# Residues of Tritium-Labeled Morantel in Lactating Dairy Cattle

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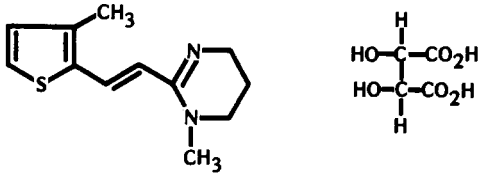
Residues of morantel and its metabolites were monitored in plasma, urine, and milk of five lactating dairy cattle that received an oral dose of [*4,4-pyrimidyl*-$^3H_2$]morantel tartrate at 10 mg/kg. Drug-related radioactivity peaked in plasma at 8 h and in milk by the second milking, postdose, and was 170 and 84 ng/mL, respectively. The fraction of total residues in milk convertible to the marker compound, *N*-methyl-1,3-propanediamine, was 0.38 on the basis of a comparison of the areas under the curves for total and marker residues. Five days after dosing, 3.9% of the total radioactivity in liver was recovered as tritium water. Total drug-related residues in this target tissue averaged 1.15 μg/g. About half of the drug-related residues in liver was unextractable and was classified at "bound".

Morantel tartrate [1,4,5,6-tetrahydro-1-methyl-2-[*trans*-2-(3-methyl-2-thienyl)vinyl]pyrimidine tartrate] is



MORANTEL TARTRATE

an anthelmintic that is effective against mature and immature nematodes that infect ruminants (Jones et al., 1978; Pott et al., 1979; Jones, 1981). It has been approved for the control of gastrointestinal nematode infections when given as a single oral treatment at approximately 9.7 mg/kg of body weight, either in feed or as a conventional type bolus (Rumatel). The effect of morantel tartrate on improving the production of milk of dairy cattle has been reported (Block and Gadbois, 1986).

The metabolism of morantel has been studied under in vivo and in vitro conditions for cattle and laboratory animals (Lynch et al., 1986a). Earlier studies defined the absorption, distribution, and excretion of morantel in beef cattle (Faulkner and Davidson, 1971) and its analogue pyrantel (Faulkner et al., 1972; Figdor et al., 1978) in swine, cattle, sheep, and laboratory animals. These studies demonstrated that pyrantel and morantel are metabolized to an array of metabolites by stepwise oxidation of the thiophene and tetrahydropyrimidine nuclei as well as by conjugation with glutathione.

Analytical methods have been described for the detection of residues of morantel and its metabolites in the target tissue, liver (Lynch and Bartolucci, 1982a,b), and in milk (Lynch et al., 1986b,c). These methods are based on converting the drug and major metabolites to the marker compound *N*-methyl-1,3-propanediamine and the drug and minor metabolites to 3-(3-methyl-2-thienyl)acrylic acid by alkaline hydrolysis procedures. The depletion and statistical distribution of these compounds have been described for dairy cattle dosed with morantel tartrate (Lynch et al., 1986d). The following study was primarily conducted to assess the levels and depletion of total and marker residues in milk of lactating dairy cattle dosed with tritium-labeled morantel tartrate. A secondary objective was to assess the levels of total residues of morantel in plasma and liver and the availability of these residues in the target tissue when subjected to extraction with polar solvents.

