Distribution of [2-\(^{14}\text{C}\)]Merbarone in Mice by Autoradiography of Whole-Body Cryosections

Brian H. Kemmenoe and Louis Malspeis

The Ohio State University Cancer Center, Columbus, Ohio 43210

ABSTRACT

The distribution of radiolabel in male mice was studied by autoradiography of whole-body cryosections at intervals during 24 h after i.v. injection (46.6 mg/kg) and during 4 h after oral administration (140 mg/kg) of [2-\(^{14}\text{C}\)]merbarone. Following injection, radioactivity levels in the blood and highly vascular tissues declined to 8 h at which time only low levels were present in the systemic circulation. Only very low levels were seen in the brain and spinal cord at 0.5–3 min after dosing and levels were barely above background in autoradiograms obtained at 0.5–1 h. Radiolabel was concentrated in those regions which lack an effective blood-brain barrier particularly within the choroid plexuses. Radioactivity was rapidly taken up by the liver and kidneys and as the blood and body radioactivity levels decreased, these organs remained densely labeled. Significant biliary excretion had occurred by 30 min and the autoradiograms at 24 h showed radiolabeled compounds in the intestinal lumen. Between 1 and 8 h, the liver exhibited a stippled appearance as a result of labeling around branches of the portal vein due to enterohepatic recycling. The stippling was substantially diminished at 16 h. High levels of radioactivity were present in the kidney at 0.5–3 min after injection with both the kidney cortex and medulla initially densely labeled. At 4 h and thereafter, the radioactivity levels in the kidney were lower with most of the labeled compounds in the medulla. Accumulation in the liver and kidney was very low at 16–24 h after dosing and most of the merbarone dose had cleared from the body.

Rapid absorption of merbarone occurred after oral administration with radiolabel first observed in the liver and kidney at 3–6 min after dosing. Peak levels in these organs and systemically were seen between 0.5 and 2 h. At 4 h, the radioactivity had largely cleared from the systemic circulation. The liver exhibited a stippled appearance soon after oral dosing similar to that observed following i.v. dosing affording evidence for enterohepatic recycling after i.v. administration. The relatively low systemic levels observed after oral dosing suggests that the liver binds much of the absorbed drug and its metabolites limiting the levels which reach the systemic circulation.

INTRODUCTION

Merbarone (NSC 336628), 5-(\(N\)-phenylcarboxamido)-2-thiobarbituric acid (Fig. 1), was selected for clinical trials based upon its good antitumor activity in four i.p. implanted murine tumor models, the P388 and L1210 leukemias, the B16 melanoma, and the M5076 sarcoma (2, 3). Retention of the antitumor efficacy against the L1210 leukemia was observed when the tumor was implanted s.c. and merbarone was administered on a multiple-dose schedule i.p. or p.o., however, diminished efficacy was found upon i.v. administration of the drug (2).

The mechanism of the cytotoxic action of merbarone has not been determined. Initial studies (4) have shown that after exposure of L1210 cells to merbarone (10–50 µM) for 16–24 h, the DNA from these cells exhibit dose-related single strand breaks. The single strand breaks were not protein associated and no formation of DNA-protein cross-links were demonstrated. The compound does not appear to function as an alkylator or a direct respiratory inhibitor. Upon exposure of L1210 cells to 10 µM merbarone for 24 h, there were no significant alterations in their nucleotide or amino acid pools. The cytotoxicity of merbarone could not be reversed by maximally tolerated concentrations of preformed purines, pyrimidines, or amino acids. The synthesis of nucleic acids and proteins was not significantly inhibited by short exposure to the drug.

Preclinical toxicological studies following i.v. administration were conducted in mice, rats, and beagle dogs (5). In all three species, clinical observations suggested central nervous system toxicity. The target organs of toxicity were bone marrow in rats and lymphoid tissues, bone marrow, and liver in dogs. Histopathology indicated renal degeneration in rats and thymic atrophy in dogs.

In this study, we demonstrate, using whole-body autoradiography, the distribution of merbarone and its metabolites in mice after the i.v. and oral administration of [2-\(^{14}\text{C}\)]merbarone.

