Pharmacokinetics of $[^{14}C]$Methylglyoxal-bis(guanylhydrazone) in Patients with Leukemia

Michael G. Rosenblum, Michael J. Keating, Boh Seng Yap, and Ti Li Loo

Department of Developmental Therapeutics, The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston, Texas 77030

ABSTRACT

Methylglyoxal-bis(guanylhydrazone) (MGBG; NSC 32946), a competitive inhibitor of S-adenosyl-L-methionine decarboxylase (EC 4.1.1.50), is currently being reevaluated for its clinical antileukemic activity. MGBG labeled with $^{14}$C in the guanylhydrazone moiety was administered i.v. (150 $\mu$Ci; specific activity, 1.9 $\mu$Ci/$\mu$mol; 20 mg total) to six patients with leukemia. All patients in the study had normal renal and hepatic function. $[^{14}C]$MGBG underwent no in vivo metabolism; it disappeared from the plasma with an average terminal $t_{1/2}$ of 4.1 hr. The 72-hr cumulative urinary excretion was only 14.5 ± 2.2% (S.E. M.) of the total radioactive dose. The apparent volume of distribution was 661 ml/kg and the total clearance appeared from the plasma with an average terminal $t_{1/2}$ of 4.1 hr. The 72-hr cumulative urinary excretion was only 14.5 ± 2.2% (S.E. M.) of the total radioactive dose. The apparent volume of distribution was 661 ml/kg and the total clearance appeared from the plasma with an average terminal $t_{1/2}$ of 4.1 hr. The 72-hr cumulative urinary excretion was only 14.5 ± 2.2% (S.E. M.) of the total radioactive dose.

To facilitate the renewed clinical trials with MGBG, it is necessary to understand its pharmacokinetic behavior in humans. Accordingly, we have synthesized $[^{14}C]$MGBG and studied its pharmacokinetics and metabolism in patients with leukemia.

MATERIALS AND METHODS

Radioactive MGBG labeled with $^{14}$C in the guanylhydrazone moiety was synthesized according to the procedure of Oliverio and Denham (18). Analysis of the product by both paper chromatography (18) and high-pressure liquid chromatography (23) showed that the product was greater than 99% pure chemically and radiochemically. Unlabeled MGBG was supplied by the Drug Development Branch, Division of Cancer Treatment, National Cancer Institute.

Patient Studies. Patients with advanced and progressive leukemia taking part in the Phase I reevaluation of MGBG were selected for this study. None of the patients had received other chemotherapy for at least 2 weeks before the study, and informed written consent was obtained according to institutional guidelines. The results of the renal and hepatic function tests of these patients were within normal limits. Labeled MGBG was prepared by the Drug Development Branch, Division of Cancer Treatment, National Cancer Institute.

MATERIALS AND METHODS

Radioactive MGBG labeled with $^{14}$C in the guanylhydrazone moiety was synthesized according to the procedure of Oliverio and Denham (18). Analysis of the product by both paper chromatography (18) and high-pressure liquid chromatography (23) showed that the product was greater than 99% pure chemically and radiochemically. Unlabeled MGBG was supplied by the Drug Development Branch, Division of Cancer Treatment, National Cancer Institute.

Patient Studies. Patients with advanced and progressive leukemia taking part in the Phase I reevaluation of MGBG were selected for this study. None of the patients had received other chemotherapy for at least 2 weeks before the study, and informed written consent was obtained according to institutional guidelines. The results of the renal and hepatic function tests of these patients were within normal limits. Labeled MGBG was prepared by the Drug Development Branch, Division of Cancer Treatment, National Cancer Institute.
samples were filtered and chromatographed with a Waters Associates (Milford, Mass.) Model 204 liquid chromatograph equipped with a Model M600A pump, a variable wavelength UV detector (Varian Var-Chrom; Varian Associates, Palo Alto, Calif.), and a Varian Model 1976 recorder. An analytical reverse-phase C\textsubscript{18}Bondapak column (Waters; 4 mm x 30 cm) was used for separation. The mobile phase was 0.03 M sodium acetate buffer adjusted to pH 4.3 with glacial acetic acid and contained 5% methanol. Flow rate was 2 ml/min, and the column eluate was fractionated into 1-ml aliquots and assayed for \textsuperscript{14}C activity in scintillation vials containing 10 ml Aquasol scintillant.