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## MATERIALS AND METHODS

**Synthesis of [*4,4-pyrimidyl*-$^3H_2$]Morantel Tartrate.** A method described for pyrantel (Figdor et al., 1970) was modified for morantel. In this synthesis, the imino ether of 3-methyl-2-thiopheneacrylonitrile was prepared by bubbling dry HCl gas through a mixture of 3-methyl-2-thiopheneacrylonitrile (94 g, 0.64 mol) and anhydrous methanol (26 mL 0.64 mol), which was cooled by an ice bath. After standing overnight at 0 °C, the imino ether hydrochloride (102 g) was recovered by filtration. A mixture of 3-methyl-2-thiopheneacrylonitrile imino ether hydrochloride (5.60 g, 25.9 mmol), [3-$^3$H]-*N*-methyl-1,3-propanediamine (2.04 g, 25.2 mmol; prepared by New England Nuclear Corp, by the Raney nickel reduction of *N*-methyl-3-aminopropionitrile in the presence of tritium gas), and anhydrous methanol (10 mL) was refluxed for 18 h with the exclusion of light and moisture. All subsequent extraction procedures were conducted with solvents cooled to approximately 5 °C and performed as rapidly as possible. The reaction mixture was cooled, NaOH (2 N, 75 mL) was added, and the resultant mixture was extracted with several portions of methylene chloride. The methylene chloride was in turn extracted with several portions of HCl (1 N) and this extract basified by the addition of NaOH solution and once again extracted with methylene chloride. This extract was concentrated to an oil and chromatographed over a column of Fisher basic alumina (100 g) prepared in methylene chloride. The column was eluted with methylene chloride, and fractions containing [$^3$H]morantel were combined and concentrated to yield 3.4 g (15.5 mmol) of the free base. The product was dissolved in ethanol (25 mL) and a hot solution of tartaric acid (2.32 g, 15.5 mmol) in ethanol (25 mL) added. The product crystallized with cooling, yielding 4.36 g (50%) with a specific activity of 194 mCi/mmol. A product with lower specific activity was prepared by dilution with nonlabeled morantel tartrate (82.8 g) in 1.8 L of ethanol, followed by boiling, filtration, and cooling, yielding 75.7 g, with a specific activity of 11.9 mCi/mmol. Chemical and radiochemical purity (HPLC, TLC) was >99%.

**Determination of Radioactivity in Bovine Plasma, Milk, Urine, and Liver Specimens.** Aqueous samples consisting of 2 mL of milk, 1 mL of plasma, and 0.1 mL of urine were transferred to scintillation vials and each was mixed with 15 mL of Scintolsol (ISOLAB) scintillator. All samples were measured for tritium radioactivity in a Searle Analytical Inc. Model 6880 (Mark III) liquid scintillation counter. The samples were counted for 20 min or until they gave 40 000 cpm. Each sample was then corrected for quench by the addition of tritium–toluene as an in-

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**Table I. Urinary Excretion of Radioactivity following Oral Administration of [$^3$H]Morantel Tartrate to Five Lactating Dairy Cattle**

| | daily excretion of radioact, % of dose | | | | |
|---|---|---|---|---|---|
| | day 1 | day 2 | day 3 | day 4 | total |
| | 9.7 | 6.2 | 2.7 | 1.0 | 19.6 |
| | 7.5 | 4.5 | 1.3 | 0.4 | 13.7 |
| | 8.0 | 5.6 | 2.0 | 1.0 | 16.6 |
| | 6.6 | 7.0 | 2.6 | 1.3 | 17.5 |
| | 11.2 | 5.5 | 0.7 | 0.3 | 17.7 |
| mean | 8.6 | 5.8 | 1.9 | 0.8 | 17.0 |
| SD | 1.8 | 0.9 | 0.9 | 0.4 | 2.2 |

**Table II. Excretion of Tritium Radioactivity by a Lactating Dairy Cow (L00114) following Oral Administration of [$^3$H]Morantel Tartrate at 10 mg/kg**

| collectn period postdose, h | total radioactivity in urine | | $^3H_2O$ radioact, % of dose |
|---|---|---|---|
| | % of dose | % $^3H_2O$ | |
| 0–7 | 1.1 | 0.2 | 0.002 |
| 7–24 | 8.48 | 0.4 | 0.034 |
| 23–30 | 2.96 | 0.9 | 0.027 |
| 30–47 | 3.28 | 1.1 | 0.036 |
| 47–54 | 1.17 | 2.6 | 0.031 |
| 54–71 | 1.45 | 4.0 | 0.058 |
| 71–78 | 0.43 | 5.7 | 0.025 |
| 78–95 | 0.56 | 6.0 | 0.034 |
| total | 19.51 | | 0.247 |

ternal standard and then counted for 2 min. Negative specimens of milk, urine, and plasma were assayed in the same manner to calculate the blank background for dpm calculations.