MATERIALS AND METHODS

Materials. Merbarone and [2-\(^{14}\text{C}\)]merbarone were obtained from Dr. J. A. R. Mead and Merbarone for Injection was obtained from James C. Cradock, Developmental Therapeutics Program, National Cancer Institute, NIH, Bethesda, MD. The radiolabeled compound, synthesized by Dr. John A. Kepler, Research Triangle Institute, Research Triangle Park, NC, had a specific activity of 55.7 µCi/mg (14.6 mCi/mmol). The unlabeled and radiolabeled compounds cochromatographed identically using an analytical high-performance liquid chromatographic system. Merbarone for Injection is a hypolipidemic powder which after reconstitution with 5 ml of Sterile Water for Injection, USP, contains 10 mg/ml of merbarone and 20 mg/ml of meglumine and has a pH of 9.0–10.5. The autoradiographic Ultrofilm and tape were purchased from LKB Instruments (Gaithersburg, MD).

Animals and Treatment. Male CD\(_2\)F\(_1\) mice (mean weight 30.0 g) were injected in the tail vein during 1 min with 46.6 mg/kg (s. a., 7.0 µCi/mg) of [2-\(^{14}\text{C}\)]merbarone in reconstituted Merbarone for Injection using an injection volume of 0.2 ml. At 3 min, 30 min, 1 h, 2 h, 4 h, 8 h, 16 h, and 24 h from the start of injection, two animals at each time were deeply anesthetized with chloroform and rapidly frozen in a hexane/dry ice bath (−70°C). In order to study the initial CNS distribution of radiolabel, one animal was injected i.v. during 5 s with 47.0 mg/kg (s. a., 17.1 µCi/mg) of [2-\(^{14}\text{C}\)]merbarone in reconstituted Merbarone for Injection using an injection volume of 0.09 ml and was sacrificed at 30 s.

Male CD\(_2\)F\(_1\) mice (mean weight 25.8 g) were given 140.0 mg/kg (s. a., 17.1 µCi/mg) p.o. of a solution (0.25 ml) of [2-\(^{14}\text{C}\)]merbarone in reconstituted Merbarone for Injection. The oral dose was administered using a number 18 gavage cannula and the mice were sacrificed as described above at 6 min, 30 min, 2 h, and 4 h after dosing.

Autoradiography. Serial sectioning was performed using an LKB model 2250 PMV cryomicrotome (LKB Instruments, Gaithersburg, MD). The mice were mounted in 6% carboxymethylcellulose which forms a firm support matrix around the specimen on a microtome stage. The cryomicrotome operating at −25°C was used to cut 50-µm-
thick sections from a minimum of six levels within the body of the mice injected i.v. with radiolabeled merbarone having specific activity 7.0 μCi/mg. Sections of 25-μm thickness were obtained similarly from the animals treated with the radiolabeled drug having specific activity 17.1 μCi/mg. The sections were picked up on 3M type 810 tape, freeze-dried in the cryostat for 24-48 h, and apposed to LKB Ultrofilm. The film was exposed for 7 days in the studies using radiolabeled drug with the lower specific activity and for 2.5 days in studies with the higher specific activity. After exposure, the sections were removed from the film and the film was developed. Overlay of the autoradiograms on the sections and microscopic examination of hematoxylin and eosin stained formalin-fixed sections permitted determination of the tissues and organs in which the radioactive drug and/or metabolites were localized.

Radioactivity in Tissues. Triplicate samples of each tissue were placed in tared Combusto-cones (Packard Instrument Co., Downer’s Grove, IL) containing cellulose powder (150 mg) and weighed to obtain sample weights by difference. The samples were air dried for 24 h and were combusted to CO2 and water in a Packard model 306 sample oxidizer. A mixture of Oxisorb-CO2/Oxiprep-2 (9/13, v/v) (New England Nuclear, Boston, MA) was used to trap the CO2 and the solutions were counted in a liquid scintillation spectrometer (LS-6800; Beckman Instruments, Fullerton, CA). Recovery of radioactivity from sample oxidation was determined by combusting calibrated [14C]methyl methacrylate chips (New England Nuclear) under similar conditions. The efficiency of counting the samples was determined by the internal standard method using Oxi-Test standards (Radiomatic Instruments, Tampa, FL).

