

Bioavailability File : Ornidazole

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Summary

Ornidazole is a 5-nitroimidazole derivative drug which has antimicrobial action. It is used in the treatment of protozoal infections, and also in the treatment and prophylaxis of anaerobic bacterial infections. The mean ornidazole elimination half-life is 12 hours, significantly longer than that of some nitroimidazole derivatives. This is a particular advantage for reducing the dosage frequency and duration of therapy in many of the relevant clinical infections. Ornidazole acts by damage of DNA strands or inhibition of their synthesis. It is widely distributed in body tissues and fluids, including the cerebrospinal fluid. Ornidazole is metabolized in the liver. It is excreted in the urine, mainly as conjugates and metabolites, and to a lesser extent in the feces and bile. Ornidazole is administered orally, vaginally, or intravenously. In this review, physicochemical, pharmacological and pharmacokinetic properties in addition to bioavailability of ornidazole are discussed.

Key Words : Ornidazole, bioavailability, pharmacokinetics, stability, physicochemical properties.

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Özet

Ornidazol, antimikrobiyal etkisi olan 5-nitroimidazol türevi bir ilaçtır. Protozoal enfeksiyonların tedavisinde, ayrıca anaerobik bakteriyel enfeksiyonların tedavisi ve profilaksisinde kullanılır. Ornidazolün ortalama eliminasyon yarı ömrü 12 saattir ve bu değer bazı nitroimidazol türevlerinin eliminasyon yarı ömründen daha uzundur. Bu özellik, dozaj sıklığının azaltılması ve birçok klinik enfeksiyonun tedavisinin sürekliliği açısından önemli bir avantajdır. Ornidazol, DNA zincirinde hasar oluşturarak veya DNA sentezini inhibe ederek etki gösterir. Vücutta, serebrospinal sıvı da dahil olmak üzere tüm sıvı ve dokularda geniş olarak dağılır. Ornidazol karaciğerde metabolize olur. Atılımı, çoğunlukla konjugatları ve metabolitleri halinde idrarla, daha az olarak ise feçes ve safrayla olur. Ornidazol oral, vajinal ve intravenöz yolla verilebilir. Bu derlemede, ornidazolün fizikokimyasal, farmakolojik ve farmakokinetik özellikleri ile birlikte biyoyarlanımı tartışılmıştır.

Anahtar Kelimeler : Ornidazol, biyoyarlanım, farmakokinetik, stabilite, fizikokimyasal özellikler.

INTRODUCTION

Nitroimidazole drugs have been used for over 20 years, not only as major antimicrobial drugs but also as sensitizers of hypoxic tumors in conjunction with radiotherapy, thus possessing a wider spectrum of useful clinical activity than any other antibiotics^{1,2}.

Ornidazole is a 5-nitroimidazole derivative and is used in the treatment of susceptible protozoal infections and also in anaerobic bacterial infections. It has been used for amebic liver abscesses, duodenal ulcers, giardiasis, intestinal lamblasis and vaginitis³⁻⁵. Ornidazole has recently been used with success in patients with active Crohn's disease⁶. It is more ef-

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fective against amebiasis than metronidazole, which is the most commonly used nitroimidazole derivative in therapy^{7,8}. Ornidazole has also been preferred for surgical prophylaxis because of its longer elimination half-life and excellent penetration into lipidic tissues versus other nitroimidazole derivatives^{9,10}.

The plasma elimination half-life of ornidazole is 11 to 14 hours. Oral absorption of the drug is almost complete, with bioavailability of 90% and *t*_{max} ranging between 2 and 4 hours. Plasma protein binding is approximately 11 to 13%. It is metabolized to five metabolites. Two of the major active metabolites are M1 and M4, with M1 stemming from an oxidative pathway and M4 via hydrolysis. Ornidazole and its metabolites are primarily excreted in the urine. Between 43 and 63% of the dose was recovered from urine, with <4% of the dose recovered as unchanged drug^{3,11-13}.