Triplicate 1-g liver samples, obtained from whole liver homogenates from each cow, were combusted in a Packard Model 306 Tri-Carb sample oxidizer. Each liver sample was weighed into a combustion cone (Combusto Cone) containing an absorption pad. An additional pad was placed on top, and the samples were lyophilized and burned. The oxidation time was set at 1.5 min with combustion products being trapped with 18 mL of Monophase 40 Plus. A sample of Spec-Chec-$^3$H-Standard (Packard) of known specific activity was combusted to calculate the combustion efficiency (85%) of the system and to correct data. Negative samples of liver were combusted to calculate the blank background used for dpm calculations.

**Determination of the Tritiated Water Content of Plasma, Milk, Urine, and Liver in Bovine Specimens.** The tritium water content of whole liver homogenates, milk, urine, and plasma was determined by a lyophilization procedure. Samples consisting of 0.2–0.5 g of liver and 1, 2, and 5 mL of plasma, urine, and milk, respectively, were placed in distillation flasks, frozen with the aid of a solid $CO_2$–acetone bath, and distilled under vacuum. The lyophiles were collected in flasks immersed in a solid $CO_2$–acetone bath. Aliquots consisting of 0.1, 0.5, 0.2, and 2 mL of the distillates from liver, plasma, urine, and milk were assayed for radioactivity.

**Determination of Morantel-Related Residues in Bovine Milk by Chemical Assay.** The analytical method used in this experiment was validated for the determination of morantel-related residues in bovine milk at levels ranging from 0.5 to 2 times the projected peak level of 0.025 ppm. The method is based on hydrolyzing the *N*-methyltetrahydropyrimidine portion of morantel and its metabolites to *N*-methyl-1,3-propanediamine (MAPA), followed by converting the diamine to an *N*,*N*′-bis[2-nitro-4-(trifluoromethyl)phenyl] derivative. The addition of an internal standard, the *N*-desmethyl-*N*-ethyl homologue of pyrantel, to the milk sample circumvents any potential problem that could arise from variable reaction yields and eliminates the true recovery as a factor affecting the accuracy and precision of the procedure (Lynch et al., 1986b). The concentrations of the derivatives are determined by pulsed electron-capture gas chromatography over a linear dynamic range that is equivalent to 12.5–50 ppb of morantel. The method has been evaluated at the 0, 12.5, 25, and 50 ppb levels in fortified bovine milk and in withdrawal samples containing physiologically incurred morantel residues (Lynch et al., 1986b,d).

**Dairy Cattle.** Following urethral catheterization of five healthy Holstein lactating cows, 2–7 years old, each was given a capsule containing trituim-labeled morantel tartrate to provide a dose of 10 mg/kg. Blood for plasma separation was collected at 2, 5, 8, 24, 32, 48, 56, 72, 80, and 96 h, and milk and urine were collected twice daily, in the morning and evening for 4 consecutive days posttreatment. The cows were sacrificed for collection of liver samples on the fourth day.

## RESULTS AND DISCUSSION

It was shown in earlier radiotracer metabolism studies with ruminants (Faulkner et al., 1972) that a major portion of the radioactivity derived from pyrantel labeled with tritium at the C-4 pyrimidyl position was recovered from tissues as the alkaline hydrolysis product: *N*-methyl-1,3-propanediamine. This information, coupled with the need to dose five lactating dairy cattle at 10 mg/kg and the expectation of finding ppb residues in milk, prompted synthesis of morantel with tritium positioned at the C-4 pyrimidyl carbon.

In the study described here, five lactating dairy cattle excreted 17% of the dose in urine (range 14–20%; Table I) over a 0–96-h period with less than 0.25% of the dose recovered as tritium water (Table II), indicating absorption and stability of the label. Mean drug-related concentrations in plasma peaked at 170 ng/mL (range 92–223 ng/mL) 8 h after dosing and at 84 ng/mL (range 71–93 ng/mL) in milk by the second milking (Tables III and IV). When compared to plasma (Figure 1), residues in milk declined at the same rate with a half-life of 1 day but were half as high, indicating that residues of morantel do not preferentially distribute into milk from plasma.