RESULTS

Distribution following i.v. Injection

Representative autoradiograms of sagittal sections of a mouse at intervals after dosing are shown to illustrate the time course of the distribution of the radiolabel after i.v. injection (Figs. 2–5). At 3 min after dosing the levels of radioactivity in the blood were high and the tissues which are highly perfused with blood showed the presence of radiolabel. At 30 min and thereafter, when the levels in the blood decreased, those organs in which there was accumulation of radioactivity were readily discerned. A description of the relative concentrations of radioactivity in various organs follows.

Liver. The liver very rapidly accumulated a high amount of the injected compound. Accumulation was high at 3 min after dosing (Fig. 2) and as the blood and body radioactivity levels decreased, the liver retained a high concentration of radiolabel. The liver exhibited a stippled appearance in the autoradiograms obtained 1-8 h after dosing (Fig. 4). An enlargement of the autoradiogram obtained at 8 h after dosing (Fig. 6) showed that the stippled effect within the liver is the result of labeling around branches of the portal vein draining the alimentary tract. The stippling was substantially diminished by 16 h and at 24 h some radioactivity remained in the liver (Fig. 5).

Gallbladder and Gastrointestinal Tract. A high concentration of radiolabel was seen in the gallbladder as soon as 3 min after dosing (Fig. 2) and the duodenum was densely labeled at 30 min (Fig. 3). All the autoradiograms from 0.5 to 24 h showed...
dense labeling in the intestinal lumen due to biliary excretion.

Kidney. Radioactivity was rapidly taken up by the kidneys with high levels present at 3 min (Fig. 2). At 0.5–2 h both the kidney cortex and medulla were densely labeled (Fig. 3). However, by 4 h kidney levels had fallen significantly with most of the labeled compounds in the medulla (Fig. 4). The presence of label predominantly in the medulla at 8 h is clearly seen in an enlargement of the midsection of an autoradiogram (Fig. 6). Substantially lower levels of radioactivity were still present in the medulla at 16 and 24 h after dosing (Fig. 5).

Central Nervous System. Low levels of radioactivity were seen in the brain and spinal cord at 0.5–3 min after dosing. The levels markedly declined and appeared to be just above background in autoradiograms obtained at 0.5–1 h. Enlargement of an autoradiogram of the head at 0.5 min after dosing (Fig. 7) shows that the blood-brain barrier significantly restricts the entry of merbarone into the parenchyma of the CNS. Radiolabel was concentrated in the areas with a much less effective blood-brain barrier including the choroid plexuses, the area postrema, the pineal body, and the posterior pituitary (6). Lower levels were also seen in the cerebrospinal fluid within the ventricles. Radioactivity in the brain was not detected in the later autoradiograms.

Circulatory System. The peak levels of radioactivity in blood after i.v. dosing (Figs. 2 and 3) declined until at 8 h the levels were only slightly above background. The levels in the heart and walls of blood vessels paralleled the levels in blood with no specific uptake occurring in these tissues.

Respiratory System. Apart from the apparent accumulation in the bronchial walls observed at 30 min to 4 h (Figs. 3 and 4), the levels in the lung parenchyma did not exceed the levels in blood at any time after dosing.

Endocrine Organs. The pituitary and pineal body were densely labeled at 0.5 min (Fig. 7) and at 3 min after the injection. The radioactivity progressively decreased in these organs and none was detected at 2 h. Radiolabel in the thyroid was distinct at 2 h after dosing and low levels were present in the autoradiograms to 24 h after the injection. Levels of radiolabel, comparable to the blood levels, were observed throughout the pancreas between 3 min and 1 h. The activity was not specifically associated with the endocrine pancreas.

Lymphatic and Myeloid Tissues. The levels of radioactivity in the spleen, thymus, and lymphatic nodes did not exceed the levels in the blood at any time after dosing. The thoracic lymph duct was labeled at 0.5–4 h (not shown) with peak levels occurring at 2 h.

Lacrimal and Salivary Glands. The Harderian auxiliary lacrimal gland showed high accumulation at 30-min postinjection (Fig. 3). Periocular drainage via the lacrimal ducts into the oral cavity was observed until 4 h after dosing (Fig. 4). The submandibular salivary gland showed levels similar to that in blood at 3 min (Fig. 2) and by 1 h the levels had declined below the levels present in blood.

