Effect of Food on the Pharmacokinetics of Oral MMI270B (CGS 27023A), a Novel Matrix Metalloproteinase Inhibitor

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ABSTRACT

MMI270B is a matrix metalloproteinase inhibitor (MMPI) with in vitro and in vivo activity. To exert optimal target inhibition, MMPI must be given chronically, and therefore, oral bioavailability is important. We analyzed the effect of food intake on AUC0–8 h, Cmax, and Tmax. Seventeen patients were entered into the study. Doses of MMI270B were 150, 400, and 600 mg. The first day, patients ingested the drug in a fasted state and were not allowed to eat for 2 h. The second day, patients ingested the drug 30 min after a light breakfast. Mean AUC0–8 h was not significantly influenced by food intake. Plasma concentrations were well above the IC50 of several MMPs at all doses tested. Mean Cmax was significantly decreased after food intake. Mean Tmax was significantly delayed after food intake. Food intake did not result in a significant change in exposure to MMI270B (AUC0–8 h) but did result in a significant, although not clinically relevant, decrease in peak plasma levels and time to reach peak plasma levels. No specific guidelines concerning the ingestion of MMI270B in either a fed or a fasted state are recommended.

INTRODUCTION

MMPs2 are a class of structurally related enzymes responsible for the degradation of extracellular matrix that constitutes connective tissue. Activity of MMP is controlled by naturally occurring inhibitors, but in several disease states, such as cancer, an imbalance between the activity of MMP and their inhibitors results in an increased extracellular matrix degradation. In cancer, this degradation facilitates local invasive growth and increases the potential for metastasis. Inhibiting MMP seems an attractive goal in anticancer treatment. Inhibitors of MMP should not have a direct cytotoxic effect but should control the metastatic process (1).

MMI270B (previously CGS 27023A) is a novel MMPI with an IC50 of 33 nM for recombinant human collagenase (MMP 1), 8 nM for recombinant human M, 92,000 gelatinase (MMP 9), and 13 nM for recombinant human stromelysin-1 (MMP 3). Preclinical studies with oral MMI270B in vivo showed growth-inhibitory effects in breast carcinoma, prostate, bladder, colon, lung adenocarcinoma, glioblastoma, and ovarian carcinoma cell lines. MMI270B is rapidly absorbed after oral administration in rats and dogs. In fasted rats, bioavailability after a single oral dose is 44%. Thus far, only one clinical study with oral MMI270B has been presented (2). Data concerning bioavailability in humans, and the possible influence of food intake, have not been published previously. In view of the mechanism of action of MMPIs, prolonged and continuous administration will result in optimal target inhibition, and therefore, oral treatment is preferred. We performed a Phase I and pharmacological study with oral MMI270B in patients with miscellaneous solid tumors (2). As part of this study, we analyzed the influence of food intake on the pharmacokinetics of MMI270B, comparing AUC0–8 h (area under the plasma concentration versus time profile), Cmax (peak plasma level), and Tmax (time to peak plasma level) at different dose levels of MMI270B, after ingestion in both a fasted and fed state.

PATIENTS AND METHODS

Eligibility Criteria. Patients with a cytologically or histologically confirmed diagnosis of a solid tumor refractory to standard treatment or for which no standard treatment was available were eligible for the Phase I and pharmacological study. Further eligibility criteria included: age ≥21 years, WHO performance state ≤2, life expectancy of ≥12 weeks, no anticancer treatment in the previous 4 weeks (6 weeks for mitomycin C or nitrosoureas), no radiotherapy in the previous 2 weeks, adequate function of bone marrow [WBC ≥4.109/l, platelets ≥100.109/liter, hemoglobin ≥9 g/dl (5.59 mmol/l)], normal hepatic and renal functions (alanine aminotransferase within three times the normal upper limit, bilirubin within 1.25 times the normal upper limit, and creatinine within 1.25 times the normal upper limit). Exclusion criteria were pregnant women, the evidence of cerebral metastases, or a clinically significant abnormal electrocardiogram at baseline.

All patients gave written informed consent for the Phase I and pharmacological study. Patients enrolled in the fasted/fed study gave additional and specific written informed consent.

