Similarity of Metabolism for CAI (NSC 609974) in Human Liver Tissue *in Vitro* and in Humans *in Vivo*¹

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ABSTRACT

Metabolism of a new antitumor agent, CAI (NSC 609974), was investigated in human liver tissue *in vitro* and in plasma and urine of patients receiving CAI. Metabolites identified by HPLC following ¹⁴C-labeled CAI incubation with human liver microsomes and reported as percentage of total metabolites formed were M₁ (0–3.4%), M₂ (4.5–33%), M₃ (60–79%), and M₄ (7.2–19%). Ketoconazole, an inhibitor of cytochrome P₄₅₀ 3A₄, prevented formation of M₁, M₃, and M₄ (concentration of drug that inhibited metabolite formation by 50% when compared to maximum uninhibited activity, ≥50 μM). CAI incubated with recombinant human P₄₅₀ 3A₄ microsomes produced metabolites M₃ and M₄. Conjugation of M₃, most likely a glucuronide, was observed after incubation of ¹⁴C-labeled CAI and UDP-glucuronic acid with human liver 13,000 × g supernatant. Plasma samples from patients receiving CAI contained CAI (3.1–5.0 μg/ml), M₁ (0.9–2.6 μg/ml), and M₂ (1.0–2.2 μg/ml). CAI and M₂ but not M₄ were observed in the urine samples. After incubation of the urine samples with β-glucuronidase, CAI concentrations increased 67%, M₃ increased up to 9-fold, and M₄ was detected. CAI is metabolized *in vitro* and *in vivo* by both Phase I and Phase II enzymes and is metabolized to M₃ and M₄ by P₄₅₀ 3A₄. These studies suggest that elevated levels of CAI may result from P₄₅₀ 3A₄ inhibition by ketoconazole if these two drugs are coadministered. Correlation between CAI metabolism *in vitro* and results obtained in patients demonstrates the usefulness of liver metabolism studies *in vitro* in the early stages of drug development.

INTRODUCTION

CAI (NSC 609974), a substituted carboxamido-triazole (Fig. 1), has been developed for clinical trials based on its inhibitory effects on cancer cell proliferation, adhesion, and motility *in vitro* and in human xenograft models of ovarian cancer and melanoma progression (1, 2). Current studies show the mechanism of action is inhibition of calcium influx-sensitive signal transduction pathways important in the regulation and activation of metastasis and proliferation (2–6). No information concerning CAI metabolism has been reported. However, we observed two significant potential metabolite peaks in the plasma of patients treated with CAI in an ongoing Phase I study at the National Cancer Institute (7). This observation prompted us to investigate the metabolism of this new antitumor agent.

The importance of drug metabolism by microsomal P₄₅₀ enzymes and the therapeutic and toxic consequences are now well recognized. Drugs that require metabolic activation or are cleared from the body by metabolic processes can have the circulating levels of their pharmacological or toxic species profoundly affected by genetic polymorphism and enzyme inhibition or induction during multiple drug therapy (8–10). The recent isolation and classification of P₄₅₀ enzymes responsible for drug metabolism has prompted investigators to develop techniques using human liver tissue *in vitro* to identify the specific P₄₅₀ enzymes responsible for a drug’s metabolism. The demonstration of the usefulness of these *in vitro* techniques in the early stages of drug development as tools for probing metabolic pathways and potential drug interactions is of significant interest.

The three major P₄₅₀s in adult liver involved in drug metabolism belong to families 1, 2, and 3. P₄₅₀ 3A₄ varies widely among individuals, accounting for up to 60% of the total P₄₅₀ present in some liver specimens (10). We studied Phase I metabolism of CAI *in vitro* by human liver microsome preparations and examined the effect of ketoconazole, a potent cytochrome P₄₅₀ 3A₄ inhibitor, on the microsomal metabolism of CAI. To further establish the P₄₅₀ enzyme partially responsible for the metabolism of CAI, we incubated CAI with rh3A₄³ microsomes. One of the more common Phase II reactions is the combination of glucuronic acid with various acceptor groups to form the corresponding water-soluble glucuronide conjugate. Phase II metabolism of CAI was investigated by adding UDPGA to incubations of CAI with the S9 fraction of human liver tissue. Plasma and urine samples from patients receiving