Reproductive System. The testes showed a low level of radioactivity at 30 min (Fig. 3) and by 2 h the level in the testes was similar to that in the skeletal muscle. Dense labeling of the most vascular region of the caput epididymis was seen at 3 min (Fig. 2) and label was present until 1 h after dosing. The labeling of this specific region of the epididymis was demonstrated by an overlay of the autoradiogram with a hematoxylin and eosin-stained formalin-fixed section.
Adipose Tissue. At 0.5–3 min after injection, the brown dorsal fat appeared to be densely labeled (Figs. 2 and 7) with levels similar to that in blood in contrast to the abdominal white fat which contained little radioactivity. With a decline in blood radioactivity levels, no accumulation in adipose tissue was seen.

Comparative Tissue Distribution at 8 H. In order to determine whether the autoradiograms describe adequately the relative levels of merbarone and/or metabolites in the tissues, the relative levels were determined after dissection and measurement of the levels of radioactivity in the tissues. [2-14C]Merbarone (48.2 mg/kg, 9.79 μCi) was injected i.v. into three mice. The animals were sacrificed at 8 h after dosing and the relative concentrations of merbarone radioactive equivalents in various tissues to that in blood and muscle were measured by oxidative combustion of the tissues, trapping the radioactive CO2, followed by liquid scintillation counting. The tissue/blood and tissue/muscle ratios (Table 1) show that the autoradiograms reflect very well the relative levels in tissues but that very low levels may not be readily perceived in the autoradiograms. It is noted that unavoidable residual blood with the brain tissue may account for some of the radioactivity determined in the brain in the combustion experiment.

Distribution following Oral Dosing

The time course of the distribution of radioactivity to 4 h after oral dosing is illustrated by the representative autoradiograms shown in Fig. 8. These autoradiograms can only be compared qualitatively with those obtained after i.v. administration since the doses and their specific activity were higher than those administered i.v. At 6 min after oral dosing, systemic absorption was demonstrated by accumulation of radioactivity in the liver and kidney (Fig. 8a), however, blood and body levels were extremely low. The maximum systemic levels were observed in the autoradiograms obtained at 30 min and 2 h (Fig. 8, b and c) and by 4 h, the systemic levels had declined significantly (Fig. 8d). Generally, the peak systemic levels appeared to be low and the overall patterns of distribution and tissue accumulation were similar to those following i.v. administration. The levels in the CNS were only slightly above background at 0.5 and 2 h and were below detection limits at 6 min and at 4 h. Accumulation occurred principally in the liver and kidney.

After oral dosing, the concentration of radioactivity in the liver increased until at 30 min (Fig. 8b) high levels were present and radiolabel had entered the gallbladder (not shown). Similar high concentrations were seen in the liver at 2 h (Fig. 8c), at which time very high radioactivity levels were present in the gallbladder and bile ducts. During the following 2 h, the levels in the liver declined significantly (Fig. 8d) but the gallbladder remained densely labeled. The liver in the autoradiograms obtained at each time after dosing exhibited a stippled appearance due to labeling around the branches of the portal vein.

Significant levels of radioactivity in the kidney (Fig. 8a) and excretion into the bladder were seen as early as 6 min after the oral dose. At 0.5 and 2 h, the kidney levels had increased with the majority of the radiolabel present in the medulla (Fig. 8, b and c). At these times, both the kidney and blood levels were low relative to the levels in the liver. At 4 h, when the levels in the blood had decreased, the levels in the kidney were also markedly lower suggesting that any enterohepatic recycling of drug and metabolites did not significantly affect the systemic levels.
Fig. 5. Whole-body autoradiograms of a mouse 24 h after i.v. injection of [2-14C]merbarone (46.6 mg/kg; s. a., 7.0 μCi/mg). Light areas, high concentrations of labeled compounds. KM, kidney medulla; L, liver; IL, intestinal lumina; TH, thyroid; GB, gallbladder; U, urine.

