Single-Dose Pharmacokinetics and Penetration of BMS 284756 into an Inflammatory Exudate

R. Wise, T. Gee, G. Marshall, and J. M. Andrews*

Department of Medical Microbiology, City Hospital NHS Trust, Birmingham, United Kingdom

Received 2 July 2001/Returned for modification 16 September 2001/Accepted 10 October 2001

The pharmacokinetics of a single dose of BMS 284756 were determined following oral administration of a 600-mg dose to eight healthy male volunteers. Concentrations of the drug were measured in plasma and a cantharidin-induced inflammatory exudate by a microbiological assay. The mean peak concentration in plasma of 10.4 μg/ml (standard deviation [SD], 1.3 μg/ml) was attained at a mean time of 1.2 h (SD, 0.5 h) after the dose. The penetration into the inflammatory exudate was 82% (SD, 15.7%). A mean peak concentration of 7.2 μg/ml (SD, 2.4 μg/ml) was attained in the inflammatory exudate at 5.3 h (SD, 1.5 h). The elimination half-lives from plasma and inflammatory fluid were 9.8 h (SD, 1.1 h) and 8.5 h (SD, 1.9 h), respectively. The areas under the concentration-time curves for plasma and inflammatory fluid were 96.7 μg·h/ml (SD, 10.3 μg·h/ml) and 77.9 μg·h/ml (SD, 19.2 μg·h/ml), respectively.

BMS 284756 (T-3811ME) is a novel, orally and parenterally available, 6-des-fluorinated quinolone antimicrobial which displays a high degree of in vitro activity against a broad range of bacterial pathogens (1, 3). Preliminary data (D. A. Gajjar, D. M. Grasela, A. Bello, Z. Ge, and L. Christopher, 40th ICAAC, abstr. 2259, p. 36, 2000) suggest that the pharmacokinetics of this agent are dose related and that the elimination half-life supports a once-daily dosing regimen. There is little information on the ability of this agent to penetrate tissues. Here, we studied the pharmacokinetics of a single 600-mg oral dose in healthy adult volunteers and measured penetration into a cantharidin-induced inflammatory exudate (5).

Eight healthy male volunteers, with a mean age of 28.1 years (range, 22 to 41 years), a mean weight of 78.4 kg (range, 73.6 to 84.9 kg), and a mean height of 178 cm (range, 173 to 185 cm) gave written informed consent to participate in this study following hospital ethics committee approval. Exclusion criteria for the study included any history of significant illness or atopy, recent participation in another drug trial, and the use of prescription or nonprescription drugs within the 7 days of the study. All volunteers underwent a full medical history, examination, hematological and biochemical profiles, urinalysis, and drugs-of-abuse screening prior to enrollment, all of which were normal. A 12-lead electrocardiogram (ECG) was performed on enrollment, within 24 h prior to dosing and 24 h postdose. The hematological and biochemical profiles were similarly repeated.

The volunteers received 600 mg of BMS 284756 (as 200- plus 400-mg tablets) on the morning of the study following a 12-h overnight fast. The tablets were taken with 240 ml of water. The volunteers received only clear fluids for 2 h thereafter, and then a full diet was resumed.

Two 0.2% cantharidin-impregnated plasters were placed on the volunteers’ forearms about 12 h prior to drug administration, in order to induce blister formation. Blood (10 ml) and inflammatory fluid (50 μl) samples were taken at 0, 0.5, 1, 1.5, 2, 4, 6, 8, 12, and 24 h postdose.

A microbiological plate assay was performed in triplicate on all samples within 1 h of specimen collection. Iso-Sensitst agar (Oxoid, Basingstoke, United Kingdom) was employed. The indicator organism was Escherichia coli 4004 (Bayer AG, Wuppertal, Germany). The BMS 284756 standard range in plasma and inflammatory exudate was 0.06 to 1 μg/ml. Calibration standards were prepared in human serum, 70% human serum in a pH 7 phosphate buffer (used as a surrogate for inflammatory exudate), plasma, and inflammatory fluid samples. Internal control samples were prepared in plasma and 70% human serum. Incubation was for 24 h, after which the plates were read with an image analyzer (Image Associates, Temel, United Kingdom). The between-assay coefficients of variation for internal controls were 5.7 and 5.6% for plasma and inflammatory exudate, respectively, and all quality assurance samples, irrespective of matrix, were within 15% of the assigned concentration.

BMS 284756 plasma and inflammatory exudate concentration data were analyzed by model-independent methods with WinNonLin (version 3.0; Pharsight Corp. Mountain View, Calif.). The following data were calculated: maximum concentration in plasma or inflammatory fluid (Cmax), time to Cmax (Tmax), areas under the plasma concentration-time and inflammatory exudate concentration-time curves from time zero to 24 h (AUC0-24), terminal elimination half-life (t1/2), and percent penetration into inflammatory fluid (ratio of the AUC0-24 in inflammatory exudate to that in plasma). At least five data points were utilized to determine t1/2 in plasma and inflammatory fluid.