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³ The abbreviations used are: rh3A₄, recombinant human P₄₅₀ 3A₄; UDPGA, UDP-glucuronic acid; S9, fraction obtained by collecting the supernatant of the tissue homogenate following centrifugation at 13,000 × g for 20 min; IC₅₀, concentration of drug that inhibited metabolite formation by 50% when compared to maximum uninhibited activity; RT, retention time.
CAI were analyzed using HPLC and these observations were compared to the metabolic profile of CAI in human liver tissue in vitro.

MATERIALS AND METHODS

Human liver specimens, medically unsuitable for transplantation, were acquired under the auspices of the Washington Regional Transplant Consortium (Washington, DC) or the International Institute for the Advancement of Medicine (Exeter, PA). Microsomal protein (rh3A4) from human cells transfected with cDNA-encoded CYP3A4 and control microsomal protein (without rh3A4) were obtained from Gentest (Woburn, MA). 14C-labeled CAI (13.3 mCi/mmol; 31.4 mCi/mg, 99%) was obtained from the Drug Synthesis and Chemistry Branch, National Cancer Institute (Bethesda, MD). Acetonitrile, methanol, and isopropanol were HPLC grade and used as purchased. Other reagents were obtained from Sigma Chemical Co. (St. Louis, MO).

Preparation of Liver Microsomes. Human liver samples were obtained and immediately sectioned and stored at −80°C until used. Microsomes were prepared by tissue homogenization and differential centrifugation as described by Lake (11). The S9 fraction was obtained by collecting a portion of the supernatant of the tissue homogenate following centrifugation at 13,000 × g for 20 min. The final pellet (microsomes) was resuspended in 100 mM sodium phosphate, with 5 mM MgCl₂, and 1 mM EDTA (pH 7.4). Protein concentration of the microsomal fractions was measured using the Bio-Rad (Hercules, CA) method and the fractions were stored at −80°C until used. The metabolic competence of the microsomes has been characterized for the major human drug-metabolizing enzymes.

Metabolism of CAI by Human Liver Microsomes. Preliminary experiments demonstrated that the formation of CAI metabolites by human liver microsomes increased in a linear fashion for incubation times up to 2 h and over substrate concentrations ranging from 12 to 47 μM. Experiments with increasing microsomal protein concentration demonstrated that 1 mg microsomal protein produced the best results. Each incubation mixture contained 1 mg microsomal protein, 14C-labeled CAI, and 10 μl of a NADPH generating system in a 1-ml solution containing: BSA (0.25%), 0.1 mM sodium phosphate buffer (pH 7.4), 1 mM EDTA, and 5 mM MgCl₂. 14C-labeled CAI (2.5–3.0 mM, dissolved in ethanol) was added to a final concentration of 25–30 μM. The NADPH generating system consisted of 10 mM glucose-6-phosphate, 1 mM NADP⁺, 5 mM MgCl₂, and 1 unit/ml glucose-6-phosphate dehydrogenase. The BSA was added to limit the precipitation of CAI (a highly lipophilic drug) in the aqueous medium. Following a 2-h incubation at 37°C in a shaking water bath, the reaction was stopped and the protein was precipitated by the addition of 5.0 ml acetonitrile. After vortex mixing and centrifugation, 3.0 ml supernatant were dried under vacuum, reconstituted in 100 μl mobile phase, and 25-μl injections were analyzed using HPLC. 14C-labeled CAI added to control samples incubated with heat-inactivated microsomes, without NADPH, and samples incubated for 0 min were analyzed.

Incubations and sample preparation with S9 fractions were performed as described above with substitution of the S9 fraction protein (1 mg) for the microsomal protein (1 mg).

