \( t_{\text{max}} \) to reach the observed maximum concentration \( C_{\text{max}} \) in plasma and saliva was determined from the concentra-

Table 1. Lipid partition coefficients of sarmoxicillin and amoxicillin

<table>
<thead>
<tr>
<th>Compound</th>
<th>pH</th>
<th>Partition coefficient*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>Sarmoxicillin</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>7.4</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>1.4</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>2</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>7.4</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>0.03</td>
</tr>
</tbody>
</table>

* Partition coefficient is the concentration in n-octanol/concentration in buffer, I; n-octanol; II, chloroform organic phase.
dimethyl sulfoxide. The hydrolysis scheme is presented in Fig. 1.

The hydrolysis of sarmoxicillin to amoxicillin is presented in Table 2. Sarmoxicillin disappeared from human, dog, and monkey sera with a half-life of 20 to 25 min, with the appearance of amoxicillin and 8 to 16% degradation to antibiotically inactive compounds. Hydrolysis was 2 to 5 times faster in rabbit and rat sera with 33% degradation to inactive compounds in the rabbit serum. Nonezymatic hydrolysis was demonstrated in pH 1.2 (t1/2, 27 min) and 7.4 (t1/2, 16 min). Although sarmoxicillin was not degraded at pH 1.2, extensive degradation was observed in phosphate buffer at pH 7.4. Degradation did not occur in 1:1 phosphate buffer-human serum solution.

Human study no. 1. (i) Phase I: sarmoxicillin administration. Antibiotic activity was not detected in mouth rinses after oral administration of two ground sarmoxicillin tablets in capsules (formulation C). Of the 24 subjects, 2 had detectable amoxicillin levels (0.06 and 0.6 µg/ml in the final mouth rinse at 5 min), and two subjects had high saliva levels of antibiotic activity (4.6 and 7.3 µg/ml) in the absence of detectable plasma levels after two sarmoxicillin tablets (formulation A). The comparative mouth rinse-saliva-plasma level profiles led to the decision to reject initial saliva levels when there were detectable mouth rinse levels, saliva levels in the absence of plasma levels, and initially high saliva levels which decreased to a minimum and then rose again.

Amoxicillin and sarmoxicillin were detected in saliva and plasma after oral administration of ground tablets in capsules (formulation C) and intact tablets (formulation A) (Table 3). The onset and rise in saliva concentrations were more delayed with formulation C than A, presumably due to the time required for capsule disintegration.

(ii) Phase II: amoxicillin administration. The Cmax and AUC of plasma amoxicillin were dose proportional and indicative of linear pharmacokinetics over an amoxicillin dose range of 250 to 1,000 mg (Fig. 2 and Table 4). The apparent plasma clearance (Clp) was 0.365 liter/kg per h. Comparison to the reported value for amoxicillin Clp after intravenous administration (0.320 liter/kg per h) (16) indicated that oral amoxicillin was 88% bioavailable.

Urinary excretion of amoxicillin accounted for 48 ± 10% of the dose in 12 h (Table 4). There was no significant difference in the percent urinary recovery of amoxicillin over the 250 to 1,000-mg dose range, and the renal clearance (Clr) was 0.182 liter/kg per h. Comparison to the reported Clr for amoxicillin after intravenous administration (0.18 liter/kg per h) (16) also supported the use of the reported intravenous Clr as the true plasma clearance. Apparent nonrenal clearance, the difference between Clp and Clr (0.18 liter/kg per h), could be due to biliary excretion and metabolic clearance of amoxicillin (16).

### Table 2. Hydrolysis of sarmoxicillin to amoxicillin in aqueous systems and serum

<table>
<thead>
<tr>
<th>Solution</th>
<th>t1/2* (min)</th>
<th>Degradation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human serum</td>
<td>25</td>
<td>7.5</td>
</tr>
<tr>
<td>Human serum, 4°C</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>Dog serum</td>
<td>21</td>
<td>15.9</td>
</tr>
<tr>
<td>Monkey serum</td>
<td>20</td>
<td>15.2</td>
</tr>
<tr>
<td>Rabbit serum</td>
<td>13</td>
<td>32.6</td>
</tr>
<tr>
<td>Rat serum</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>0.1 N HCl (pH 1.2)</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>0.1 M phosphate (pH 7.4)</td>
<td>16</td>
<td>40</td>
</tr>
<tr>
<td>0.1 M phosphate (pH 7.4)-human serum (1:1)</td>
<td>25</td>
<td>0</td>
</tr>
</tbody>
</table>

* t1/2, Half life for disappearance of sarmoxicillin.
* Degradation to antibiotically inactive compounds in 1 h.
* All incubations were performed at 37°C unless indicated otherwise.