The mean time-concentration profiles for plasma and inflammatory fluid are found in Fig. 1, and the derived pharmacokinetic parameters are summarized in Table 1. The mean Cmax of BMS 284756 in plasma was 10.4 μg/ml at a Tmax of 1.2 h after administration. The mean t1/2 of BMS 284756 from plasma was 9.8 h, with a range of individual values from 8.8 to 12.1 h. The AUC0-24 was 96.7 μg·h/ml.
BMS 284756 penetrated moderately rapidly into the inflammatory exudate: the mean $T_{\text{max}}$ was 5.3 h postdose, with a range of 4 to 8 h. The mean $C_{\text{max}}$ was 7.2 $\mu$g/ml. The mean $t_{1/2}$ from the inflammatory fluid was 8.5 h (range, 8.0 to 11.6 h). The mean percentage penetration was 82.0%, with a range of 65.2 to 107.4%.

Physical examination, including ECG (and measurement of the rate-corrected QT interval, QTc interval) and hematological and biochemical parameters, revealed no abnormalities attributable to administration of BMS 284756. No side effects were reported by the volunteers. In particular, the QTc interval declined between the predose and postdose ECG in six volunteers and increased insignificantly in two (351 to 361 ms and 377 to 390 ms).

There are limited data on the pharmacokinetics of BMS 284756 (Gajjar et al., 40th ICAAC) which suggest a dose-linear response over 200 to 800 mg. At 600 mg, the earlier study showed some minor differences from that reported here. The plasma $C_{\text{max}}$ was previously reported as 6.98 $\mu$g/ml, as against our observation of 10.4 $\mu$g/ml. The earlier study noted a plasma $t_{1/2}$ of 13.4 h, against our finding of 9.8 h. The difference may be explained by intersubject variation or by the longer sampling schedule followed in the earlier study, i.e., 72 h versus 24 h in this study. The earlier study employed liquid chromatography with tandem mass spectroscopy, and the present study used a microbiological procedure. However, the assay we employed was cross-validated with that employed in the earlier study (data not shown). In the earlier study, BMS 284756 was administered as a capsule formulation and not the tablet formulation used in the present study. It is important to note that the plasma AUC values were, however, similar.

BMS 284756 penetrated well into the inflammatory exudate. The mean penetration was 82.0%, which compares with 117% for gatifloxacin (4) and 64% for trovafloxacin (6). It is possible that the penetration of BMS 284756 is related to the moderate protein binding of 87% (J. Fung-Tomc, E. Huczko, B. Kolek, et al., Prog. Abstr. 40th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 2262, p. 37, 2000).

The mean 24-h concentrations of BMS 284756 exceeded 1 $\mu$g/ml in both plasma and inflammatory fluid, which is greater than the MIC at which 90% of strains of the respiratory pathogens *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* are inhibited (R. N. Jones, M. A. Pfaller, D. J. Biedenbach, and M. Stilwell, 40th ICAAC, abstr. 1042, p. 172, 2000) even when the protein-free concentration is taken into account and suggests that once-daily dosing would be appropriate.

It has been suggested (2) that certain pharmacodynamic parameters are predictive of clinical response. The ratio of AUC to MIC is said to reflect clinical efficacy. For *S. pneumoniae*, for which the MIC at which 90% of strains are inhibited is 0.06 $\mu$g/ml (Jones et al., 40th ICAAC), this ratio is about 1,500, which is markedly greater than those for the other fluoroquinolones (2). Similarly, the ratio of $C_{\text{max}}$ to MIC may

---

**FIG. 1.** Concentrations of BMS 284756 in plasma (solid line) and inflammatory fluid (dotted line) following an oral dose of 600 mg. SDs are shown as vertical bars.

**TABLE 1.** Pharmacokinetic parameters following a 600-mg dose of BMS 284756

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Plasma</th>
<th>Inflammatory exudate</th>
<th>% Penetration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$C_{\text{max}}$ ($\mu$g/ml)</td>
<td>$T_{\text{max}}$ (h)</td>
<td>$t_{1/2}$ (h)</td>
</tr>
<tr>
<td>Mean</td>
<td>10.4</td>
<td>1.2</td>
<td>9.8</td>
</tr>
<tr>
<td>SD</td>
<td>1.3</td>
<td>0.5</td>
<td>1.1</td>
</tr>
<tr>
<td>Minimum</td>
<td>8.6</td>
<td>0.5</td>
<td>8.8</td>
</tr>
<tr>
<td>Maximum</td>
<td>11.9</td>
<td>2.0</td>
<td>12.1</td>
</tr>
</tbody>
</table>
predict the likelihood of the emergence of resistance during therapy, and for *S. pneumoniae* this exceeds 150, which is markedly greater than ratios for similar agents (2). However, the protein binding of BMS 284756 will reduce the free-drug ratios of both of these parameters. These properties suggest that BMS 284756 will be successful in the treatment of respiratory tract infections and that resistance will be less likely to emerge with the new agent than with less active established compounds.

We thank P. O’Grady of Bristol Myers Squibb for advice and financial support.

REFERENCES