Incubations with microsomes or the S9 fraction were performed in the presence or absence of UDPGA and the results compared. UDPGA was added to a final concentration of 2.3 mM in the incubation mixtures. Fractions of the acetonitrile supernatant from these incubations of CAI with S9 fractions were dried and reconstituted in water containing BSA (0.25%). Duplicates of these reconstituted samples were incubated with and without β-glucuronidase as described below for the incubation and analysis of the urine samples.

Metabolism of CAI by rh3A4 Microsomes. Incubations with rh3A4 microsomes were performed in the same manner as those for the liver microsome incubations. 14C-labeled CAI (17.6 mM, dissolved in methanol) was added to a final concentration of 176 μM and incubated with 1 mg or 2 mg rh3A4 microsomal protein for 1 and 2 h. 14C-labeled CAI (176 μM) was also incubated with control microsomes (2 mg protein) prepared by Gentest from the same cell line without rh3A4 in order to eliminate the possibility of metabolism by enzymes native to the cell line. The incubated samples were prepared and analyzed using HPLC following the procedure for microsomes.

Inhibition of CAI Metabolism in Microsomes. Concentration response inhibition studies with ketoconazole were performed by incubating CAI (28 μM) with human liver microsomes for 2 h in the presence of 0.5–100 μM ketoconazole. The results were compared to samples (maximum uninhibited activity) incubated in the absence of ketoconazole. Ketoconazole vehicle control samples were incubated with 10 μl 0.05 M HCl and analyzed. IC₅₀ values were calculated by fitting the experimental data to an inhibitory sigmoid Eₘₐₓ model with the following equation:

\[ E = E_{max} \cdot \frac{C^*}{IC_{50}^* + C^*} \]

using SigmaPlot (Jandel Scientific, San Rafael, CA).

Preparation and Evaluation of Standard Curves. A standard curve in blank plasma was prepared with concentra-
Extraction of Plasma and Urine Samples. Plasma samples from two patients receiving CAI (12) were obtained before treatment and following dosing with CAI for 28 days. A sample following 28 days of dosing was also obtained from a third patient. Extraction of plasma and urine samples were identical, except for preparation of the samples before placement on the extraction column. For plasma, 0.5 ml of sample was added to 1 ml water, mixed, and placed on conditioned 200 mg C18 extraction cartridges (Varian, Harbor City, CA). To 1.5 ml of each urine sample, 0.5 ml 0.5 mM phosphate buffer (pH 7.4) was added before placing on the extraction cartridge. Following washes with 4 ml 0.05 mM ammonium acetate (pH 6.8) and 4 ml 20% acetonitrile in ammonium acetate, the samples were eluted with 3 ml acetonitrile. The resulting eluants were dried under vacuum, reconstituted in 100 μl mobile phase, and 25 μl were analyzed using HPLC.

HPLC Analysis of CAI and Metabolites. Samples for HPLC analysis were injected on a Hewlett-Packard 1090 HPLC system with UV detection at 263 nm. The separation of CAI and its metabolites was accomplished on an Alltech Adsorbosphere C18 column (3 μm, 4.6 × 100 mm; Alltech, Deerfield, IL). The mobile phase was 50 mM ammonium acetate, acetonitrile, and isopropyl alcohol (60:26:14, v/v) and was pumped at a flow rate of 0.5 ml/min.

For the metabolism studies in vitro containing 14C-labeled CAI, a Radiomatic Flo-OneBeta detector (Packard Instrument Co., Meriden, CT) was connected following the UV detector to monitor the column effluent for radioactivity.

Values reported for metabolites in plasma and urine samples are in terms of CAI equivalents in μg/ml. The UV spectra for CAI, M1, M3, and M4 are very similar. Comparison of relative radioactive peak areas to relative UV peak areas in the microsomal studies indicate that the UV responses for these four compounds were about the same. The spectrum for M2 was different from CAI and the other metabolites. A similar comparison of radioactive to UV peak responses for M2 suggests that a correction factor of approximately 1.9 is needed to report results for this metabolite as CAI equivalents.