### Table 3. Plasma and saliva concentrations of sarmoxicillin and amoxicillin after oral administration of formulations A and C (human study no. 1, phase I)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Fluid</th>
<th>Assay</th>
<th>Concn (µg/ml) at*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0 min</td>
</tr>
<tr>
<td>A Plasma</td>
<td>Ester</td>
<td>0 (0)</td>
<td>0.06 (0.12)</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin</td>
<td>0 (0)</td>
<td>0.03 (0.06)</td>
</tr>
<tr>
<td></td>
<td>Ester</td>
<td>0 (0)</td>
<td>0.6 (1.2)</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin</td>
<td>0 (0)</td>
<td>0.7 (1.6)</td>
</tr>
<tr>
<td>C Plasma</td>
<td>Ester</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin</td>
<td>0 (0)</td>
<td>0.02 (0.04)</td>
</tr>
<tr>
<td></td>
<td>Ester</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin</td>
<td>0 (0)</td>
<td>0.01 (0.03)</td>
</tr>
</tbody>
</table>

* All values are expressed as mean with standard deviation in parentheses.
* Ester is sarmoxicillin.
Salivary concentrations of amoxicillin after oral amoxicillin administration were sporadic and variable (Table 4). Amoxicillin could not be detected in saliva at the 250-mg dose. At the 500-mg dose, 9 of 12 subjects had detectable saliva amoxicillin (0.03 to 0.07 μg/ml) at anywhere from 1 to 6 h. At the 1,000-mg dose, 2 of 12 subjects had detectable saliva amoxicillin (0.04 to 0.2 μg/ml). The best estimate of salivary amoxicillin half-life at the 1,000 mg dose was 2.6 ± 1.7 h.

**Phase II: sarmoxicillin administration.**
Plasma and saliva concentrations of intact ester (sarmoxicillin) and amoxicillin after oral administration of 250, 500, and 1,000 mg of sarmoxicillin are presented in Fig. 3, 4, and 5. Sarmoxicillin and amoxicillin were both detected in plasma and saliva. The pharmacokinetic parameters are listed in Table 5. The plasma half-life (t₁/₂, 0.35 h) and t //</ref>

**Table 4. Pharmacokinetic parameters for amoxicillin (human study no. 1, phase II) after oral administration of amoxicillin**

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Plasma</th>
<th></th>
<th>Saliva</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt; (μg/ml)</td>
<td>t&lt;sub&gt;max&lt;/sub&gt; (min)</td>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
</tr>
<tr>
<td>250</td>
<td>3.8 (1.2)</td>
<td>89 (29)</td>
<td>1.1 (0.1)</td>
</tr>
<tr>
<td>500</td>
<td>6.4 (1.7)</td>
<td>106 (40)</td>
<td>1.1 (0.3)</td>
</tr>
<tr>
<td>1,000</td>
<td>10 (2)</td>
<td>108 (39)</td>
<td>1.3 (0.5)</td>
</tr>
</tbody>
</table>

<sup>a</sup> All values expressed as mean with standard deviations in parentheses.

<sup>b</sup> Percent recovery of amoxicillin dose in 24 h.
Comparison of saliva levels after amoxicillin and sarmoxicillin indicated that both the levels and profiles of total antibiotic activity were dependent on the presence of intact ester in plasma. There were appreciable levels of amoxicillin in saliva after sarmoxicillin administration. The mean peak levels, reached by 30 to 45 min, were 0.2 µg/ml at 250 mg, 0.3 µg/ml at 500 mg, and 0.5 µg/ml at 1,000 mg. The mean saliva amoxicillin half-lives apparently increased with increasing dose (P < 0.05): 37 min at 250 mg, 50 min at 500 mg, and 115 min at 1,000 mg. This increase in half-life could be due to the ability to analyze more of a polyexponential curve as saliva levels increased above the minimum detectable concentrations at the higher sarmoxicillin doses.

The saliva amoxicillin C_max and AUC increased linearly with sarmoxicillin dose over a range of 250 to 1,000 mg. Linear regression analyses of the ratio of salivary antibiotic concentration (sarmoxicillin plus amoxicillin) to plasma ester concentration at specific times indicated that there was a superproportional increase (P < 0.01) in saliva uptake with increasing dose (Fig. 6) and that the ratio increased with time because the elimination of sarmoxicillin from saliva was slower than from plasma (t_1/2 of saliva, 37 to 115 min; t_1/2 of plasma, 21 min).