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2 The abbreviations used are: MMP, matrix metalloproteinase; MMPI, MMP inhibitor; MMI270B, N-hydroxy-2-(R-[4-methoxysulfonyl][3-picolyl] amino)-3-methylbutaneamide hydrochloride (monohydrate).
Table 1  Summary of MMI270B Pharmacokinetic Data after oral administration\(^a\)

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Fed</th>
<th>Fasted</th>
<th>95% CL(^b)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(AUC) (ng·h/ml)</td>
<td>150</td>
<td>799.3 ± 501.9</td>
<td>967.0 ± 556.8</td>
<td>-282&lt;(\Delta)&lt;-54.0</td>
</tr>
<tr>
<td>400</td>
<td>2422 ± 1246</td>
<td>2406 ± 1127</td>
<td>-319&lt;(\Delta)&lt;-351</td>
<td>0.901</td>
</tr>
<tr>
<td>600</td>
<td>6787 ± 3151</td>
<td>7711 ± 3592</td>
<td>-2859&lt;(\Delta)&lt;-1009</td>
<td>0.297</td>
</tr>
<tr>
<td>(C_{\max}) (ng/ml)</td>
<td>150</td>
<td>485.0 ± 340.6</td>
<td>1091 ± 536.4</td>
<td>-1080&lt;(\Delta)&lt;-131</td>
</tr>
<tr>
<td>400</td>
<td>1754 ± 969.8</td>
<td>2838 ± 2015</td>
<td>-3041&lt;(\Delta)&lt;-872</td>
<td>0.199</td>
</tr>
<tr>
<td>600</td>
<td>4406 ± 2264</td>
<td>7432 ± 5158</td>
<td>-6401&lt;(\Delta)&lt;-349</td>
<td>0.072</td>
</tr>
<tr>
<td>(T_{\max}) (h)</td>
<td>150</td>
<td>1.14 ± 0.78</td>
<td>0.53 ± 0.04</td>
<td>-0.58&lt;(\Delta)&lt;1.81</td>
</tr>
<tr>
<td>400</td>
<td>1.18 ± 0.46</td>
<td>0.50 ± 0.01</td>
<td>0.11&lt;(\Delta)&lt;1.26</td>
<td>0.030</td>
</tr>
<tr>
<td>600</td>
<td>0.91 ± 0.35</td>
<td>0.92 ± 0.42</td>
<td>-0.17&lt;(\Delta)&lt;-0.41</td>
<td>0.975</td>
</tr>
</tbody>
</table>

* Data were obtained from 17 cancer patients treated on day 1 with MMI270B at dose levels of 150 mg (\(n = 4\)), 400 mg (\(n = 5\)), or 600 mg (\(n = 8\)) after an overnight fast (Fasted) and on day 2 at 30 min after a light breakfast (Fed). Data were calculated by noncompartmental analysis and represent mean values ± SD.

* 95% CL, 95% confidence limits for the mean difference.

* Probability value from a two-sided paired Student’s \(t\) test.

Pretreatment Assessment and Follow-Up Studies.

Prior to therapy, a complete medical history was taken, and a physical examination was performed. A complete blood count, including WBC differential, and serum chemistries including sodium, potassium, calcium, phosphorus, creatinine, total protein, albumin, glucose, alkaline phosphatase, bilirubin, aspartate aminotransferase, alanine aminotransferase, \(\gamma\)-glutamyl transpeptidase, and lactate dehydrogenase were performed, as were urine analysis, electrocardiogram, and tumor markers, if appropriate. Patients enrolled in the fasted/fed study were admitted to the hospital for 2 consecutive days for pharmacokinetic sampling.

Drug Administration.

MMI270B was supplied by Novartis Pharma AG (Basel, Switzerland), as a chiral hydroxamic acid derived from \(d\)-valine. It was supplied in capsules of 25, 100, or 300 mg. Capsules had to be stored at temperatures <25°C and protected from light and had to be swallowed with 250 ml of water. Prophylactic antiemetics were not given routinely. For pharmacokinetic purposes, capsules were swallowed once daily on days 1 and 2. For the fasted/fed analysis, capsules were swallowed in a fasted state on day 1, and patients were not allowed to eat or drink for 2 h after ingestion. On the second day of treatment, patients swallowed the capsules 30 min after they had eaten a light breakfast.

Pharmacokinetic Studies.

Five-ml blood samples were taken from an i.v. cannula that was inserted in the foream. On day 1, blood samples were taken predose and 30, 60, and 90 min and 2, 3, 4, 6, 8, 12, and 24 h postdose, prior to the morning dose. On day 2, blood samples were taken predose, 30, 60, and 90 min and 2, 3, 4, 6, and 8 h postdose. Blood samples were collected in heparin-containing Vacutainer tubes that were gently inverted 8–10 times. Within 30 min after collection, samples were centrifuged at 2500 rpm at room temperature for 15 min, after which plasma was transferred into plastic tubes with a pipette and stored at -20°C until analysis. Determination of plasma concentrations of MMI270B was performed using a validated high-performance liquid chromatography method. MMI270B and the internal standard (CGS 26835) were extracted from acidified human plasma by ether:methylene chloride (2:1). The organic layer was transferred and evaporated to dryness under nitrogen, and the residue was reconstituted in high-performance liquid chromatography mobile phase for sample injection. Chromatographic separation of the compounds was achieved on a 5-μm Zorbax SB-C\(_8\) analytical column (4.6 mm inside diameter × 150 mm), using acetic acid (pH 3.00): acetonitrile with 9% methanol (80:20, v/v) as the mobile phase at a flow rate of 1 ml/min. The effluent from the column was monitored by UV detection at 242 nm. The lower limit of quantitation was 20 ng/ml, and the method had a linear range over the concentration range of 20 to 2000 ng/ml. The noncompartmental pharmacokinetic parameters \(AUC_{0–\infty}\), \(C_{\max}\) and \(T_{\max}\) data were calculated using WinNonlin Professional version 1.5 software (Scientific Consulting, Inc.). For \(AUC_{0–\infty}\) and \(C_{\max}\), the fed:fasted ratio was determined; for \(T_{\max}\), the time difference fed:fasted was determined.