Ornidazole is well tolerated, with the most common side effects being nausea, abdominal pain, vertigo, headache, diarrhea, flatulence, and skin rash^{14,15}.

Physicochemical Properties

Ornidazole has a heterocyclic structure consisting of a nitroimidazole-based nucleus with a 2-hydroxy-3-chloro-propyl group in position 1 and a methyl group in position 2. It is synthesized from 5-nitroimidazole derivatives. Ornidazole is known chemically as 1-(2-hydroxy-3-chloropropyl)-2-methyl-5-nitroimidazole (C₇H₁₀ClN₃O). Its molecular weight is 219.63 (C 38.28%, H 4.59%, Cl 16.14%, N 19.13%, O 21.85%) and the chemical formula can be seen in Figure 1^{7,12,16}. Ornidazole is a white to yellowish microcrystalline powder, with a melting point between 358-360 K. Its 1% aqueous solution has a pH of approximately 6.6. Ornidazole is soluble in water, ether, ethanol and chloroform (2.6, 2.4, over 50, over 50%, respectively).

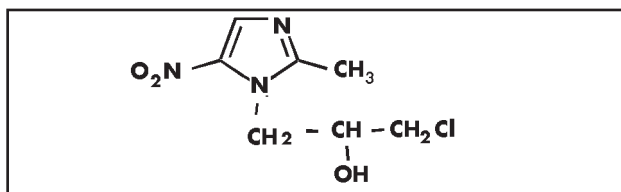


Figure 1. Structural formula of ornidazole.

Its pK_a was detected as 2.4±0.1^{4,5,11,16,17}.

The effect of gamma rays on ornidazole was investigated and it was found that gamma irradiation of ornidazole produces free radicals which are detectable by electron spin resonance (ESR) and appear relatively stable¹⁸.

When the literature about stability of ornidazole is examined, it can be seen that ornidazole neither yields the nucleus nor undergoes complete decomposition. It yields ornidazole diol and intermediate ornidazole epoxide in alkaline medium. The degradation kinetics of ornidazole have been found to be of the first order both in solution and solid state (Fig. 2)^{19,20,21}.

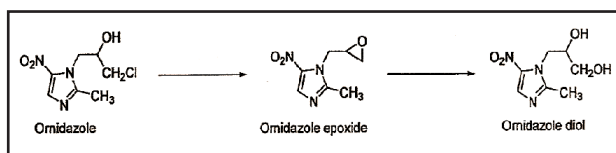


Figure 2. Reported degradation products of ornidazole.¹⁹

The stability studies of ornidazole in alkaline conditions were done at a drug concentration of 1 mg/mL in 0.1 M NaOH and the solution was heated at 80°C for 8 hours. The reaction in these conditions was so fast that the drug was degraded in a short time. For oxidative conditions, initial studies were done at drug strength of 1 mg/mL in 3% H₂O₂ and 30% H₂O₂. The drug was kept under the conditions of room temperature for a period of 24 hours. The drug was found to degrade in hydrogen peroxide. It was decomposed to an extent of 8% in 3% H₂O₂, and the degradation increased to 53% in 30% H₂O₂. Reports also exist on the stability of the drug in 0.9% sodium chloride and PVC bags under different storage conditions^{22,23}.

Identification and Quantification Methods

Polarographic, spectrophotometric, colorimetric, potentiometric, microbiologic, thin layer chromatographic, high-pressure liquid chromatographic (HPLC) and electrochemical methods have been described for determination of ornidazole in the dosage forms^{10,22,24-28}. Pulse polarography, gas chro-

matography (GC) and HPLC procedures are reported for its analysis in biological fluids^{10,27,29}. The measurement of ornidazole in biological fluids allows the dosage to be adjusted in patients suffering from malabsorption or pathological conditions which modify excretion of the drug.

