Disposition and Metabolism of Pentamethylmelamine and Hexamethylmelamine in Rabbits and Humans

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ABSTRACT

The disposition and metabolism of pentamethylmelamine (PMM) and hexamethylmelamine (HMM) were studied in the rabbit, and the disposition of PMM was studied in humans. Parent compound and metabolites were identified by thin-layer chromatography, gas chromatography, and gas chromatography/mass spectrometry analyses. Plasma elimination in both species following i.v. administration of each drug was best described by a two-compartment open model. Both compounds were extensively demethylated with less than 1% of the total dose administered recovered in the urine over 24 hr. The areas under the plasma time-concentration curves of PMM and HMM following p.o. administration to rabbits were 5 and 25% of the areas following i.v. administration. Gastrointestinal absorption was rapid and efficient with 75 to 89% of drug equivalents recoverable in the urine after p.o. administration of [ring-14C]PMM or [ring-14C]HMM to rabbits. Reduced bioavailability of PMM and HMM p.o. appears to be a consequence of rapid metabolism presumably in the liver.

INTRODUCTION

PMM and HMM are a-triazine derivatives currently under study as antitumor agents. HMM has been studied in clinical trials for over a decade. It has activity against a number of human tumors including small cell carcinoma of the lung, ovarian adenocarcinoma, lymphoma, and breast carcinoma (3, 6, 10). Nausea, vomiting, and cumulative neurological toxicity are dose limiting for HMM (6, 10). Little information is available on the disposition of HMM prior to HMM in a variety of animal tumor models, a parenteral form of PMM was selected recently for clinical study.

In mice, rats, and humans, HMM is extensively demethylated as evidenced by the recovery of multiple demethylated metabolites and little parent compound in the urine (5, 12, 14, 15). Little information is available on the disposition of HMM primarily because assays have been insufficiently sensitive to quantitate HMM and its metabolites. Recently D'Incalci et al. (9), using a gas chromatographic assay, reported marked variability in plasma concentrations of HMM in patients given the drug p.o. Plasma concentrations of metabolites were not reported.

The mechanism of action of PMM and HMM is not known. It has been suggested that these drugs have alkylating activity (3, 6, 11), but HMM and its demethylated analogs (including PMM) do not react with 4-[(p-nitrobenzyl)pyridine (14), and some tumors refractory to known alkylating agents are sensitive to HMM (10). It has also been suggested that other metabolic intermediates such as formaldehyde (4) or methylol intermediates formed during oxidative N-demethylation (7, 12, 14) may be the active compound. Low levels of covalent binding of both [ring-14C]HMM and [methyl-14C]HMM to liver macromolecules following i.p. administration to mice have been reported (12). The antitumor activity of demethylated HMM analogs decreases below the pentamethyl derivative (6–8), suggesting that metabolism of the parent melamines (HMM or PMM) or at least one of the more fully methylated intermediates (such as N2,N2,N4,N6-tetramethylmelamine, N2,N2,N4,N6-trimethylmelamine, or N2,N2,N4,N6-trimethylmelamine) is important to cytotoxic activity.

We developed a sensitive and specific GC assay for PMM and HMM and have demonstrated that the concentrations of these drugs can be quantitated in plasma and urine following doses of drug tolerable in humans (1). We now report studies on the disposition and metabolism of PMM in humans and rabbits and of HMM in rabbits.

MATERIALS AND METHODS

Chemicals. HMM, PMM hydrochloride, N2,N2,N4,N6-tetramethylmelamine hydrochloride, N2,N2,N4,N6-trimethylmelamine hydrochloride, N2,N2,N4,N6-trimethylmelamine hydrochloride, monomethylmelamine hydrochloride, and melamine were supplied by Leonard H. Kedda, Drug Synthesis and Chemistry Branch, Division of Cancer Treatment, National Cancer Institute, Bethesda, Md. [ring-2,4,6,14C]HMM (13.0 mCi/mmol) and [ring-2,4,6,14C]PMM hydrochloride (12.6 mCi/mmol) were supplied by Dr. Robert Engle, Chemical Resources Section, Pharmaceutical Resources Branch, Division of Cancer Treatment, National Cancer Institute, Bethesda, Md. All compounds were greater than 99% pure by GC and thin-layer chromatographic analyses. All other chemicals and solvents were reagent or chromatographic grade.