RESULTS

CAI Metabolism by Human Liver Fractions. After a 2-h incubation of 14C-labeled CAI (25 μM) with human liver microsomes, at least four radioactive HPLC peaks were observed (Fig. 2A) which were not present in any of the control incubations. The retention times for the metabolites were 7.1

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Fig. 2 Chromatographic analysis of CAI and metabolites. Chromatograms showing CAI and its metabolites (M1, M2, M3, M4) following a 2-h incubation of 14C-labeled CAI (25-30 μM) with 1 mg of human liver microsomes (A), S9 fraction (B), and S9 fraction with the addition of UDPGA (C). The metabolite at 5.2 min is thought to be a glucuronide conjugate of M3. Radioactive peaks (upper traces) are measured about 0.6 min following detection by UV (lower traces).
Table 1  Metabolism of CAI in microsomes from five human livers and rh3A4 microsomes

<table>
<thead>
<tr>
<th>Microsomal protein</th>
<th>Metabolites (% of total radioactivity)</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>M4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HL-IVT</td>
<td>0.41 ± 0.09</td>
<td>2.84 ± 0.19</td>
<td>22.4 ± 1.15</td>
<td>2.75 ± 0.24</td>
<td></td>
</tr>
<tr>
<td>HL-2</td>
<td>0.76 ± 0.09</td>
<td>1.81 ± 0.11</td>
<td>29.1 ± 2.66</td>
<td>5.97 ± 0.62</td>
<td></td>
</tr>
<tr>
<td>HL-3</td>
<td>n.d.†</td>
<td>2.78 ± 1.05</td>
<td>9.75 ± 1.13</td>
<td>1.44 ± 0.25</td>
<td></td>
</tr>
<tr>
<td>HL-4</td>
<td>n.d.‡</td>
<td>3.55 ± 0.19</td>
<td>6.37 ± 0.22</td>
<td>0.77 ± 0.13</td>
<td></td>
</tr>
<tr>
<td>HL-9</td>
<td>1.41 ± 0.32</td>
<td>1.85 ± 0.34</td>
<td>28.7 ± 1.08</td>
<td>7.87 ± 0.78</td>
<td></td>
</tr>
<tr>
<td>rh3A4 (1 mg)</td>
<td>n.d.‡</td>
<td>n.d.</td>
<td>1.07†</td>
<td>0.18‡</td>
<td></td>
</tr>
<tr>
<td>rh3A4 (2 mg)</td>
<td>n.d.‡</td>
<td>n.d.</td>
<td>1.56‡</td>
<td>0.26‡</td>
<td></td>
</tr>
</tbody>
</table>

" Incubations of '4C-labeled CAI with microsomes from five individual human livers for 2 h or rh3A4 microsomes for 1 h. Results are mean ± SD of four observations.

b n.d., not detected.

c Results are average of two observations.

Table 2  Effect of UDPGA on the metabolite M3 and the M3 conjugate in incubations with S9 fractions

<table>
<thead>
<tr>
<th>Donor code</th>
<th>M3 conjugate</th>
<th>M3</th>
<th>CAI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>UDPGA</td>
<td>Control</td>
</tr>
<tr>
<td>HL-2</td>
<td>1.64 ± 0.30</td>
<td>29.6 ± 1.85</td>
<td>20.9 ± 0.54</td>
</tr>
<tr>
<td>HL-4</td>
<td>n.d.†</td>
<td>3.51 ± 0.29</td>
<td>2.36 ± 0.34</td>
</tr>
<tr>
<td>HL-9</td>
<td>0.44 ± 0.14</td>
<td>28.0 ± 0.83</td>
<td>19.3 ± 0.49</td>
</tr>
</tbody>
</table>

" S9 fractions from three individual human livers were incubated with '4C-labeled CAI for 2 h with UDPGA. The control samples were incubated under the same conditions without the addition of UDPGA. Results are expressed as percentage of total radioactivity and are the mean ± SD of four observations.

b n.d., not detected.

c Results are average of two observations.