Spectrophotometric determination of ornidazole is a simple method and is based on the reduction of a nitro group to a primary amino group which is then reacted with p-dimethylaminobenzaldehyde (p-DA-BA) to give a red-colored product. During spectrophotometric studies, a linear correlation was obtained between absorbance and ornidazole concentrations over the range of 0.75-5 µg/mL²⁴. The GC method for blood involves a derivatization step, and the metabolites are not determined³⁰. HPLC method is rapid, selective and reproducible, by using an internal standard. Furthermore, the method allows metabolites to be separated and measured. In HPLC studies, the limits of quantifications were: 0.5µg/mL (plasma, cerebrospinal fluid) and 0.6µg/mL (urine) for ornidazole; and 0.05µg/mL (plasma, cerebrospinal fluid) and 0.3µg/mL (urine) for both M4 and M1^{10,26}. Electrochemical method for the determination of ornidazole has the advantage of being rapid, simple and inexpensive²⁸.

Pharmacology

Mechanism of action

5-Nitroimidazoles belong to the nitroheterocyclic family of compounds widely used for the treatment or prophylaxis of infections due to anaerobic bacteria and protozoa. They have also received much attention in cancer therapy as radiosensitizers of hypoxic tumors and by their direct cytotoxic effects towards hypoxic cells. Nitroimidazoles are thought to produce their bactericidal activity through four phases:

- (I) entry into the bacterial cell
- (II) nitro group reduction
- (III) action of the cytotoxic by products
- (IV) production of inactive end products

Bactericidal activity appears to be dependent on the formation of a redox intermediate metabolite in the bacterium. This toxic metabolite may interact primarily with DNA, RNA or intracellular proteins; however, its main effects are DNA strand breakage, inhibited repair and ultimately disrupted transcription and cell death^{3,31-35}.

Owing to its similar chemical properties, ornidazole shares the same mechanism of action and spectrum of microbiological activity as other nitroimidazole agents against anaerobes and protozoa^{3,31,36-38}. Therefore, it is a drug of choice for treatment of a large variety of diseases, including intra-abdominal, pulmonary and brain abscesses, chronic sinusitis and otitis, and genital tract infections^{10,32,39}.

Uses and Administrations

Ornidazole is given by mouth in tablets after food, or intravenously. When given intravenously, solutions of ornidazole should be diluted to 5 mg or less per mL and 100 or 200 mL infused over 15 to 30 minutes. It has also been given by vaginal pessary¹².

In amebiasis, 500 mg of ornidazole is given twice daily by mouth for 5 to 10 days. Patients with amebic dysentery may be given 1.5 g as a single daily dose for 3 days. In severe amebic dysentery and amebic liver abscess, ornidazole may be given by intravenous infusion in a dose of 0.5 to 1 g initially, followed by 500 mg every 12 hours for 3 to 6 days^{12,40,41}.

In giardiasis, 1 or 1.5 g of drug is given by mouth as a single daily dose for 1 or 2 days^{12,42-44}. In trichomoniasis, a single dose of 1.5 g is given by mouth or 1 g by mouth together with 500 mg vaginally is given; alternatively, a 5-day course of ornidazole 500 mg twice daily by mouth, with or without 500 mg vaginally, is also used. Sexual partners should be treated concomitantly⁴⁵⁻⁵².

For the treatment of anaerobic bacterial infections, ornidazole is given by intravenous infusion in an initial dose of 0.5 to 1 g, followed by 500 mg every 12 hours for 5 to 10 days; oral therapy with 500 mg

every 12 hours should be substituted as soon as possible^{12,53-58}.

For the prevention of post-operative anaerobic bacterial infections, 1 g is given by intravenous infusion about 30 minutes before surgery^{9,12,59-61}.