Morantel-related residues that are convertible to *N*-methyl-1,3-propanediamine peaked at 28 ng/mL (range

**Table III. Total Residues of Morantel in Plasma of Five Lactating Dairy Cattle following Oral Administration of [$^3$H]Morantel Tartrate at 10 mg/kg**

| | | [$^3$H]morantel equiv hours postadmin, ng/mL | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | predose | 2 | 5 | 8 | 24 | 32 | 48 | 56 | 72 | 80 | 96 |
| | <1 | 16 | 143 | 202 | 109 | 113 | 75 | 21 | 13 | 18 | 33 |
| | <1 | 8 | 44 | 92 | 80 | 68 | 35 | 25 | 17 | 13 | 5 |
| | <1 | 12 | 117 | 223 | 162 | 160 | 87 | 71 | 47 | 42 | 28 |
| | <1 | 9 | 81 | 162 | 124 | 88 | 56 | 36 | 34 | 29 | 18 |
| | 1 | 17 | 94 | 173 | 136 | 85 | 38 | 36 | 25 | 18 | 17 |
| mean | <1 | 12 | 96 | 170 | 122 | 103 | 58 | 38 | 27 | 24 | 20 |
| SD | | 4 | 37 | 50 | 31 | 36 | 23 | 20 | 14 | 12 | 11 |

**Table IV. Total Residues of Morantel in the Milk of Five Lactating Dairy Cattle following Oral Administration of [$^3$H]Morantel Tartrate at 10 mg/kg[a]**

| | [$^3$H]morantel equiv milkings postdose, ng/mL | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| | 42 | 92 | 77 | 60 | 42 | 28 | 23 | 18 |
| | 30 | 77 | 64 | 45 | 21 | 16 | 10 | 10 |
| | 32 | 71 | 70 | 50 | 33 | 22 | 17 | 13 |
| | 28 | 87 | 77 | 52 | 35 | 20 | 16 | 9 |
| | 30 | 93 | 68 | 36 | 15 | 9 | 6 | 3 |
| mean | 32 | 84 | 71 | 49 | 29 | 19 | 14 | 11 |
| SD | 5.5 | 9.6 | 5.7 | 8.9 | 11.0 | 7.1 | 6.6 | 5.5 |

[a] $AUC_{0-\infty} = AUC_{0-5th\ milking}$ + concn 5th milking/$K_{el}$, where $K_{el}$ = elimination constant. $AUC_{0-\infty}$ = 251 + 29/0.37 = 329 ng milking mL$^{-1}$.

**Table V. Morantel-Related Residues in the Milk of Five Lactating Dairy Cattle following Administration of [$^3$H]Morantel Tartrate at 10 mg/kg[a]**

| | | morantel in milkings postdose determined by conversion to MAPA, ng/mL | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | predose | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| | <12.5 | 15 | 23 | 22 | 19 | 13 | <12.5 | <12.5 | NA |
| | <12.5 | 16 | 28 | 21 | 15 | (11) | <12.5 | <12.5 | NA |
| | <12.5 | 16 | 30 | 23 | 16 | (12) | <12.5 | <12.5 | NA |
| | <12.5 | 14 | 30 | 20 | 15 | 16 | <12.5 | <12.5 | NA |
| | <12.5 | 15 | 30 | 21 | (11) | (10) | <12.5 | <12.5 | NA |
| mean | <12.5 | 15 | 28 | 21 | 15 | (12) | <12.5 | <12.5 | |
| SD | | 0.8 | 3.0 | 1.1 | 2.9 | 2.3 | | | |

[a] $AUC_{0-\infty} = AUC_{0-5th\ milking}$ + concn 5th milking/$K_{el}$, where $K_{el}$ = elimination constant. $AUC_{0-\infty}$ = 85 + 12/0.29 = 126 ng milking mL$^{-1}$.

