

Reduced bioavailability of oral Metronidazole in postoperative ileus

A Manafi¹, MR Panjehshahin², M Ghorbanpour Saravi², SA Emami¹, SK Forootan¹

¹Department of Surgery, School of Medicine, Iran University of Medical Science, Tehran, Iran,

²Department of Pharmacology, School of Medicine, Shiraz University of Medical Science, Shiraz, Iran

Abstract

Background: Metronidazole has been reported to reduce postoperative anaerobic infections following surgical procedures. Because of high cost and poor availability of intravenous metronidazole compared with that of oral preparation, we decided to measure the serum level of metronidazole after oral administration in patients during postoperative ileus, and to evaluate the substitution of intravenous metronidazole for the oral product.

Methods: The present study comprised 45 adult patients undergoing major abdominal surgery via long laparotomy incision from Aug to Nov 2003. (500 mg of Metronidazole was administered as a single dose orally to each patient twice, one in ileus condition and the other in nonileus condition. Blood sampling was done 1 hour after each episode of the drug administration).

Results: A significant reduction ($P < 0.001$) was found between the mean serum metronidazole concentration (2.90 ± 2.29 SD g/ml) during postoperative ileus, and that of controls (11.07 ± 6.72 SD g/ml). In majority of patients (62.5%), the serum level of metronidazole in ileus did not reach its minimum inhibitory concentration ($3 \mu\text{g/ml}$) for the most clinically important anaerobic bacteria.

Conclusions: Postoperative ileus significantly affected the oral absorption of metronidazole. As a result, if we want to control an active anaerobic infection with a prompt antibiotic therapy, it seems that initiating of the therapeutic regimen with oral Metronidazole postoperatively is not justified.

Keywords: Metronidazole; Ileus; Oral

Introduction

Metronidazole has been used for the treatment of various protozoal infections and has proved to be effective against most of the clinically important anaerobic bacteria.

In addition to efficient antimicrobial coverage, favorable pharmacokinetic properties, and few major

side effects related to conventional doses as well as low cost have made metronidazole to be one of the best antimicrobial agents with extensive applications. Metronidazole has been reported to reduce postoperative anaerobic infections following procedures such as appendectomy, colorectal surgery, and abdominal hysterectomy.^{1,2} In regard to the pharmacokinetics, peak serum concentration of metronidazole (approximately 5 and 10g/ml) was attained after administration of 250mg and 500mg of the drug. Time of peak concentration that showed the rate of absorption,

*Correspondence: Ali Manafi, MD, Assistant Professor of Department of Surgery, School of Medicine, Iran University of Medical Science, Tehran, Iran,
P.O. Box: 13185-1678; Tel: +98-21-66439463
Fax: +98-21-66919206; e-mail: dramanafi@yahoo.com

varied between 15 minutes to 4 hours averaging approximately one hour.³ Postoperative ileus is certainly the most common cause of ileus, and indeed it is inevitable to some degree, even after the most trivial intra abdominal procedures. In ileus, many pathophysiologic changes occur in gastrointestinal tract as the site of absorption with expected alteration in absorption, and bioavailability of oral preparation. However, no specific study has been reported on effect of ileus on absorption of oral metronidazole. In view of the high cost and poor availability of intravenous metronidazole, the oral formulation seemed to be a suitable substitute. The low cost and excellent absorption of the oral metronidazole with its bioavailability of about 100%, prompted us to measure its serum level after administration to patients during post laparotomy while they were in postoperative ileus. The aim of present investigation was to determine the oral absorption of metronidazole in ileus, and its substitution for intravenous formulation as *iv-to-po* switch therapy has become the mainstay of antibiotic therapy for the majority of patients.⁴

Materials and Methods

The present study was carried out in Sina Hospital affiliated to Tehran University of Medical Sciences from Aug-Nov 2003, and comprised 60 adult patients aged over 14 years, who had undergone a major abdominal surgery via long laparotomy incision with extensive ileus. 500 mg of single dose of metronidazole was administered orally to each patient and blood sample were taken one hour after. Patients undergoing elective surgery received two oral doses of 500 mg of metronidazole. The first dose was administered at least 48 hours before and the second dose, 5 to 8 hours after operation while the patients were completely conscious. In patients who had emergency laparotomy, the first dose was administered 5 to 8 hours post laparotomy when they were fully conscious. The second dose was prescribed before discharging the patients while they were completely free of ileus (at least after the first bowel movement). Therefore, we had 2 samples from each patient. One was taken 5 to 8 hours after the operation while the patient was in postoperative ileus (sample with ileus or test sample). The other sample was taken before the operation (in elective patients) or after postoperative ileus (in emergency patients). The latter sample (sample without ileus) was considered as a control

factor. As a result, each patient was his/her own control in this study.