Crohn's disease is a chronic disorder that causes inflammation of the digestive or gastrointestinal tract. It most commonly affects the end of the small intestine (ileum) and the beginning of the large intestine (colon). The inflammation can cause pain and make the intestines empty frequently, resulting in diarrhea^{60,62}. Ornidazole is an effective and safe drug for the treatment of active Crohn's disease. It has also been used as maintenance treatment with promising results. Ornidazole is given to patients in doses of 20 mg/kg BW (body weight) per day in two separate doses for the treatment. Mechanism of action could be related either to its action against anaerobes or on the immune system^{6,63-65}.

Helicobacter pylori is the cause of chronic type B gastritis and is associated with most cases of peptic ulcer disease. Ornidazole is one of the most frequently used antibiotics for curing *Helicobacter pylori* infection. In the treatment, 500 mg ornidazole is used with 30 mg lansoprazole and 1 g amoxicillin⁶⁶.

Adverse Effects and Precautions

Ornidazole is contraindicated in patients hypersensitive to ornidazole and other nitroimidazoles. Nitroimidazoles and also ornidazole are considered safe drugs as only minor side effects have been observed. The most frequent side effects are an unpleasant taste, nausea, vomiting, abdominal discomfort and diarrhea. Serious side effects such as seizures and peripheral neuropathy are very rarely encountered in conventional doses. Side effects may occur more frequently following large, single doses but were reported to subside rapidly^{5,6,14,15,67}.

The acute oral LD₅₀ of ornidazole in rats is 1.780 mg/kg. Reported LD₅₀ value for mice is 1.420 mg/kg orally. Ornidazole administered orally in mice at a dose le-

vel of 400 mg/kg/day for 13 weeks did not produce any toxicity except weight loss⁵.

Nitroimidazoles are generally considered mutagenic chemicals. The nitrogen group present in nitroimidazole derivatives is considered responsible for the mutagenicity of these compounds. In a study, mutagenicity was observed with *Klebsiella pneumoniae* and *Salmonella typhimurium* TA.100^{68,69}. Ornidazole was revealed to be mutagenic in *Salmonella typhimurium*, but negative results have been observed in other tests, such as micronucleus in mice and chromosome aberrations. Long-term carcinogenicity studies were also conducted with ornidazole (high dose 400 mg/kg/day) by administering in rats for two years. At the end of this study no carcinogenicity was recorded for ornidazole⁵.

Like other nitroimidazoles, ornidazole is widely distributed in the body, cross the placenta and appears in breast milk. When administered during pregnancy, no teratogenic effect was observed with ornidazole in mice, rats and rabbits⁵. Local and systemic tolerability of ornidazole was excellent in humans when used in pregnancy, and patients showed complete remission without premature delivery. Children born to the trial patients showed normal initial development and their growth was normal. There was no evidence of ornidazole accumulation, and the pharmacokinetic parameters were very similar to those seen in healthy subjects. Therefore, dosage regimen requires no adjustment during pregnancy^{5,8,15,70}.

Ornidazole has the advantage of fewer side effects in rats in which species its antifertility action has been documented⁷¹⁻⁷⁴. It has contraceptive properties in male, but not female, rats. It produces infertility by inhibiting epididymal sperm motility in terms of decreased sperm velocity⁷⁵⁻⁷⁹. These effects are rapidly reversible after the cessation of treatment⁸⁰⁻⁸².

Ornidazole, the therapeutic use of which is quite distinct from the treatment of chronic alcoholism, may produce a disulfiram-like reaction with alcohol (flushing of the face and neck, palpitations, dizzi-

ness, nausea, etc.) in some cases. The mechanism of this reaction is thought to be related with an inhibition of acetaldehyde dehydrogenase. Patients should be warned against the possibility of interactions with alcohol^{15,41,83}.

Besides interaction with alcohol, ornidazole potentiates the effect of coumarin-type oral anticoagulants. The dosage of the anticoagulant has to be adjusted accordingly. Ornidazole also prolongs the muscle-relaxant effect of vecuronium bromide⁸⁴.