Table 3  Effect of β-glucuronidase on the metabolite M3 and the M3 conjugate in S9 fractions incubated with UDPGA

<table>
<thead>
<tr>
<th>Donor code</th>
<th>M3 conjugate</th>
<th>M3</th>
<th>CAI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Glucuronidase</td>
<td>Control</td>
</tr>
<tr>
<td>HL-2</td>
<td>25.80</td>
<td>n.d.†</td>
<td>n.d.</td>
</tr>
<tr>
<td>HL-4</td>
<td>2.44</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>HL-9</td>
<td>23.30</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

" The remainder of the acetonitrile supernatant from the samples in Table 2 were dried, rediluted, and incubated with and without (Control) β-glucuronidase as described in "Materials and Methods." Results are expressed as percentage of total radioactivity and are the average of two observations.

b n.d., not detected.
ketoconazole concentrations <5 \mu M; in fact, the production of M2 appeared to increase under these conditions at the lower ketoconazole concentrations. With the inhibition of the formation of M1, M3, and M4, the concentration of CAI would be higher over the duration of the experiment. More substrate is then available to produce M2. However, at ketoconazole concentrations >50 \mu M production of M2 was also inhibited. There was no substantial effect on the amount of metabolism in the vehicle control samples when compared to samples with maximum uninhibited activity.

**Metabolites of CAI in Human Plasma.** Fig. 5A compares plasma samples from one patient before and after 28 days of treatment with CAI. Analysis of three post-dose samples resulted in concentrations of 4.5 \mu g/ml, 5.0 \mu g/ml, and 3.1 \mu g/ml for CAI. Calculation of CAI equivalents in \mu g/ml for the two metabolites resulted in amounts ranging from 25 to 53% (M1) and 17 to 70% (M2) as percentage relative to the amount of CAI present in each sample.

**Metabolites of CAI in Human Urine.** Pre-dose and random urine collections obtained 24 h or 28 days following daily or every other day p.o. dosing of CAI were obtained and analyzed using HPLC. Fig. 5B compares a pretreatment urine sample and another sample obtained following dosing with CAI for 28 days. In addition to CAI and M3, a number of significant peaks are observed with retention times between 4 and 10 min which were not present in the pre-dose urine sample. Similar differences in the HPLC chromatograms in the region between 4 and 10 min were observed in two additional patients for which pre- and post-dose urine samples were available for analysis. In addition, random urine collections (blanks) were obtained from five healthy subjects and analyzed. In these samples there were no peaks with responses greater than 20 milli absorbance units between 4 min and 10 min of the chromatographic run.

![Figure 3](https://example.com/figure3.png)

**Figure 3** Effect of rh3A4 on CAI metabolism. Comparison of chromatograms following incubation for 1 h of 176 \mu M CAI with 2 mg of rh3A4 microsomes (——) and 2 mg of control (—). The presence of M1 and M3 increased. M2 could not be confirmed due to the number of peaks in the elution region expected for these compounds and M4 was not detected in the untreated sample. After incubation of the urine sample with \beta-glucuronidase one additional metabolite, M4 (RT = 43 min), was observed and the amount quantitated for both CAI and M3 increased.

Table 4 summarizes the results of six post-dose urine samples that were analyzed using HPLC. Compounds quantitated in non-\beta-glucuronidase-treated urines ranged from 0.2 to 1.9 \mu g/ml for CAI, from not detectable to 0.2 \mu g/ml for M3 and not detectable in all urine samples for M4. After treatment of the urine samples with \beta-glucuronidase CAI urine concentrations increased by 67% \pm 42 SD, M3 was observed in two additional samples and the concentration of M3 in all other samples increased dramatically. M4 was observed in all urine samples treated with \beta-glucuronidase ranging from 0.1 to 2.5 \mu g/ml in terms of CAI equivalents.