RESULTS

Pharmacokinetic parameters were computed by standard techniques after nonlinear regression analysis of the plasma MGBG concentration versus time data. Fitting of the curves to the experimental data was excellent ($r^2 = 0.92$ to 1.00). Chart 1 shows the mean disappearance of \textsuperscript{[14]C}MGBG from plasma of 6 patients with leukemia. Elimination of \textsuperscript{[14]C}MGBG appeared to be triphasic; the calculated mean initial $t_{1/2}$ was 1.5 min while the terminal $t_{1/2}$ was 247 min (4.1 hr). The extrapolated apparent volume of distribution was 661 ml/kg, similar to the total body water or the antipyrine space in humans (4). Total clearance of MGBG from the plasma was 21.2 ml/kg/min. The 72-hr cumulative urinary excretion of MGBG (Chart 2) was only 14.5 ± 2.2% (S.E. M.) of the total dose administered. Analysis of the radiolabel in urine (Chart 3) and plasma by high-pressure liquid chromatography showed that the label was present as unchanged MGBG. Leukemic leukocytes of patients 4 hr after administration of \textsuperscript{[14]C}MGBG showed no significant radiolabel present.

DISCUSSION

MGBG is the first clinically active antineoplastic agent which interrupts essential polyamine biosynthesis by the competitive inhibition of S-adenosyl-L-methionine decarboxylase (EC 4.1.1.50) a key enzyme in the biosynthesis of spermidine and spermine (25). The polyamines putresine, spermidine, and spermine have been found to accumulate in mammalian tissues.

Chart 1. Plasma disappearance of \textsuperscript{[14]C}MGBG in 6 patients with leukemia. Duplicate 0.1-ml plasma aliquots from each patient were assessed for radioactivity in 10 ml Aquasol scintillant. Points, means; bars, S.E. M.

Chart 2. Urinary excretion of \textsuperscript{[14]C}MGBG. Urine samples were collected from 6 patients for 72 hr after \textsuperscript{[14]C}MGBG administration. Duplicate 0.1-ml aliquots were assessed for radioactivity in 10 ml Aquasol scintillant.

Chart 3. A, high-pressure liquid radiochromatographic profile of authentic \textsuperscript{[14]C}MGBG; B, radiochromatographic profile of urine from Patient 1, 24 hr after \textsuperscript{[14]C}MGBG administration; C, radiochromatographic profile of urine from Patient 6, 24 hr after \textsuperscript{[14]C}MGBG administration.
with high rates of RNA and protein synthesis (2, 6, 24); subsequently, it was shown that the requirement for polyamines in macromolecular synthesis was absolute (5, 19). In addition, the intracellular biosynthesis and accumulation of polyamines appear to be linked to the biochemical events which control both normal and neoplastic growth (3, 20, 24).

The cellular penetration of MGBG into leukemic leukocytes in vitro was demonstrated by Field et al. (7) to occur via a carrier-mediated membrane transport system which is also responsible for polyamine transport. In the present study, no radioactivity was detected in leukocytes isolated from patients after [14C]MGBG administration. Many factors may account for the differences between in vitro and in vivo observations. However, it is likely that the high endogenous polyamine levels in plasma may inhibit MGBG penetration into WBC after a low dose.

The present study shows that in humans [14C]MGBG was rapidly cleared from the plasma but only slowly excreted in the urine. This suggests that MGBG may be sequestered in the body at a site outside the vasculature. However, it is possible that higher therapeutic doses may result in altered retention of drug in the body. Oliverio et al. (17) have shown that in mice and dogs MGBG is neither excreted into the bile nor metabolized to 14CO2 to a significant extent. The prolonged biological half-life of MGBG in humans may account for the cumulative toxicity with MGBG therapy observed earlier (15, 16). Although MGBG is an active antineoplastic agent, it is apparent from our pharmacological studies that frequent administration of this agent may result in accumulation of the drug in the body resulting in serious toxicity.

REFERENCES

Pharmacokinetics of $[^{14}\text{C}]$Methylglyoxal-bis(guanylhydrazone) in Patients with Leukemia


Updated version

Access the most recent version of this article at: [http://cancerres.aacrjournals.org/content/41/5/1748](http://cancerres.aacrjournals.org/content/41/5/1748)

E-mail alerts

Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions

To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.