Pharmacokinetics and Bioavailability

Absorption

The pharmacokinetics of oral and intravenous ornidazole have been studied in a variety of populations,

including healthy individuals, neonates and infants, those with renal and hepatic dysfunction, and those receiving single therapeutic doses for various clinical conditions (Table 1)³.

Ornidazole is almost completely absorbed from the small intestine when administered orally, with bioavailability of >90% and t_{max} ranging between 2 and 4 hours. Food does not affect extent but does affect rate of absorption of ornidazole^{3,12}.

In a study of Ramamurthy et al.⁸⁵, bioequivalence of two marketed ornidazole formulations were determined in healthy volunteers. Relative bioavailability of ornidazole (1.5 g single dose of test product) versus that of standard reference was investigated. Blood samples were collected at selected time intervals. Drug assay was done using high performance thin layer chromatography (HPTLC) method. The mean

Table 1. Pharmacokinetics of ornidazole³

Dose (mg)	n	Schedule F(%)	C_{max} (mg/mL)	V_{ss} (L/kg)	AUC _{24h} (mg/L.h)	$t_{1/2\beta}$ (h)	Cl (L/h) ^a
1500 PO	50	S	23.6 (1h)			10.9	
1000 IV	14	S	24	0.9 ^b		14.1	2.82
750 PO	4	S	10.9	0.87		14.4	
1500 PO	5	S	31.5			13.8	
1000 IV	10	S		0.86		14.1	3.04
20 mg/kg IV	12 (neonates/infants)	S		0.96	511	14.7	0.80
							mL/min/kg
1000 IV or PO	8 (with variable renal function)	S 102(n=6)		0.70	311 (PO)	12.7	2.94
500 IV	8 (CRF, no dialysis)	S		0.73	185.0 ^c	10.8	2.78
500 IV	7 (dialysis)	S					3.84
1000 IV or PO	6 (dialysis)	S 97 (n=2)		0.78	308	11.0	3.91
500 IV	5 (CAPD)	S		0.79	185.6 ^c	11.8	2.87
	10 (cirrhosis)	S		0.84		21.9	2.09
	10 (cirrhosis)	S		0.81		19.3	2.24
	10 (hepatitis)	S		0.90		19.3	2.01
	10 (CA)	S		0.74		17.4	1.57
	11 (liver transplant)	S		9.11			
1000 IV	5 (PG)	M	20.71	0.79	375 ^c	15.2	3.4

^a Normalized to a bodyweight of 70 kg. ^b Approximate value ^c AUC from zero to infinity

AUC₂₄ = area under the concentration-time curve over 24 hours; **CA**=pancreatic cancer; **CAPD**=continuous ambulatory peritoneal dialysis; **Cl**=total body clearance; **C_{max}**=peak plasma drug concentration; **CRF**=chronic renal failure; **F**=bioavailability; **IV**=intravenous; **M**=multiple; **n**=number of participants; **PG**=pregnant; **PO**=oral; **S**=single; **t_{1/2β}**=elimination half-life; **V_{ss}**=volume of distribution at steady state.

peak plasma concentration (C_{\max}) of 32.67 ± 4.45 $\mu\text{g/mL}$ was achieved at 1.54 ± 0.81 hours following administration of test product versus mean C_{\max} of 31.55 ± 5.04 $\mu\text{g/mL}$ at 1.79 ± 0.89 hours for the reference standard. The area under time concentration curve [AUC(0-12)] was 261.67 ± 77 $\mu\text{g/mL}$ hours with reference standard and 265.41 ± 30.82 $\mu\text{g/mL}$ hours for test product. As a result, there was no statistically significant difference between the two formulations and the two products.

Distribution

Ornidazole is widely distributed in body tissues and fluids, including cerebrospinal fluid. Antibacterial concentrations are achieved in vaginal secretions, appendix and intestinal tissues. Ornidazole concentrations have been measured in the colonic (8.7 $\mu\text{g/g}$) and abdominal (3.6 to 4.4 $\mu\text{g/g}$) walls and epiploic fat (3.4 to 4.7 $\mu\text{g/g}$) throughout colorectal surgery in those receiving a 1 g intravenous dose for surgical prophylaxis⁹. Although ornidazole concentrations in cerebrospinal fluid have only been assessed in animal models, it is expected that it should penetrate the central nervous system³.