Concerning the lack of toleration to oral metronidazole, post-drug ingestion vomiting or missing of the test samples in some of the patients, 15 patients were excluded from the study. Of all 45 patients, 41 of them had paired blood samples of test and control, and the other 4 had test samples only and their control samples (samples without ileus) were missed. In six cases, who were taking multiple drug doses, metronidazole was administered according to the protocol (multiple dosages of 500mg 8 hourly). For exclusion of the cumulative effect of the drug, samples from patients and control subjects who concurrently received metronidazole were considered separately. In six cases, metronidazole was using with multiple dose regimens of 500 mg every 8-hour. For exclusion of the cumulative effect of the drug, we considered test or control samples in the case of co-administration of metronidazole separately unless there was at least a 72-hour interval between discontinuation of Metronidazole and sampling. Other cases did not take metronidazole for at least one week before the study. Patients requiring intravenous metronidazole, having resection and anastomosis either in esophagus or stomach were excluded from the study. Other cases for exclusion comprised pregnant women, patients with renal or liver failure, and those in a state of shock or poor general condition. The blood specimen was taken for measuring serum level of metronidazole. Blood samples, 2 ml was taken from patients one hour after each drug administration. The specimen was centrifuged immediately and the serum was removed and stored at -20° C until used. The following procedure was used to measure metronidazole concentrations. An equal volume of 100g/l solution of trichloroacetic acid was added to each serum sample, thoroughly mixed and centrifuged at 2000g for two minutes in an Eppendorf bench-top centrifuge. Using a High Performance Liquid Chromatography, 20 microliters of the clear supernatant fluid were then injected into the system. Paired and two sample t-test and correlation analysis were applied for statistical evaluation of data.

Results

Twenty eight of the patients were male and other 17 were female. The average of Patient's ages were 48 ± 19 years. Other details are shown in Table 1.

Table 1: Age distribution of patients in regard to gender

Gender	Number	Mean ± SD (year)	Min	Max
Male	28	45.9±19.2	14	70
Female	17	50.9±18.8	15	70
Total	45	48±19	14	70

There were no significant correlation between the serum level of metronidazole in both test and control and patients age and gender. We had available 40 samples of test and 37 samples of control from the subjects that did not have the co-administration of metronidazole (multiple dosages of 500mg 8 hourly). The serum level of metronidazole was 2.90±2.29 g/ml in cases and 11.07±6.72 g/ml in controls. In the patients who had pair samples the serum level of the drug was 3.02±2.40 g/ml for test and 10.75±6.77 g/ml for control (P<0.001) (Table 2). We chose the pair condition for a better comparison of test and control; therefore, we could use paired sample t-test, which was a stronger test compared with two-sample t-test. It shows a strong statistical relationship (P<0.001) between the serum levels of metronidazole in test and control (t=7.56, df=34.00). The mean of the serum level of the drug in test compared with control had a significant reduction (73.8%).

Table 2: The serum level of metronidazole after a single oral dose of 500mg in test and control patients of both genders

Gender	Test (with ileus)		Control (without ileus)	
	Number	Mean±SD (g/ml)	Number	Mean±SD (g/ml)
Male	19	2.59±1.90	19	9.94±6.43
Female	16	3.52±2.86	16	11.71±7.25
Total	35	3.02±2.40	35	10.75±6.77

In the control group with 37 cases, the serum level of metronidazole was ≥ 6 µg/ml in 29 cases (78.4%), ≥3-6 µg/ml in 4 cases (10.8%), and also it fell less than 3 µg/ml in the last 4 cases (10.8%). In contrast, in the test group with 40 cases the serum level of the drug was less than 3 µg/ml in 25 patients (62.5%) and 10 of them (25.0%) had the serum level of ≥3-6 µg/ml. Only in 5 patients (12.5%) the serum level of metronidazole reached ≥6 µg/ml (Fig. 1).

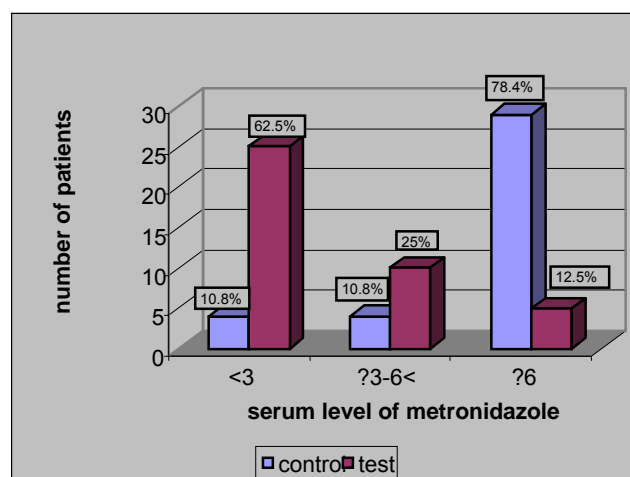


Figure 1: The serum level of Metronidazole after a single 500 mg oral metronidazole according to MIC (≥3 µg/ml) and MBC (≥6 µg/ml) for susceptible anaerobic organisms in ileus condition (test) and without it (control)

