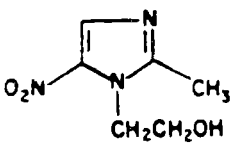
METRONIDAZOLE

IDENTITY

Chemical name: 2-methyl-5-nitroimidazole-1-ethanol
1-(2-hydroxyethyl)-2-methyl-5-nitro-imidazole

Synonyms: Flagyl and sold under at least another 20 trade names

Structural formula:



Molecular formula: $C_6H_9N_3O_3$

Molecular weight: 171.16

OTHER INFORMATION ON IDENTITY AND PROPERTIES

Pure active ingredient:

Appearance: cream-colored crystals

Melting point: 158-160°C

(Windholz, 1983)

RESIDUES IN ANIMALS AND THEIR EVALUATION

CONDITIONS OF USE

General

Metronidazole is not approved for use in food-producing animals. The drug is used in human medicine for the treatment of histomoniasis and anaerobic bacterial infections.

The treatment of bovine trichomoniasis with metronidazole by the oral, intravenous or topical route has been investigated. (Gasparini, 1963)

RESIDUE DEPLETION AND METABOLISM STUDIES

General

The residue depletion and metabolism of metronidazole in food-producing animals has not been studied. However, work has been done in bacteria, rats, dogs and man.

TOTAL RESIDUE DEPLETION

Rats

Female rats weighing 200 g were administered a single 10 mg/kg dose of metronidazole labeled with 14C in the 2-position of the ring. The animals were sacrificed at 1, 4, 8, and 24 hours post dosing and various tissue samples taken. The tissues were analyzed for total radioactivity by combustion analysis. The results are presented in Table I. The

terminal $t_{1/2}$ values are approximately: muscle, 8 hours; liver, 10 hours; and kidney, 34 hours. (Ings, et. al, 1975)

Table I. Concentration of Radioactivity in Tissues of Rats At Various Times After Receiving a Single 10 mg/kg Dose of 14C-Metronidazole (ppm)

Withdrawal Time (hours)	Muscle	Liver	Kidney
1	5.71	11.04	8.57
4	2.48	6.84	5.04
8	1.12	3.41	1.98
24	0.29	1.06	1.57

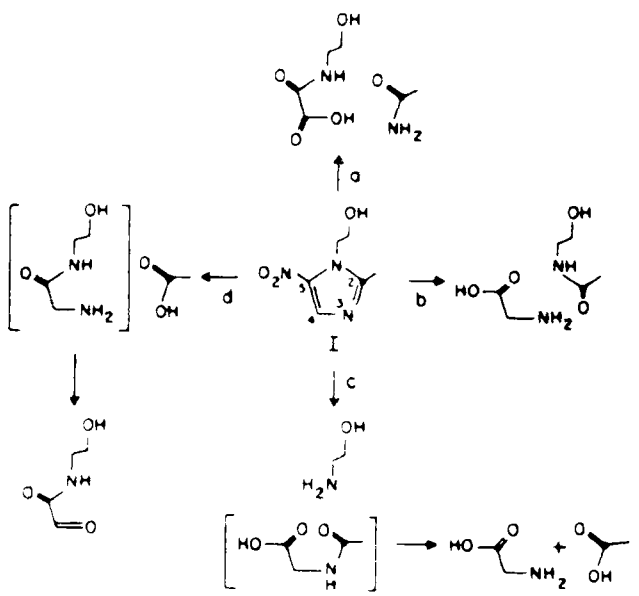
METABOLISM

Bacteria and Other in Vitro Systems

The metabolism of metronidazole by Clostridium perfringens or the microflora of the rat cecum has been examined. Metronidazole, labeled with 14C in the 1- and 2-positions of the ethanol side chain, was incubated with the rat cecal contents or C. perfringens. Under those conditions, acetamide and N-(2-hydroxyethyl)oxamic acid were identified. These metabolites are complementary in the sense that together they contain all the carbon and nitrogen atoms of metronidazole except that in the nitro group. The products could result from the cleavage of a partially reduced nitroimidazole at the 1-2 and 3-4 positions of the ring. (Koch and Goldman, 1979; Koch, et al., 1979)

Acetamide and N-(2-hydroxyethyl)oxamic acid in the above studies represented only a small fraction of the products formed from the metabolism of metronidazole. Therefore, a reductive system including milk xanthine oxidase was used in an attempt to characterize other possible products. The metabolites identified from the reduction of metronidazole mediated by xanthine oxidase included: ethanolamine, N-glycoylethanolamine, N-(2-hydroxyethyl)oxamic acid, N-acetylethanolamine, acetate, acetamide and glycine. From these results it was proposed that metronidazole could fragment in 4 ways. As shown in Figure 1, pathway a leads to N-(2-hydroxyethyl)oxamic acid and acetamide; pathway b to N-acetylethanolamine and glycine; pathway c to ethanolamine, acetate and glycine; and pathway d to N-glycoylethanolamine and acetic acid. (Crystal, et al., 1980; Goldman, et al., 1986)

Figure 1. Fragmentation Patterns of Metronidazole



Rats

The urine of rats administered a single 10 mg/kg dose of metronidazole was examined by chromatography 24 hours after treatment. Fourteen products were detected in the urine. Six of the components were identified as: metronidazole, the sulfate and glucuronide conjugates of metronidazole, 1-(2-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole, 1-(2-hydroxyethyl)-2-carboxyl-5-nitroimidazole, and 2-methyl-5-nitroimidazol-1-yl-acetic acid. (Ings, et al., 1975)