Determination of the minimal inhibitory concentrations (MIC) of the causative organism is necessary for optimization of treatment. In vitro susceptibility studies have shown that, compared with metronidazole, ornidazole has similar or slightly lower MIC values against a variety of anaerobic bacteria and protozoa. Compared with tinidazole, ornidazole MIC values are either similar or slightly higher^{3,47,86}.

Metabolization

Ornidazole is extensively metabolized in the liver before excretion by renal pathway. Ornidazole is largely excreted in the urine and to a lesser extent in the feces, mainly as conjugates and metabolites. Only 4% of unchanged drug was excreted in the urine. 85% of a single oral dose has been reported to be eliminated within five days, 63% in the urine and 22% in the feces. Biliary excretion may be important in the elimination of ornidazole and its metabolites^{3,12}.

Ornidazole is metabolized to five metabolites. Two of the major metabolites are M1 and M4, with M1 stemming from an oxidative pathway and M4 via hydrolysis³. The metabolism of ornidazole was studied in the rat, dog and humans using the drug labelled with ^{14}C at position 2 in the ring. Metabolites were extracted and isolated from urine and their structure determined by mass- and nuclear magnetic resonance (NMR)-spectroscopy. The drug is metabolized differently in rat, dog, and humans. The pattern of free ornidazole and metabolites was different in the three species: while ornidazole predominated in humans, ornidazole and metabolite **M1** in the dog, the most extensive metabolic pattern was found in the rat. The following metabolites were identified: **M1**, 1-chloro-3-(2-hydroxymethyl-5-nitro-1-imidazolyl)-2-propanol; **M2**, 2-methyl-5-nitroimidazole; **M3**, N-(3-chloro-2-hydroxypropyl) acetamide; **M4**, 3-(-2-methyl-5-nitro-1-imidazolyl)-1, 2-propanediol; **M5**, acetamide. The following general metabolic scheme is indicated in Figure 3^{5,31,87}.

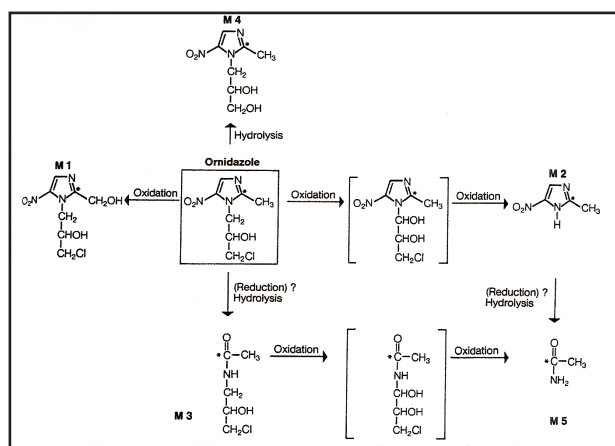


Figure 3. Scheme for the metabolism of ornidazole. Ornidazole, **M1**, **M2**, **M3**, and **M4** were present in the urine both free and in the form of conjugates (glucuronides or sulfates). **M5** was found only in free form. Structures in square brackets represent postulated intermediates which have not been identified (**M1**: 1-chloro-3-(2-hydroxymethyl-5-nitro-1-imidazolyl)-2-propanol; **M2**: 2-methyl-5-nitroimidazole; **M3**: N-(3-chloro-2-hydroxypropyl)acetamide; **M4**: 3-(-2-methyl-5-nitro-1-imidazolyl)-1, 2-propanediol; **M5**: acetamide)³¹.