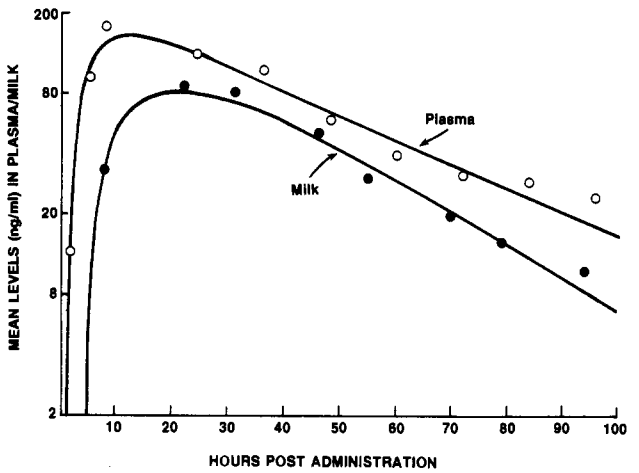


**Figure 1.** Depletion of total residues of morantel in plasma and milk of dairy cattle orally dosed with tritium-labeled morantel tartrate at 10 mg/kg.

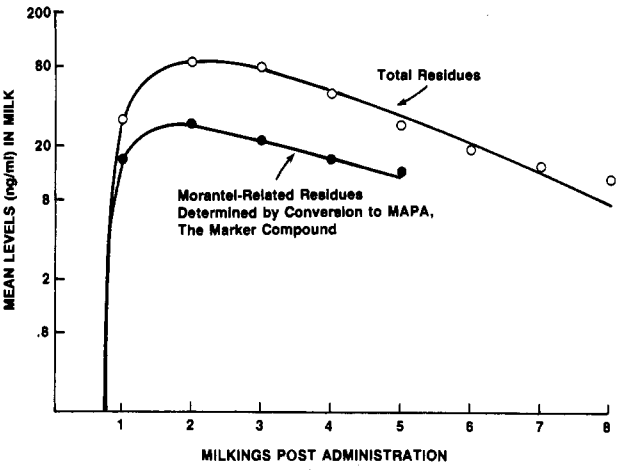


**Figure 2.** Depletion of total and marker (MAPA) residues of morantel in milk of lactating dairy cattle orally dosed with tritium-labeled morantel tartrate at 10 mg/kg.

23–30 ng/mL) by the second milking (Table V) and paralleled the decline of total residues of morantel (Figure 2). On the basis of a comparison of the areas under the depletion curves (Tables IV and V) for total (329 ng milking mL$^{-1}$) and marker residues (126 ng milking mL$^{-1}$), the fraction of total residues of morantel measured by chemical assay is 0.38. Thus, the chemical assay for the marker residue, *N*-methyl-1,3-propanediamine, provides a convenient way to monitor and to estimate total residues of morantel.

In parallel with these studies in milk, total drug-related residues were determined in liver 4 days after dosing (Table VI). These levels averaged 1.15 μg/g (range 0.83–1.47 μg/g) and were comparable to results found in beef cattle (Faulkner and Davidson, 1971). A significant portion of the residue, 57%, was unextractable and classified as "bound" (Table VI). At this withdrawal time, 3.9% (range 3.1–5.1%) of the total radioactivity in liver was recovered as tritium water. The analysis of unextractable, morantel-related residues in bovine liver by conversion to *N*-methy-1,3-propanediamine has been described (Lynch and Bartolucci, 1982a).

**Table VI. Total and Bound Residues of Morantel and the Percent of Total Radioactivity as Tritium Water in the Liver of Five Lactating Dairy Cattle 4 Days following Oral Administration of [$^3$H]Morantel Tartrate at 10 mg/kg**

| | [$^3$H]morantel equivs,[a] μg/g | bound,[b] % | total radioact as $^3H_2O$,[c] % |
|---|---|---|---|
| | 1.35 ± 0.02 | 53 | 5.1 |
| | 0.83 ± 0.04 | 61 | 3.8 |
| | 1.47 ± 0.06 | 58 | 3.2 |
| | 0.97 ± 0.01 | 61 | 4.3 |
| | 1.14 ± 0.01 | 51 | 3.1 |
| mean | 1.15 ± 0.26 | 57 ± 4.8 | 3.9 ± 0.8 |

[a] Average of three determinations with standard deviations. Samples were lyophilized and combusted to determine total residues. The results are expressed as μg of [$^3$H]morantel equiv/g of wet tissue. [b] Approximately 10 g of liver successively extracted with three 100-mL volumes of methanol, acetonitrile, and acetone, dried, and combusted. Residual radioactivity was classified as bound. [c] Single determination of $^3H_2O$ in lyophilized liver samples.