Fig. 6. Enlargement of the midsection of a whole-body autoradiogram of a mouse 8 h after i.v. injection of [2-14C]merbarone (46.6 mg/kg; s. a., 7.0 μCi/mg) showing that the stippled labeling in the liver results from the concentration of radiolabel around branches of the portal vein. Dense labeling is present within the intestinal lumen and lower levels are present within the renal medulla and inner cortex. PV, portal vein; KM, kidney medulla; IL, intestinal lumina.
Table 1 Relative concentration of radioactive merbarone equivalents in the tissues of mice (N = 3) at 8 h after an i.v. bolus dose of 48.2 mg/kg (9.79 μCi)

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Tissue/blood ratio</th>
<th>Tissue/muscle ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>19.72 ± 2.87</td>
<td>33.61 ± 17.08</td>
</tr>
<tr>
<td>Large intestine</td>
<td>11.33 ± 6.33</td>
<td>20.95 ± 18.92</td>
</tr>
<tr>
<td>Kidney</td>
<td>8.14 ± 1.06</td>
<td>12.94 ± 3.36</td>
</tr>
<tr>
<td>Small intestine</td>
<td>7.10 ± 2.45</td>
<td>12.14 ± 4.25</td>
</tr>
<tr>
<td>Stomach</td>
<td>3.65 ± 1.85</td>
<td>5.31 ± 0.74</td>
</tr>
<tr>
<td>Lung</td>
<td>2.16 ± 0.59</td>
<td>3.31 ± 0.50</td>
</tr>
<tr>
<td>Heart</td>
<td>2.09 ± 0.61</td>
<td>3.20 ± 0.49</td>
</tr>
<tr>
<td>Spleen</td>
<td>1.48 ± 0.58</td>
<td>2.40 ± 1.11</td>
</tr>
<tr>
<td>Testes</td>
<td>0.76 ± 0.06</td>
<td>1.28 ± 0.57</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.68 ± 0.27</td>
<td>0.68 ± 0.27</td>
</tr>
<tr>
<td>Brain</td>
<td>0.12 ± 0.02</td>
<td>0.19 ± 0.06</td>
</tr>
</tbody>
</table>

* Mean ± SD.

DISCUSSION

The observations suggesting CNS toxicity of merbarone in mice, rats, and dogs during the preclinical toxicological evaluation (5) and the structural similarity of merbarone, a 5-monosubstituted thiobarbiturate, to the CNS-depressant 5,5-disubstituted barbiturates inevitably will prompt comparisons of the distribution, disposition, and pharmacodynamics of merbarone with these compounds. In our preclinical pharmacological studies (7), the incidence of convulsions after the i.v. injection of the LD₁₀ dose to mice appeared to be related to the rapid rate of administration suggesting that the CNS effects may be attributable to peak levels of the parent drug.

The autoradiograms demonstrate that after i.v. injection exceedingly low levels of merbarone were present in the brain parenchyma and somewhat higher levels were present in the cerebrospinal fluid. The highest of these levels occurred immediately after injection. Thus, the blood-brain barrier effectively restricted entry of the compound and its metabolites into the brain parenchyma. The complex tight junctions between the endothelial cells and the substantial basement membrane surrounding the capillaries of the CNS form the basis of this functional and morphological barrier (6, 8). The less substantial barrier to transport into the cerebrospinal fluid involves the cuboidal epithelium of the choroid plexuses, which is generally considered to behave as a lipoidal membrane (8, 9). In these studies, the areas in which radiolabel was observed to concentrate correspond to tissues which lack a barrier or in which the barrier is less effective.

Merbarone exhibits a pKa value of 4.0 (3), similar to that of 5-monosubstituted barbiturates (10, 11), whereas the pKa values of 5,5-disubstituted barbiturates are in the range of 7.2–8.4 (11, 12). This suggests that the relatively low degree of transport of merbarone into the CNS may be related to ionization of the drug at physiological pH. Accordingly, compared with most 5,5-disubstituted barbiturates, merbarone is likely to exhibit low CNS-depressant activity. However, in the phase I clinical trial in cancer patients, i.v. doses will be escalated to establish the maximally tolerated dose. Therefore, despite the small fraction of the dose which enters the CNS, it is anticipated that somnolence may occur in patients at the higher doses.
Fig. 8. Autoradiograms of a mouse following oral dosing of $[2-^{14}C]$merbarone (140 mg/kg s. a., 17.1 μCi/mg). Time after dosing: a, 6 min; b, 30 min; c, 2 h; d, 4 h. Light areas, high concentrations of labeled compounds. HG, Harderian gland; DF, dorsal fat; LU, lung; KM, kidney medulla; SG, submandibular salivary gland; V, venous blood; VC, vena cava; ES, esophagus; TH, thyroid; H, heart; CE, caput epididymis; PD, periocular drainage; GB, gallbladder; U, urine.
The autoradiograms show that there is rapid uptake of very low levels of merbarone by the brain following i.v. injection and subsequent rapid exit as the blood levels decreased. The short duration of entry suggests that the CNS effects are due to unchanged merbarone since the levels of metabolites should not be appreciable at very early times.