Elimination

The plasma elimination half-life of ornidazole is 11 to 14 hours^{3,12}. Plasma protein binding is approximately 11 to 13%. Reported V_{ss} values range from 0.73 to 0.90 L/kg, with AUC values for single intravenous 500 mg doses of 185 mg/L.h and for 1 g doses of 375 mg/L.h. The mean Cl value of ornidazole is 47 mL/min (2.82 L/h) for 1 g intravenous dose^{11,14,15}.

Much of the available pharmacokinetic information about ornidazole has been obtained in healthy volunteers; these data cannot be uncritically used as if they were valid also for patients. Therefore, the pharmacokinetics of ornidazole have been studied in a variety of populations including patients with renal and hepatic dysfunction¹⁵.

The pharmacokinetics of ornidazole are not influenced by any degree of renal dysfunction. As shown in several studies, the $t_{1/2\beta}$ of ornidazole in patients with renal dysfunction is similar to that observed in those with normal renal function. Ornidazole is easily removed during hemodialysis because of its low molecular weight and low protein binding. In patients undergoing hemodialysis, the extraction ratio by the dialysis procedure was 42%. Therefore, it is recommended that doses should be administered after dialysis. In contrast, continuous ambulatory peritoneal dialysis (CAPD) has been shown to remove only about 6% of an ornidazole dose over 48 hours. Thus, no dosage changes are needed for patients with renal dysfunction or those receiving CAPD^{3,14}. Mean plasma concentrations of ornidazole and its metabolites in healthy volunteers and in the three groups of patients are shown in Figure 4. In all groups of patients, decline in plasma concentration of ornidazole and its metabolites over time was slower than in volunteers⁸⁸.

Due to its extensive metabolism, the elimination of ornidazole is impaired in patients with severe liver disease. This drug is eliminated mainly by biotransformation through the liver, and its pharmacokinetics are impaired in severe liver diseases: mean plas-

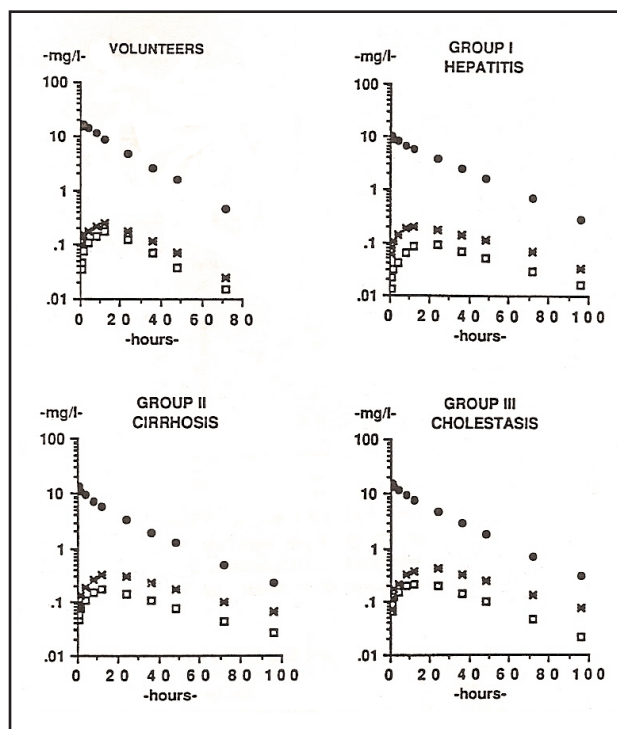


Figure 4. Mean plasma concentration of ornidazole (●) and its two metabolites, M1 (□) and M4 (★), in healthy volunteers and in the three groups of patients. Volunteers were injected with 1 g ornidazole and patients with 0.5 g⁸⁶.

ma clearance is decreased by approximately 30%, leading to an increased half-life ($t_{1/2}$). As compared with healthy volunteers, plasma clearance is reduced from 3.04 to 1.57 L/h in patients with pancreatic cancer, 2.01 L/h in patients with acute viral hepatitis, 2.09 L/h in patients with severe alcoholic cirrhosis, and 2.34 L/h in patients with biopsy-proven liver cirrhosis. Both hydroxylated metabolites of ornidazole accumulated in the patients; however, the t_{max} for the metabolite was significantly delayed. To avoid excessive accumulation of ornidazole after repeated administration in patients with hepatic impairment, the dosage should be adjusted appropriately and the administration interval should be doubled^{3,13,14,88,89}.