Statistical Considerations.

The correlation between individual \(AUC_{0–\infty}\) values and the administered dose was evaluated by means of Spearman’s correlation coefficient (\(\rho\)) and linear regression analysis. Interpatient differences in pharmacokinetic parameters were assessed by the coefficient of variation, expressed as the ratio of the SD and the observed mean. Variability in parameters between the two treatment courses and the various MMI270B dose levels was evaluated by a two-sided paired Student’s \(t\) test plus the 95% confidence limits for the mean difference (5) and the Kruskal-Wallis statistic, respec-
tively. Statistical calculations were performed using Number Cruncher Statistical System (version 5.X; Jerry Hintze, East Kaysville, UT). Probability values of <0.05 were regarded as statistically significant.

The 90% confidence intervals for the ratio of means fed versus fasted for the parameters $AUC_{0–8h}$ and $C_{max}$ were calculated using the ANOVA program of WinNonlin Professional version 1.5 (Scientific Consulting, Inc.).

RESULTS

Seventeen patients were entered into the study. In one patient, blood sampling on day 2 was done until 6 h postdose. Doses studied were 150, 400, and 600 mg. None of the patients used prokinetic medication, antacids, or other concomitant medication expected to alter gastrointestinal motility.

Pharmacokinetic Results. Mean drug exposure ($AUC_{0–8h}$) was related to dose (fed: Spearman’s $p=0.876$ and $P=0.0007$; fasted: Spearman’s $p=0.869$ and $P=0.0008$), whereas the influence of food intake on drug exposure was diverse; in 12 patients, food intake resulted in a decreased drug exposure, whereas in 4 patients, an opposite effect was noted (Fig. 1; Table 1). In one patient, food intake had no effect on drug exposure. Overall, mean exposure to MMI270B was reduced by 10% after food intake. The 90% confidence interval for the ratio of means fed versus fasted (0.816–0.986) lies within the range 0.8–1.25, indicating no significant effect of food intake on $AUC_{0–8h}$. Both in the fed and fasted states and at all doses analyzed, plasma levels of MMI270B were well above the IC$_{50}$ for the target enzymes collagenase-MMP 1, gelatinase-MMP 9, and stromelysin-MMP 3 for considerable periods of time after administration.

Mean peak plasma levels were strongly correlated to dose (fed: Spearman’s $p=0.850$ and $P=0.0013$; fasted: Spearman’s $p=0.691$ and $P=0.0116$). In three patients, peak plasma levels in the fed state were higher than in the fasted, whereas in 14 patients, peak plasma levels decreased after food intake. Mean $C_{max}$ was 40% lower in the fed state. The 90% confidence interval for the ratio of means fed versus fasted (0.457–0.778) almost entirely falls outside the range (0.7–1.43), indicating a significant effect of food intake on $C_{max}$.

Mean time to reach peak plasma levels (1.04 ± 0.488 h fed state, 0.704 ± 0.388 h fasted state) was significantly increased by food intake ($P=0.042$; 95% confidence limits for the mean difference: 0.04<δ<0.65). The absolute increase in mean time to reach peak plasma levels was 0.34 h (or 20 min).

DISCUSSION

We have performed a pharmacological study with the oral MMPI MMI270B to analyze the influence of food intake on the pharmacokinetic parameters $AUC_{0–8h}$, $C_{max}$, and $T_{max}$.

The results of this study show that exposure to MMI270B was not significantly influenced by food intake, and plasma levels of MMI270B in both the fasted and fed state, at all dose levels studied, remained well above the IC$_{50}$ of the MMP 1, MMP 3, and MMP 9 for prolonged periods of time. Peak plasma levels of MMI270B were significantly influenced by food intake, and a correlation between change in overall drug exposure and change in peak plasma level could be determined. Although food intake significantly slowed the rate of absorption of MMI270B, the absolute change in $T_{max}$ is not clinically relevant, especially when taking into account that MMPIs have to be administered on a continuous and prolonged basis to exert optimal target inhibition.

The results of this pharmacokinetic study indicate that although food intake slows the rate of absorption of MMI270B and significantly decreases peak plasma levels, overall drug exposure is not significantly influenced. No specific guidelines concerning the ingestion of MMI270B in either a fed or a fasted state are recommended.

REFERENCES


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