The pharmacodynamics of the 5,5-disubstituted barbiturates are distinguished by differences in hypnotic activity and the onset and duration of action (13). Thiobarbiturates generally exhibit a shorter duration of action than the corresponding oxybarbiturates. Thiopental, 5-ethyl-5-(1-methylbutyl)-2-thio-barbituric acid, has a very short onset and duration of action and is widely used as a general anesthetic whereas the action of phenobarbital, 5-ethyl-5-phenylbarbituric acid, is slow to develop and is prolonged (13). After the i.v. injection of [3H]-thiopental in mice, whole-body autoradiography studies demonstrated high levels of radioactivity present in the brain, evenly distributed in the grey matter, between 30 s and 2 min after dosing and after 5 min, the radioactivity levels in brain had greatly decreased (14). In contrast, following the i.v. administration of [2-14C]phenobarbital to mice, very low radioactivity levels were observed in autoradiograms of brain at 30 s and the amounts increased thereafter with the highest levels recorded between 5 min and 4 h after injection (14). The principal decline in brain levels occurred between 12 and 24 h after dosing. Unlike these barbiturates, the levels of merbarone in the brain were extremely low, however, the pattern of rapid uptake of merbarone by the brain and subsequent exit is more analogous to that of thiopental than the long-acting 5,5-disubstituted barbiturates.

The plasma concentration-time profile of the parent drug, determined using high-performance liquid chromatography, following a 1-min i.v. infusion of 34.2 mg/kg of merbarone to male CD-1 mice exhibited biexponential decay with a terminal half-life of 2.53 h (7). The plasma levels of merbarone decreased from 73.5 μg/ml at 2 min after dosing to 2.07 μg/ml at 8 h after dosing.4 Therefore, the decline in the radioactivity blood levels qualitatively described by the autoradiograms was consistent with that determined quantitatively. Radioactivity in blood and highly perfused tissues was not detectable in the autoradiograms obtained at 16 and 24 h after dosing and the plasma levels of merbarone in mice at these times were also below the assay sensitivity.

Toxicity to liver and kidney was observed in dogs and rats, respectively, in the preclinical toxicological evaluation of merbarone (5). In the present studies, the liver and kidney were the principal organs in which accumulation of radiolabel occurred. Providing that the distribution of merbarone and its metabolites is similar in the species, the toxicity to liver and kidney may be related to the affinity of the compounds for these organs.

The autoradiograms have shown that the principal route of excretion of merbarone and its metabolites in mice is via the bile. Bilary excretion of high levels of the drug and its metabolites may have contributed to the gastrointestinal disturbance observed in dogs following i.v. administration (5).

The accumulation of radiolabel around the larger branches of the hepatic portal vein, which drains the gastrointestinal tract, after i.v. administration of radiolabeled merbarone (Fig. 6) is indicative of enterohepatic recycling. The liver removes much of the reabsorbed drug and metabolites before they reach the systemic circulation. Evidence in support of this view is derived from the similar labeling pattern observed soon after oral dosing (Fig. 8, a and b). Furthermore, the presence of high levels of radiolabeled compounds in the gallbladder and bile ducts after oral administration confirms the existence of enterohepatic recycling.

Merbarone has demonstrated antitumor activity following oral administration (2). The activity of merbarone against the murine s.c. implanted L1210 leukemia following p.o. treatment of 124 mg/kg/day for 9 days was equal to that after i.p. administration of 45 mg/kg/day for 5 days (2). The larger total dose required p.o. is indicative of the low bioavailability by this route. Our results indicate that the high affinity of the liver for the drug and its rapid excretion in the bile limits the systemic blood levels thus necessitating the higher total dose required orally. The high levels of drug and metabolites in the liver and gastrointestinal tract after oral dosing suggests that this route of administration should be evaluated clinically for the treatment of hepatic and colon tumors. Oral administration may provide adequate levels of merbarone and its metabolites to the tumor sites with relatively lower systemic blood levels than from parenteral administration.

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* L. Malspeis and M. E. Lyon, unpublished observations.
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