Drug Administration and Sampling. Male white New Zealand rabbits (2.5 to 3.5 kg) were administered PMM hydrochloride or HMM by p.o. intubation (under light ketamine anesthesia) or by i.v. administration in an ear vein. For i.v. administration, HMM was dissolved in water by the addition of 1 N HCl. Plasma samples were collected from an ear vein (opposite that used for i.v. administration), and urine samples were collected via a catheter (inserted under light ketamine anesthesia). After
3 hr, the catheter was removed, and the animals were placed in metabolism cages for 24-hr urine collection. Patients received PMM hydrochloride at doses of 80 or 265 mg/sq m in 500 ml 5% dextrose in water by i.v. infusion over 2 hr. A 2-hr infusion was used because of reports of acute central nervous system toxicity in large animals following rapid injection (6).

**Patient Characteristics.** Patients receiving PMM were participating in a Phase I study of the drug sponsored by the Division of Cancer Treatment, National Cancer Institute. All patients had histological or cytological confirmation of unresectable cancer for which no other more conventional means of therapy would offer reasonable hope of cure or significant palliation. All patients were fully informed of the precise diagnosis and nature of their disease and signed informed consent forms. Patients were excluded from study according to the following criteria: leukocytes, <10/μl; platelets, <130,000/μl; hemoglobin, <10 g/dl; any elevation of direct reacting system toxicity in large animals following rapid injection (6).

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**GC Assay for Plasma and Urinary PMM and Their Demethylated Metabolites.** The assay for PMM and HMM has been reported (1). Plasma or urine samples (1 ml) were adjusted to pH 11 with 1 N NaOH, extracted with 6 ml toluene, and concentrated to dryness under a gentle stream of nitrogen. The residue was taken up in toluene (10 to 50 μl), and portions (1 to 2 μl) were injected for analysis on a Hewlett-Packard (Avondale, Pa.) 5840A gas chromatograph equipped with a nitrogen-phosphorus detector. Silanized glass columns (2 ft x 2 mm i.d.) were packed with 10% Carbowax 20 M/2% KOH on 80 to 100 mesh chromasorb W AW (Supelco, Inc., Bellafonte, Pa.) and conditioned overnight (225°). Injector and detector temperatures were 235 and 300°, respectively. An oven temperature program (170–185°; 10°/min) was used for 3 successive analyses, followed by 15 to 20 min at 190° to elute contaminants prior to injection of the next 3 samples. HMM (2 μg) was the internal standard for determination of PMM; quantitation of HMM was accomplished by the use of standard curves prepared by spiking control samples with HMM on the same day that unknown samples were analyzed.

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**For analysis of metabolites in plasma and urine samples (isolated as described below), the temperature program was modified (175–210°; 5°/min). Standard curves for Nβ,Nβ,Nβ,Nβ-tetramethylmelamine and Nβ,Nβ,Nβ,Nβ-trimethylmelamine, and Nβ,Nβ,Nβ-trimethylmelamine were prepared by the addition of known amounts of each along with HMM to control plasma samples.**

**Determination of Radioactivity.** Plasma or urine samples (100 μl) and 1 ml water were placed in glass scintillation vials, 10 ml Insta-Gel (Packard Instrument Co., Downers Grove, Ill.) were added, and the samples were counted in a Beckman Model LS-3150T scintillation counter. Quenching was determined by external standardization.