In summary, nanogram/milliliter levels of morantel and its metabolites occur in milk following oral administration of tritium-labeled morantel tartrate at the use level of 10

mg/kg. These levels as well as those of precursors of the marker compound, *N*-methyl-1,3-propanediamine, which constitute 38% of total residues, decline in parallel with a half-life of 1 day.

**Registry No.** $MeNH(CH_2)_2CHTNH_2$, 107082-64-4; $MeNH(CH_2)_2CN$, 693-05-0; MeOH, 67-56-1; $MeNH(CH_2)_3NH_2$, 6291-84-5; 3-methyl-2-thiopheneacrylonitrile (imino ether), 107082-63-3; 3-methyl-2-thiopheneacrylonitrile, 20527-86-0; tartaric acid, 87-69-4; morantel, 20574-50-9; [*4,4-pyrimidyl*-$^3H_2$]morantel (tartrate salt), 107098-03-3; [$^3H_2$]morantel, 107082-65-5.

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# Acetylation/Deacetylation Reactions of T-2, Acetyl T-2, HT-2, and Acetyl HT-2 Toxins in Bovine Rumen Fluid in Vitro[1]

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A tritiated preparation of the trichothecene mycotoxin, T-2 toxin, underwent both acetylation and deacetylation reactions when incubated with bovine rumen fluid in vitro. Products from incubations of T-2 in rumen fluid included acetyl T-2, HT-2, and acetyl HT-2. Direct studies with tritiated samples of each of these metabolites confirmed their relatively facile interconversion in the rumen. Studies with [$^3$H]HT-2 under conditions of inhibited esterase activity (added diisopropyl fluorophosphate) showed that acetylation is preferred at C-3 vs. C-4. Studies with [$^3$H]acetyl T-2 indicated that deacetylation similarly occurs with greater rapidity at C-3. There were no indications that ester hydrolysis of these trichothecenes occurred at C-8 or C-15 or that they were subjected to epoxide reduction reactions. These data suggest that acetylation of T-2 and other trichothecenes in the rumen in situ may ultimately result in the absorption of more lipophilic metabolites whose toxicological and residual properties are at present unknown.

The trichothecenes, as presently known, are a group of some 50 biologically active secondary fungal metabolites. Certain of these compounds have been implicated as causal agents in both human and animal poisonings (Ueno, 1983). One of the most widely studied trichothecenes is T-2 toxin [4$\beta$,15-diacetoxy-8$\alpha$-[(3-methylbutyryl)oxy]-3$\alpha$-hydroxy-12,13-epoxytrichothec-9-ene; Figure 1], a compound known to be of high acute toxicity to a number of vertebrate species (Marasas et al., 1969; Sato and Ueno, 1977; Chi et al., 1978). T-2 has been found in certain grains infected with *Fusarium sp.* (Hsu et al., 1972; Mirocha et al., 1976; Puls and Greenway, 1976), and the ingestion of T-2-contaminated grain has resulted in livestock poisonings (Ueno, 1983).

To better evaluate the toxicological significance of T-2, it is important to define the nature of its interactions with livestock species that may be exposed to T-2 through the diet. The present study was designed to evaluate the nature of T-2 biotransformations that occur in bovine rumen fluid.

## MATERIALS AND METHODS

**Chemicals.** Tritiated T-2 toxin was synthesized by Amersham Corp. (Arlington Heights, IL) and provided to us by the U.S. Department of Defense (Fort Detrick, MD). The label was incorporated at C-3, and the specific activity

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[1]Taken in part from a thesis by C.E.M. submitted to the Graduate College of Texas A&M University as partial fulfillment of the requirements for the Degree of Master of Science, Dec 1985.

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