**DISCUSSION**

\(^{14}C\)-labeled CAI was used to establish the metabolic profile of CAI in human liver preparations. The results of these experiments were then correlated with results from samples obtained from patients receiving CAI during a Phase I trial at the Clinical Pharmacology Branch, National Cancer Institute. Plasma levels in the range of 1–10 \mu M have recently been reported in this
Fig. 5  CAI and metabolites in human plasma and urine. Chromatograms of plasma (A) and untreated urine (B) samples obtained from subject P2 following daily doses of 500 mg CAI for 28 days (upper traces). Lower traces, corresponding pre-dose samples. Peaks corresponding to M1 and M2 are identified in the plasma. A large peak in the urine, close to M1 in retention time, appears to be composed of more than one component. The inset in B provides a less attenuated view of the chromatogram showing a small peak for M3 and the absence of M4.

The results obtained when UDPGA is added to microsomal incubations of CAI and the results following the further incubation of these samples with β-glucuronidase provide evidence for the formation of a M3 glucuronide conjugate. The rapid conversion of M3, the major microsomal metabolite, to a glucuronide conjugate provides an explanation for the inability to detect M3 in the plasma samples and the low level of M3 found in the untreated urine samples.

Analysis of the urine samples before and after treatment with β-glucuronidase suggests that CAI and M3 were present in both their conjugated and unconjugated forms and M4 was present exclusively as a conjugate. It is interesting to note that certain peaks (inset, Fig. 6) in the region between 4.5 and 10.0 min appeared to either increase or decrease after treatment of urine with β-glucuronidase. The increase of the peak at 7.2 min might represent an increase of M1, suggesting that M1 is also eliminated as a conjugate. The decreasing peak at approximately 5.2 min appears to be primarily composed of the apparent M3 conjugate. Further development of the chromatographic conditions and additional optimized studies are needed, but the decrease in other peaks might represent hydrolysis of CAI, M1, and M4 conjugates.

Ketoconazole inhibition profiles for metabolites M1, M3, and M4 were similar. The inhibition profile for metabolite M2 was different, suggesting that another cytochrome P450 enzyme is responsible for production of this metabolite. Inhibition of CAI metabolism by ketoconazole, a known inhibitor of P450 3A4, suggested that this enzyme may be primarily responsible for the metabolism of CAI. Further evidence to support this observation was obtained using rh3A4 microsomes, which produced substantial amounts of the major metabolite, M3, plus some M4. Taken together, the metabolism of CAI by rh3A4 microsomes and inhibition of CAI metabolism by ketoconazole at <5 μM (13) suggest that P450 3A4 is involved in the metabolism of CAI. Since these IC50 values are well within ketoconazole therapeutic plasma concentrations (14, 15), it is...
Table 4  Results of urine samples from patients receiving CAI

<table>
<thead>
<tr>
<th>Patient</th>
<th>CAI (µg/ml)</th>
<th>M3 (µg/ml)</th>
<th>M4 (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>0.19</td>
<td>+</td>
<td>n.d.†</td>
</tr>
<tr>
<td>P2</td>
<td>1.85</td>
<td>2.28</td>
<td>0.11</td>
</tr>
<tr>
<td>P3</td>
<td>0.45</td>
<td>0.76</td>
<td>0.18</td>
</tr>
<tr>
<td>P4</td>
<td>0.18</td>
<td>0.33</td>
<td>n.d.</td>
</tr>
<tr>
<td>P4d</td>
<td>0.54</td>
<td>1.05</td>
<td>0.17</td>
</tr>
<tr>
<td>P5d</td>
<td>0.30</td>
<td>0.34</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

† Urine samples from patients treated with CAI for 28 days were analyzed using HPLC. The results of samples not treated and those treated with β-glucuronidase are compared.

Possible that the concomitant administration of ketoconazole and CAI may result in increased CAI levels.

Our studies demonstrate that CAI is extensively metabolized in vitro in human liver tissue and is similar to the metabolic profile observed in humans receiving the drug. Additional studies are warranted to further elucidate the disposition of CAI in humans and to determine the pharmacological activity of metabolites formed.

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