**Isolation of Plasma and Urine Metabolites.** Urinary metabolites were isolated either by a modification of an ion-exchange procedure reported by Worzalla et al. (14) or by extraction with toluene. HMM, PMM, and their demethylated metabolites were demonstrated to be stable under the conditions used for isolation. In the ion-exchange column procedure, urine was acidified with 0.1 N HCl and applied to a column (1 × 4.5 cm) of Bio-Rad-Laboratories (Richmond, Calif.) AG1-X8 (Cl− form) resin, followed by 50 ml of 0.1 N HCl. The eluate was applied to a column (1 × 4.5 cm) of Bio-Rad AW50-X8 (H+ form) resin followed by 100 ml of 2.4 N HCl. The washes were discarded, and 100 ml of 6 N HCl were applied to the column and collected as a single fraction. Portions (15 ml) were lyopholized, and the residue was taken up in 1 ml concentrated NH4OH, frozen, and lyopholized. The residue was again taken up in 1 ml concentrated NH4OH, frozen, and lyopholized to remove all traces of acid. The residue was taken up in 2-methoxyethanol for analysis.

**Plasma and urine metabolites were also isolated by adjusting plasma or urine samples (1 to 10 ml) to pH 11 with 1 N NaOH and extracting with toluene (6 to 20 ml). The extracts were dried (Na2SO4), and solvent was removed in a vacuum. In some experiments, the remaining aqueous portion was further extracted with chloroform, dried (Na2SO4), and concentrated in a vacuum. The residues were taken up in 2-methoxyethanol for analysis.**

**Conjugates were hydrolyzed by treatment of urine (1 ml) with either 20 units β-glucuronidase/sulfatase (Boehringer Mannheim, Indianapolis, Ind.) in 0.1 N sodium acetate buffer (pH 4.5) at room temperature for 18 hr or with 1 N HCl (100°) for 1 hr. The urine samples were then extracted with tolune as described above and analyzed by GC for methylamines.**

**Thin-Layer Chromatography of Urinary Metabolites.** Pre-coated plastic sheets (20 x 20 cm) of Silica Gel 60 (0.1 mm) with F254 indicator were used with ethyl acetate as mobile solvent. Compounds were located by quenching of fluorescence under short-wave UV or by cutting the sheets into 0.125-inch strips and measuring radioactivity in a scintillation counter (10 ml Insta-Gel per vial).

**Pharmacokinetic Analysis.** Analysis of pharmacokinetic data was done using the SAS NLIN procedure (2). The biexponential declines in plasma concentrations of PMM and HMM were fitted by nonlinear least-square regression analysis to

\[
C = Ae^{-αt} + Be^{-βt}
\]

where \(C\) is the plasma concentration of PMM or HMM at time \(t\) after administration of i.v. drug, \(A\) and \(B\) are the intercepts at \(t = 0\), and \(α\) and \(β\) are the fast and slow disposition rate constants. A weighting factor of \(C^−1\) was used.

**GC/MS of Urinary Metabolites.** GC/MS analyses were carried out on a Hewlett-Packard 5985A GC-MS equipped with the gas chromatographic column described above (flow rate, 30 ml/min). A temperature program was used starting at 170° (0.5 min) followed by an increase at 5°/min to 220°. The source temperature was 200°. Total ion chromatograms reconstructed from continuously recorded mass spectra were obtained by standard 5985A software routines.

**RESULTS**

**Disposition of PMM and HMM in the Rabbit.** Plasma elimination of parent compound was studied in the rabbit following i.v. administration of PMM at a dose of 9 mg/kg and after administration of HMM at 10 mg/kg. The patterns of elimination were similar for both drugs. Representative log linear plasma time-concentration curves are shown in Chart 1. Drug elimination was best described by the 2-compartment open model (Table 1). In the rabbit, the half-lives of the distributive and
To determine the bioavailability of PMM and HMM after p.o. or parenteral administration, rabbits were given PMM (9 mg/kg) or HMM (10 mg/kg) p.o. and 5 days later received the same doses i.v. The plasma time-concentration curves for parent compound following p.o. and i.v. administration of PMM and HMM are shown in Chart 3. The bioavailability (as determined by comparing areas under the curve of PMM and HMM) following p.o. administration was respectively, 5 and 25% of that obtained following i.v. administration. Reversing the sequence of p.o. and parenteral administrations did not alter the reduced bioavailability of either drug p.o. To determine if the bioavailability of parent compound given p.o. was due to poor gastrointestinal absorption, [ring-14C]PMM or HMM (50 to 60 μCi in a total dose of 10 mg/kg) was administered via stomach tube to rabbits, and the plasma concentrations of parent drug and of radioactivity were measured. High concentrations of 14C drug equivalents were detected within 2 min after p.o. administration of either drug; plasma concentrations of parent drug were low (Chart 4, A and B). The recoveries of 14C equivalents of PMM and HMM in the 24-hr urine were 75 and 85%, respectively, of the total doses administered, confirming efficient gastrointestinal absorption.