Alternative Formulation Types of Ornidazole

Baloğlu et al.⁹⁰ prepared 500 mg ornidazole vaginal ovule (VO) formulation and then compared the efficacy of prepared ovules and commercially available

vaginal tablets (VT) in the treatment of bacterial vaginosis. The dissolution rate of ornidazole from the VT was higher when compared with the dissolution rate of the VO. Although the VT disintegrated rapidly, this is not required for vaginal applications as tablets are easily dissolved by vaginal secretions. Both of the formulations released 100% of ornidazole in an hour. As a result, the newly developed VO is safe and effective and may be a useful alternative to the tablet formulation for treatment of patients with bacterial vaginosis.

Krishnaiah et al.⁹¹ developed colon-targeted drug delivery systems of ornidazole using guar gum as a carrier. The core formulation containing ornidazole was directly compressed. Ornidazole core tablets were compression-coated with coat formulations containing various quantities of guar gum ranging from 65% to 85%. The compression-coated ornidazole tablets coated with 85% of guar gum did not degrade in simulated colonic fluids, whereas the formulations coated with either 75% or 65% of guar gum degraded in dissolution medium containing rat cecal contents. The results of the study show that compression-coated ornidazole tablets coated with either 65% or 75% of guar gum are most likely to provide targeted delivery of ornidazole to the colon. After this study, Krishnaiah et al.⁹² evaluated the ability of guar gum-based colon-targeted ornidazole tablets to target the drug to the human colon in healthy volunteers. In vivo studies showed prolonged absorption time, delayed t_{\max} , decreased C_{\max} and decreased absorption rate constant, indicating that the drug was not released in the stomach and small intestine, but was released in the colon.

The rectal suppositories containing either labelled or unlabelled ornidazole were prepared by fusion method using PEG 6000 by Aşıkoğlu et al.⁹³ The in vitro release of ^{131}I -ornidazole from $^{99\text{m}}\text{Tc}$ -labelled PEG 6000 was investigated in intestinal fluid at 37°C. To investigate the in vivo release ^{131}I -labelled ornidazole suppositories were administered by rectal route to rabbits. The obtained results demonstrated that a rectally administered ornidazole was observed well; gamma scintigraphy can be used to evaluate

the in vivo performance of ornidazole administered rectally. In another study of Aşıkoğlu et al.⁹⁴, ^{131}I -labelled ornidazole was investigated as a radiopharmaceutical to image experimental inflammatory lesions in animals. Results of this study showed that ^{131}I -ornidazole has some advantages over other agents: it is inexpensive, its preparation is simple, its labeling efficiency is high, and its accumulation at the target site is rapid.

CONCLUSIONS

Nitroimidazole is one of the most interesting chemicals and is widely used in the treatment of a variety of clinical conditions including amebic liver abscess and acute amebic dysentery. Ornidazole is a nitroimidazole derivative with activity against protozoa and anaerobic bacteria. It has been used successfully in patients with vaginal trichomoniasis and amebiasis, and because of its excellent penetration into lipidic tissues, prophylactically for abdominal and gynecological surgery.

The mean half-life of elimination from human plasma is 11 to 14 hours. The long serum half-life of ornidazole would permit a more convenient dosage interval, and it has an even greater antimicrobial activity compared with other nitroimidazole derivatives. Ornidazole has a large spectrum of activity and can be given in different dosage forms. Moreover, this compound is an effective drug which is relatively safe and produces only minimal side effects.

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