In 5 tests and 4 controls with concurrent administration of metronidazole, 3 patients had paired samples. Serum levels of the drug in test and controls were 12.34 versus 34.60, 11.78 versus 31.32 and 3.38 versus 36.20 g/ml. The serum level in remaining unpaired samples was 10.55 and 5.8 g/ml for tests, and 23.65 g/ml for control. The mean of the serum level of metronidazole was 8.77 g/ml OR “8.17 g/ml” for tests and 31.44 g/ml for controls in patients on oral metronidazole therapeutic regimen of 500 mg every 8 hours.

These results increased significantly compared with those found in absence of concurrent administration of metronidazole.

Discussion

The serum level of metronidazole in patients without ileus was 11.07±6.72 g/ml 1 hour after single 500 mg oral dose. The serum level of the drug reached MBCs for most susceptible bacteria (6 g/ml) in most patients without ileus (78.4%) and th did not achieve the MIC only in few patients (10.8%). In patients with ileus the serum level of metronidazole was 2.90±2.29 g/ml 1 hour after single 500 mg oral dose, which showed, a significant reduction (73.8%) compared with that of control (P<0.001). The complete absorption and 100% bioavailability for oral metronidazole in healthy subjects could not be easily applied to post-operative patients, since many pathophysiological

factors might influence the pharmacokinetics. These factors included ileus, altered blood flow through organs, such as the liver and the intestine and also significant change in permeability of mucosal barrier of the intestine as the site of absorption,⁵ altered organ function, such as the kidneys, enzyme induction possibly with formation of toxic metabolites, altered metabolism, alteration in the plasma and extracellular volume leading to altered volume of distribution changes in the extravascular albumine pool, changes in plasma binding etc.⁶

This study showed that oral absorption of metronidazole was significantly affected by postoperative ileus. The serum level of metronidazole in ileus condition in the majority of patients (62.5%) could not reach 3 g/ml as MICs for the most clinically important anaerobic bacteria. Small number of the patients (25.0%) had the serum level between 3 and 6mg/ml and only 12.5% of subjects achieved MBC (6 g/ml).

According to these findings, the therapeutic level of the drug was not achieved one hour after the first dose of 500 mg metronidazole administered post-operatively. If the aim of prescribing oral metronidazole is prompt therapy to control an active anaerobic infection, it is not recommended for patients with

overwhelming infection. In this case, intravenous metronidazole can be instituted at least for starting therapy or oral metronidazole administered 8 hours preoperatively. In some patients who used oral metronidazole, in addition to two doses according to our protocol, the serum level of the drug was 3 times higher than the concentration reached after a single dose. This cumulative effect of metronidazole was found in both patients with ileus (8.77 versus 2.90 g/ml) and in those without it (31.44 versus 11.07 g/ml). Using HPLC method, the serum levels of metronidazole detected in patients without ileus, who received 500mg metronidazole 8 hourly, was higher compared with those reported in healthy volunteers with maximal plasma concentration of 19.8 g/ml.⁶ The preoperative administration of at least a single dose of 500mg oral metronidazole in present study, produced a serum level of 8.77 g/ml which was more than MBC for susceptible anaerobes.

Despite the limited number of cases, we can probably conclude that oral metronidazole prescribed at least 8 hours preoperatively can attain its therapeutic level even with the first 500 mg in post-operative ileus.

References

- 1 Lau AH, Lam NP, Piscitelli SC, Wilkes L, Panziger LH. Clinical pharmacokinetics of metronidazole and other nitromidazole anti-infectives. *Clin Pharmacokinet* 1992;**23**:328-64.
- 2 Martin C, Saster B, Mallet MN, Bruguerolle B, Brun JP, Demicop, Gouin F. Pharmacokinetics and tissue penetration of a single 1000-milligram, intravenous dose of metronidazole for antibiotic prophylaxis of colorectal surgery. *Antimicrob Agents Chemother* 1991;**35**:2602-5.
- 3 Goodman Gilman A. *The pharmacological Basis of Therapeutics*. 8th ed., Pergmon press, New York; 1991. p. 1002-5.
- 4 Cunha BA. Intravenous to oral antibiotic switch therapy. *Drugs Today (Barc)* 2001;**37**:311-9.
- 5 Axelsson CK, Otkjaer S, Andersen ST, Arnold E. Absorption of metronidazole suppositories in patients with postoperative ileus. *Dan Med Bull* 1985;**32**:134-7.
- 6 Thiercelin JF, Diquet B, Levesque C, Ghesquiere F, Simon P, Viars P. Metronidazole kinetics and bioavailability in patients undergoing gastro intestinal surgery. *Clin Pharmacol Ther* 1984;**35**:510-9.