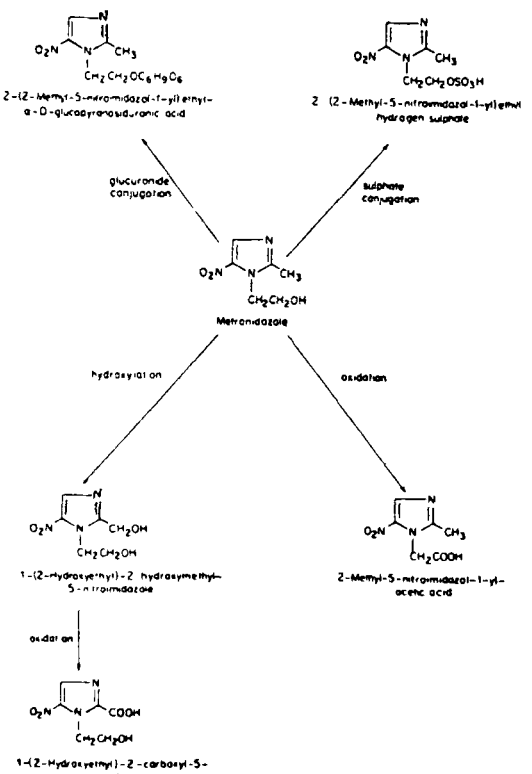
Dogs and Man

Beagle dogs were dosed by stomach tube with 100 mg/kg metronidazole, while a human was given a single oral dose of 1 g. The urine of the subjects were examined with chromatography up to nine hours post dosing. The metabolic patterns in dog and man were found to be identical. Three of the components of urine were determined to be 2-methyl-5-nitroimidazol-1-yl-acetic acid, metronidazole, and the glucuronide of metronidazole. (Ings, et al., 1966)

The urine of human subjects given 250 mg orally three times daily was collected for 24-hour periods. The urine was examined with chromatography. Six compounds were identified: metronidazole, the glucuronide of metronidazole, 2-methyl-5-nitroimidazol -1-yl-acetic acid, 1-(2-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole, the glucuronide of the latter dihydroxy metabolite, and 1-(2-hydroxyethyl)-2-carboxyl-5-nitroimidazole. (Stambaugh, et al., 1968)

From the above work, the metabolism of metronidazole in urine of man, dogs and rats can be summarized as shown in Figure 2.

Figure 2. Metabolism of Metronidazole in Urine of Man, Rats and Dogs



METHODS OF RESIDUE ANALYSIS

Because there are no approvals for metronidazole in food-producing animals, no specific methods of analysis for residues of metronidazole in edible tissues have been reported. Nevertheless, it is anticipated that polarographic assays, sensitive to the low ppb range, could be adapted for metronidazole. For example, some preliminary work has been done with metronidazole using a differential pulse polarographic assay with a claimed limit of detection of 1 ppb. (Ohst, 1987)

APPRAISAL

Metronidazole is not approved for use in food-producing animals and, consequently, specific methods of analysis are unavailable. Although relevant studies have not been done, the routes available for the metabolism of metronidazole in food-animals may be anticipated from the work done in rats, dogs and man.

REFERENCES

Chrystal, E.J.T., Koch, R.L. and Goldman, P. (1980). Metabolites from the reduction of metronidazole by xanthine oxidase. Mol. Pharmacol., 18, 105-111.

Gasparini, G., Vaghi, M. and Tardani, A. (1963). Treatment of bovine trichomoniasis with metronidazole (8823 R.P.). Vet. Rec., 75, 940-943.

Goldman, P., Koch, R.L., Yeung, T-C., Chrystal, E.J.T., Beaulieu, B.B. Jr., McLafferty, M.A. and Sudlow, G. (1986). Comparing the reduction of nitroimidazoles in bacteria and mammalian tissues and relating it to biological activity. Biochem. Pharmacol., 35, 43-51.

Ings, R.M.J., Law, G.L. and Parnell, E.W. (1966). The metabolism of metronidazole (1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole). Biochem. Pharmacol., 15, 515-519.

Ings, R.M.J., McFadzean, J.A. and Ormerod, W.E. (1975). The fate of metronidazole and its implications in chemotherapy. Xenobiotica, 5, 223-235.

Koch, R.L., Chrystal, E.J.T., Beaulieu, B.B. Jr. and Goldman, P. (1979). Acetamide-a metabolite of metronidazole formed by the intestinal flora. Biochem. Pharmacol., 28, 3611-3615.

Koch, R.L. and Goldman, P. (1979). The anaerobic metabolism of metronidazole forms N-(2-hydroxyethyl)oxamic acid. J. Pharmacol. Exp. Ther., 208, 406-410.

Ohst, E. (1987). Development of a method for detecting nitroimidazole residues in pig muscle. Report No. 1186. Submitted to FAO by BASF Aktiengesellschaft, Ludwigshafen.

Stambaugh, J.E., Feo, L.G. and Manthei, R.W. (1968). The isolation and identification of the urinary oxidative metabolites of metronidazole in man. J. Pharmacol. Exp. Ther., 161, 373-381.

Windholz, M. ed. (1983). The Merck Index 10th Edition. Rahway, N.J., Merck and Co.