**Table 1**

Summary of 2-compartment open-model pharmacokinetic analyses in rabbits and humans following i.v. administration of PMM or HMM

Male New Zealand rabbits received PMM (9 mg/kg) or HMM (10 mg/kg) (one each) by rapid i.v. infusion. Three patients received PMM (265 mg/sq m) by 2-hr infusion.

<table>
<thead>
<tr>
<th>Species</th>
<th>Drug</th>
<th>Route</th>
<th>t₁/₂α (min)</th>
<th>t₁/₂β (min)</th>
<th>Clearance (ml/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbits</td>
<td>PMM</td>
<td>Rapid i.v.</td>
<td>2.7</td>
<td>22.2</td>
<td>43.2</td>
</tr>
<tr>
<td>HMM</td>
<td>Rapid i.v.</td>
<td>6.7</td>
<td>67.1</td>
<td>23.6</td>
<td></td>
</tr>
<tr>
<td>Humans</td>
<td>PMM</td>
<td>2-hr infusion</td>
<td>1.4</td>
<td>81.3</td>
<td>11.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>17.7</td>
<td>120.9</td>
<td>12.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.8</td>
<td>85.2</td>
<td>9.5</td>
</tr>
</tbody>
</table>

postdistributive phases of elimination for HMM were 2 to 3 times as long as for PMM, 6.7 versus 2.7 min and 67.1 versus 22.2 min, respectively. Total body clearance was 23.6 ml/kg/min for HMM and 43.2 ml/kg/min for PMM. Plasma elimination of parent compound was studied after i.v. administration of PMM by 2-hr infusion in 2 patients at 80 mg/sq m and in 3 patients at 265 mg/sq m. Plasma time-concentration curves are shown in Chart 2. Because of limited data and considerable scatter, analysis of the plasma concentration curves at 80 mg/sq m was not attempted. Plasma elimination curves following 265 mg/sq m best fit a 2-compartment, open model similar to that found in the rabbit. Following 2-hr infusions of PMM at 265 mg/sq m in 3 patients, half-lives of the initial phase of plasma decay following termination of the infusion were 1.4, 17.7 and 1.8 min, and half-lives of the secondary phase of elimination were 81.3, 120.4, and 85.2 min.

The apparent prolonged initial half-life for PMM in one patient (17.7 min) resulted from the absence of data (samples lost) between 5 and 30 min which caused the computer program to overemphasize the values obtained immediately after cessation of the infusion. Inspection of the curve of plasma elimination in this patient (Chart 2, x) shows the pattern of elimination to be similar to those of the other 2 patients treated at the same dose. Total body clearances of PMM in the 3 patients treated at 265 mg/sq m were 11.5, 12.2, and 9.5 ml/kg/min.
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Chart 4. Time-concentration curves of 14C drug equivalents (x) and parent drug (O) following p.o. administration (10 mg/kg) of PMM (A) or HMM (B) to rabbits. Concentrations of parent drug were determined by the gas chromatographic assay.