**Human study no. 2.** There was no evidence for accumulation of amoxicillin or sarmoxicillin in plasma or urine after chronic administration of sarmoxicillin or amoxicillin at a dose of 250 mg every 8 h on study days 1 through 3 and 500

**Table 5. Pharmacokinetic parameters for sarmoxicillin and amoxicillin after oral administration of sarmoxicillin (human study no. 1, phase II)**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose (mg)</th>
<th>Plasma</th>
<th>Saliva</th>
<th>% Urine^a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C_max (µg/ml)</td>
<td>t_max (h)</td>
<td>t_1/2 (h)</td>
<td>AUC (µg*h/ml)</td>
</tr>
<tr>
<td>Sarmoxicillin</td>
<td>250</td>
<td>1.0 (0.6)</td>
<td>0.5 (0.1)</td>
<td>0.31 (0.16)</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>1.2 (0.3)</td>
<td>0.5 (0.5)</td>
<td>0.31 (0.11)</td>
</tr>
<tr>
<td></td>
<td>1,000</td>
<td>1.8 (0.7)</td>
<td>0.4 (0.2)</td>
<td>0.43 (0.17)</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>250</td>
<td>2.3 (0.5)</td>
<td>1.4 (0.6)</td>
<td>1.42 (0.30)</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>3.7 (0.9)</td>
<td>1.4 (0.7)</td>
<td>1.72 (0.57)</td>
</tr>
<tr>
<td></td>
<td>1,000</td>
<td>5.9 (1.7)</td>
<td>1.4 (1.0)</td>
<td>1.62 (0.30)</td>
</tr>
</tbody>
</table>

^a All values are expressed as mean with standard deviation in parentheses.

^b Percent recovery of amoxicillin dose in 24 h.

**Fig. 4. Mean plasma concentration of amoxicillin after oral administration of (△) 250 mg, (○) 500 mg, and (●) 1,000 mg of sarmoxicillin.**

**Fig. 5. Mean saliva concentration of amoxicillin after oral administration of (△) 250 mg, (○) 500 mg, and (●) 1,000 mg of sarmoxicillin.**

```
Amoxicillin 250
Sarmoxicillin
or
with
two
subjects
moxicillin
significant side effects with
cal
and urine
not
were
every
min
43
of amoxicillin
t1/2
decreased
tually
ministration
with
served
6). [53]
concentrations with time
to
8
FIG.
89
electrocardiog
8
mucosa and appear
in the systemic circulation as ampicillin (12).
Although orally administered sarmoxicillin is
hydrolyzed in the intestinal lumen or mucosa and
in the absorption process, a significant quantity reaches the systemic circulation as in-
tact ester. The lower amoxicillin Cmax and AUC
with sarmoxicillin as compared with those found
with an equivalent dose of amoxicillin could be
due to the more extensive extravascular penetra-
tion of the lipophilic ester or to decreased
absorption of the ester. Previous studies in our
laboratory indicated that the absolute bioavail-
ability of sarmoxicillin was 28% in dogs (Bristol
Laboratories, unpublished data) based on a com-
parison of area under the serum ester concentra-
tion versus time curves after oral and intrave-
nous administration. Although absolute bioa-
availability studies have not yet been conducted
in humans, it is reasonable to assume that at

mg every 8 h on study days 4 through 10. Plasma
and urine concentrations and clearance values
were not significantly different from those from
single-dose administration.
Saliva amoxicillin levels after amoxicillin ad-
ministration were sparse and sporadic and ac-
tually decreased over the dosing period. The
t1/2 of amoxicillin in saliva increased from 11 to
43 min after 3 days at 250 mg every 8 h and from
36 to 89 min after 7 days at 500 mg every 8 h;
parallel increases in saliva AUC were also ob-
served with chronic sarmoxicillin dosing (Table
6).

Safety evaluation. There were no clinically
significant side effects with multiple-dose sar-
monicillin or amoxicillin administration. Physi-
cal examinations, electrocardiograms, neurologi-
cal examinations, hematology, serum chemistry,
and urinalysis parameters remained within nor-
mal limits. Occasional episodes of loose stool
with or without mild abdominal cramping were
observed during multiple-dose administration in
two subjects on amoxicillin and three subjects
on sarmoxicillin.

![Graph showing concentration ratio of saliva amoxicillin to plasma sarmoxicillin over time](image-url)

**FIG. 6. Ratio of saliva amoxicillin to plasma sarmoxicillin concentrations with time. Initial sarmoxicillin doses: (▲) 250 mg, (○) 500 mg, and (●) 1,000 mg.**

### TABLE 6. Mean parameters for saliva antibiotic activity after multiple-dose administration of sarmoxicillin and amoxicillin (human study no. 2)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose (mg)</th>
<th>Day</th>
<th>Cmax (µg/ml)</th>
<th>tmax (min)</th>
<th>t1/2 (min)</th>
<th>AUC (µg·h/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarmoxicillin</td>
<td>250</td>
<td>1</td>
<td>0.2</td>
<td>31</td>
<td>11</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>0.2</td>
<td>35</td>
<td>43</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>4</td>
<td>0.4</td>
<td>37</td>
<td>36</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>0.4</td>
<td>24</td>
<td>89</td>
<td>0.50</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>250</td>
<td>1</td>
<td>0.02</td>
<td>100</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td></td>
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<td>3</td>
<td>0.01</td>
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<td>0.1</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>4</td>
<td>0.01</td>
<td>105</td>
<td></td>
<td>0.01</td>
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<td>10</td>
<td>0.04</td>
<td>120</td>
<td></td>
<td>0.004</td>
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least 10 to 20% of the oral sarmoxicillin dose survived first-pass intestinal-hepatic metabolism based on the ester/amoxicillin ratio in serum.

The distribution of sarmoxicillin to tissues such as salivary gland in the first hour after administration is governed by the determinants of passive diffusion, i.e., pKa, lipid partitioning, and protein binding. Maximum tissue penetration of sarmoxicillin from plasma will occur with the free (non-protein-bound), un-ionized, lipidsoluble drug (3). Amoxicillin, which is ionized and polar, should have lower tissue penetration. Serum protein binding of amoxicillin is low (20%) (14). At a plasma pH of 7.4, sarmoxicillin will exist 50% un-ionized at the amino group and 99% un-ionized at the phenolic hydroxyl. The carboxyl group of amoxicillin will be completely ionized at plasma pH 7.4. The hydroxyl function may be the dominating group in the physiological pH range of 6 to 8 in the renal transport of amoxicillin, since renal excretion is lower under alkaline conditions (18). The carboxyl group may be the regulating factor in tissue distribution, as evidenced by the saliva amoxicillin levels after sarmoxicillin administration. The results of these studies are consistent with partial first-pass hydrolysis of sarmoxicillin to amoxicillin, appearance of intact sarmoxicillin in plasma, good penetration of free, un-ionized, lipophilic sarmoxicillin into the salivary gland, poor penetration of ionized amoxicillin into the salivary gland, and subsequent hydrolysis of sarmoxicillin to amoxicillin in the salivary gland.

Although amoxicillin saliva and sputum levels of 0.3 to 0.5 μg/ml have been reported in acute, purulent exacerbations of chronic bronchitis at a serum level of 11 μg/ml (1, 17), no evidence for consistent penetration of amoxicillin into saliva was observed in the present study in normal subjects. The presence of salivary amoxicillin in chronic bronchitis patients could be due to penetration of amoxicillin into sputum through inflamed lung tissue, high intrabronchial concentrations (13) and contamination of saliva by sputum, or even by the dosing and saliva collection techniques. A similar relationship was observed between ampicillin and its methoxy-methyl ester (BL-P1761). Ampicillin only appeared in the saliva of normal subjects after administration of the ester (Bristol Laboratories, unpublished data). Low levels of amoxicillin, equivalent to the data with amoxicillin in this study, have also been demonstrated in saliva after bacampicillin and ampicillin administration in normal subjects (15).

The difference in distribution into saliva was also reflected in the pharmacokinetics of amoxicillin after sarmoxicillin administration. Plasma amoxicillin concentrations were linear, urinary recovery was constant (48 ± 10%), and bioavailability was estimated at 88% after administration of 250 to 1,000 mg of amoxicillin. Although linear amoxicillin kinetics were observed after sarmoxicillin administration, the amoxicillin half-life was 33% greater, and the plasma sarmoxicillin Cmax and AUC did not increase linearly with dose. This lack of sarmoxicillin proportionality could be attributed to (i) decreased absorption and more extensive first-pass hydrolysis of the ester at the 1,000-mg dose, (ii) saturation of first-pass metabolism with an increase in availability of the ester for distribution to tissue compartments at the high dose, or (iii) nonlinear clearance of the lipophilic ester with increasing dose. Although there was no statistical difference in amoxicillin urinary recovery, the consistent observations of lower amoxicillin recovery after sarmoxicillin (32 ± 9%) as compared with amoxicillin (48 ± 10%) in this study and other animal and human investigations could be also due to differences in the rate and extent of absorption and metabolism of sarmoxicillin.

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LITERATURE CITED