Metabolism of PMM and HMM. PMM and HMM were demethylated in vivo as evidenced by the appearance of demethylated metabolites in plasma within minutes of i.v. administration of either drug and by the appearance of demethylated metabolites in the urine. Metabolism was extensive with less than 1% of the total dose of PMM and HMM given i.v. (or p.o.) present as parent compound in the urine excreted over 24 hr. After i.v. administration of PMM to rabbits, urinary metabolites were \( N_2,N_2,N_6 \)-tetramethylmelamine, \( N_2,N_4,N_6 \)-trimethylmelamine, \( N_2,N_6,N_8 \)-trimethylmelamine, \( N_2,N_8 \)-dimethylmelamine, monomethylmelamine, and melamine (Chart 5). Each of these metabolites and PMM were present in the urine of 2 rabbits after i.v. administration of HMM (data not shown). Metabolites of PMM present in the plasma of a rabbit (after rapid i.v. injection) and in the plasma of 3 patients (during and after a 2-hr infusion) were \( N_2,N_2,N_6 \)-tetramethylmelamine and the 2 trimethylmelamine derivatives (\( N_2,N_6,N_8 \) and \( N_2,N_8,N_6 \)). Chart 6 shows the time course of the appearance and elimination of parent drug \( N_2,N_2,N_6 \)-tetramethylmelamine and the 2 trimethylmelamine metabolites following rapid i.v. infusion of PMM to a rabbit. These compounds were also present in the plasma of patients receiving PMM by 2-hr infusion (Chart 7).

Urinary metabolites were isolated by ion-exchange chromatography which permits recovery of all demethylated metabolites. The more convenient toluene method was used for isolation of plasma metabolites. The toluene procedure extracts efficiently only the more fully methylated compounds. We did not attempt to confirm the presence of dimethylmelamine, monomethylmelamine, and melamine in the plasma of rabbits and patients shown to have these metabolites present in their urine.

The identity of each metabolite was established by comparing its GC retention time and mass spectrum to that of authentic compound. The electron impact mass spectra of melamine and each of its methylated analogs contained a corresponding molecular ion as the most abundant species. The tetramethyl and trimethyl compounds were characterized by the presence of ion species formed by the loss of methyl groups. This is illustrated by the mass spectrum of \( N_2,N_2,N_6 \)-tetramethylmelamine present in the urine of a rabbit after i.v. administration of PMM (Chart 8). This spectrum, containing the molecular ion (m/e 182) and ion intensities at 167, 152, and 138, is identical to the spectrum of authentic \( N_2,N_2,N_6 \)-tetramethylmelamine (not shown). \( N_2,N_6 \)-Dimethylmelamine was tentatively identified in the urine of patients and rabbits receiving PMM i.v. This metabolite eluted from the gas chromatograph between the
Two rabbits were given \([\text{ring-}^{14}\text{C}]\text{PMM}\) (i.v. infusion), and portions of the 24-hr urine were analyzed for metabolites by the ion-exchange column procedure described in "Materials and Methods." Results are expressed as the mean of the 2 experiments. Recovery from column procedure: 

<table>
<thead>
<tr>
<th>Compound</th>
<th>Recovery from column procedure</th>
<th>% of dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N_2\text{-}N_2\text{-}N_2\text{-}N^6\text{-}N^6)</td>
<td>64</td>
<td>5</td>
</tr>
<tr>
<td>(N_2\text{-}N_2\text{-}N^6\text{-}N^6)</td>
<td>67</td>
<td>1</td>
</tr>
<tr>
<td>(N_2\text{-}N_2\text{-}N_2\text{-}N^6)</td>
<td>69</td>
<td>9</td>
</tr>
<tr>
<td>(N_2\text{-}N^6)</td>
<td>50</td>
<td>12</td>
</tr>
<tr>
<td>Monomethyl</td>
<td>28</td>
<td>7</td>
</tr>
<tr>
<td>Melamine</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

* Standard mixtures of the metabolites were carried through the column procedure.

** Estimated based on extraction efficiency and detector response of other methylmelamines.

Peaks corresponding to the 2 trimethylmelamine metabolites and monomethylmelamine (Chart 5). The mass spectrum of this metabolite showed a prominent molecular ion at \(m/e\) 154, consistent with that of a dimethylmelamine. Based on this spectrum, the GC retention time, and the reports of others that \(N_2\text{-}N_2\text{-}N^6\)-dimethylmelamine is a major urinary metabolite of HMM (12, 14, 15), we conclude that \(N_2\text{-}N^6\)-dimethylmelamine is a major metabolite of PMM in humans and rabbits.

To establish that the demethylated compounds were derived from administered PMM or HMM and to facilitate measurement of urinary metabolites, \([\text{ring-}^{14}\text{C}]\text{PMM}\) and HMM were given i.v. to rabbits. Urinary metabolites were isolated by the column procedure, separated on thin-layer plates along with authentic unlabeled compounds, and the presence or absence of radioactivity in each chromatographic spot determined. All urinary metabolites of PMM and HMM contained the label. Attempts were made to measure the urinary excretion of metabolites in 2 rabbits given \([\text{ring-}^{14}\text{C}]\text{PMM}\) i.v. Total recovery of radioactivity in the 24-hr urine from 2 animals was 87 and 89% of the total dose administered. Metabolites were isolated by the ion-exchange procedure. Approximately 28% of the radioactivity in the urine was recovered in the 2.4 N HCl wash, and 52% was eluted by 6 N HCl. No attempt was made to recover the 20% remaining on the column. Metabolites in the 2.4 N HCl fraction were not quantitated. The amounts of 6 metabolites contained in the 6 N HCl fraction were calculated on the basis of GC analysis, correcting the values for the efficiency of recovery of known metabolites carried through the column isolation procedure (Table 2).

**DISCUSSION**

PMM and HMM undergo rapid and extensive demethylation in the rabbit following p.o. and i.v. administration. In humans, we have had an opportunity to study PMM only following administration by 2-hr infusion. The finding of demethylated metabolites in human plasma a few min after starting the infusion suggests that PMM is also rapidly metabolized in humans. In either species, less than 1% of parent drug is recoverable in the first 24 hr of urinary excretion.

Our quantitative estimates for metabolites of PMM and HMM in urine of rabbits receiving the drugs i.v. or p.o. are similar to results reported by others for HMM in the rat (15). We have not yet quantitated the amounts of metabolites in the urine of humans and are doing so at doses considerably higher than those reported in this paper. The pattern of plasma elimination of PMM in humans following cessation of a 2-hr infusion is similar to that found in the rabbit following rapid i.v. administration of PMM (or HMM). These data are best described by a 2-compartment open model with elimination from the central compartment, the half-life of intact PMM in human plasma being approximately 90 min. However, the concentration of circulating PMM in humans and HMM or PMM in rabbits constitutes a relatively small amount of total concentration of drug equivalents present as metabolites.

We have demonstrated that the bioavailability of parent compound for PMM and HMM in the rabbit is much greater following i.v. administration than after p.o. administration. The facts that 75 to 85% of the total dose of either drug administered p.o. is recoverable in the urine and that much higher concentrations of drug equivalents are present in plasma compared to the...
amounts of parent compound following p.o. administration of radiolabeled HMM or PMM indicate that both drugs are readily absorbed in the gastrointestinal tract. The greater bioavailability of each drug after i.v. administration than after p.o. administration despite good absorption from the gut suggests that gastrointestinal metabolism, presumably in the liver, is responsible for reduced bioavailability p.o.

We have not had an opportunity to study the pharmacology of HMM in humans. Because of the similar pharmacological behavior exhibited by HMM and PMM in the rabbit and comparable behavior of PMM in humans, we think it is reasonable to speculate that HMM is well absorbed but rapidly metabolized when given p.o. to humans. This is of considerable interest clinically since it has been demonstrated that the antitumor activity of the demethylated metabolites of HMM decreases markedly below the pentamethyl derivative (6–8). In our studies in the rabbit, higher concentrations of PMM were achieved after i.v. administration of PMM than the total concentrations of HMM plus PMM achieved after p.o. administration of HMM. If the situation is similar in humans, one might expect i.v. PMM to have more activity than comparable doses of HMM given p.o. HMM has only been administered to humans p.o. in relatively low doses compared to those currently used in Phase I studies of PMM given i.v. Dose-limiting toxicity of HMM is nausea, vomiting, and cumulative neurological toxicity with myelosuppression occurring rarely (10). If PMM has cytotoxic activity comparable to HMM, our studies suggest that PMM given i.v. may have more activity than HMM given p.o. This has not been the case thus far. At approximately 4 times the conventional daily dose of p.o. HMM used in humans, PMM (1200 mg/sq m) has shown no cytotoxic activity (myelosuppression or tumor regression) in our study, and nausea and vomiting have been the dominant toxicity.4

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