

Plasma Concentrations of Oral Metronidazole in the Early Post-Laparotomy Periods

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Abstract

Background: The bioavailability of metronidazole after oral ingestion, in ordinary conditions, is quite similar to intravenous administration of the drug. However, the degree of its absorption is not known in the early periods after laparotomy.

Objective: To determine plasma levels of metronidazole in pediatric patients following elective abdominal surgery.

Methods: The study group was comprised of 25 pediatric patients with mean age of 8.25 years. They took 10 mg/kg metronidazole (ingested or taken via nasogastric tube) a few hours after operation, followed by every eight hours for a total of three successive doses. We obtained blood samples 1-2 hours after each drug intake.

Results: The mean±SD of plasma drug concentrations after the first, second and third doses were 1.43 ± 0.81 , 6.26 ± 3.86 and 10.21 ± 4.28 µg/ml, respectively, showing a significant rise after each dose ($p<0.001$). The majority of patients (84%) obtained a level equal to, or above the minimal bactericidal concentration (MBC) after the third dose. Ninety-two and 96% of patients achieved the plasma minimal inhibitory concentration or higher following the second and third doses, respectively, as compared to 4% after the first dose ($p<0.00001$).

Conclusion: Absorption of oral metronidazole after elective laparotomy is disturbed only temporarily, as in the majority of patients the drug attains an acceptable level before the second post-operative day. Therefore, parenteral metronidazole therapy, if necessary, is recommended only during the first 24 hours, and it may be replaced by oral preparation afterward.

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Introduction

Metronidazole is one of the safest and most effective drugs against anaerobic microorganisms.¹⁻³ In contrast to the rectal route, the bioavailability of this drug, even after a single oral ingestion, is identical to the intravenous (IV) administration.^{3,4} For this reason, it is widely used either parenterally in a variety of situations,

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Table 1: Number (%) of patients with plasma metronidazole levels (PML) equal to, or above, MIC and MBC following each ingestion of the drug after laparotomy.

Doses	Number (%) of patients with PML≥MIC	Number (%) of patients with PML≥MBC
1	1 (4)	0 (0)
2	23 (92)	9 (36)
3	24 (96)	21 (84)
p-value	<0.00001*	<0.00001**

*Dose 1 vs 2 or 3, **dose 1 vs 2; dose 2 vs 3

including post-operative periods once surgical diet is tolerated.^{1,5-10}

Recently, we showed that oral metronidazole (OM) could be used peri-operatively as a prophylactic agent in simple and complicated appendicitis with localized peritonitis which leads to acceptable serum concentrations in majority of the patients.^{11,12} However, due to the possibility of failure of the drug to reach an adequate serum level, it has not yet been given orally in the presence of generalized ileus.

The purpose of this study was to determine blood concentrations of OM in the early post-operative periods, following elective abdominal operations. Obviously, if in this situation we could prove that the levels were equal to, or above the minimal inhibitory or minimal bactericidal concentration (MIC and MBC respectively), consumption of this expensive IV drug may be replaced, at least for prophylaxis, by oral preparations.

Patients and Methods

We conducted this study in a group of 25 patients with an age range of 7 months to 14 years (mean: 8.2) who underwent elective laparotomy. The procedure was explained to the parents and their permission was obtained. Thereafter, 10 mg/kg metronidazole (syrup or tablet) was administered orally or via a nasogastric (N/G) tube 4-5 hours after the patient was fully conscious, and then every 8 hours for a total of 3 successive doses. The N/G tube was clamped for 45-60 minutes to prevent back-flow of the drug. We excluded those patients who vomited or received IV metronidazole from the study. For ethical reasons, if anti-aerobic coverage was required, other appropriate drugs were administered parenterally.

From each patient, 4 ml of blood sample was taken in an oxalated tube 1-2 hrs after each dose of OM. After the separation of plasma, the samples were stored at -20° C. The drug concentration in plasma was measured by high-pressure liquid chromatography.

For statistical analysis, we used one-way analysis of variance (ANOVA) followed by Duncan multiple range test, and Bartholomew's test (gradient in proportions).

Results

The mean±SD plasma drug levels after the first, second and third doses were 1.43±0.81, 6.26±3.86 and 10.21±4.28 µg/ml, respectively (Fig.1). The rise in the mean values after the second dose compared to the first (p<0.001) and the third to the second dose was significant (p<0.001) (Fig.1).

The plasma concentrations of the drug after the second and third doses were equal to, or higher than the MBC (6 µg/ml)¹³ in 36% and 84 of patients, respectively. None of the patients had attained such levels after the first dose (Table 1). Moreover, corresponding values, with reference to MIC (3 µg/ml)¹⁴, after the first through the third doses were 4%, 92% and 96%, respectively. This trend of increment in the percentage of patients with an acceptable level (≥MIC or MBC) after each dose was highly significant, as determined by Bartholomew's test (p<0.00001) (gradient in proportions) (Table 1).

We did not find any correlation between the time or type of the operation and the drug concentration.

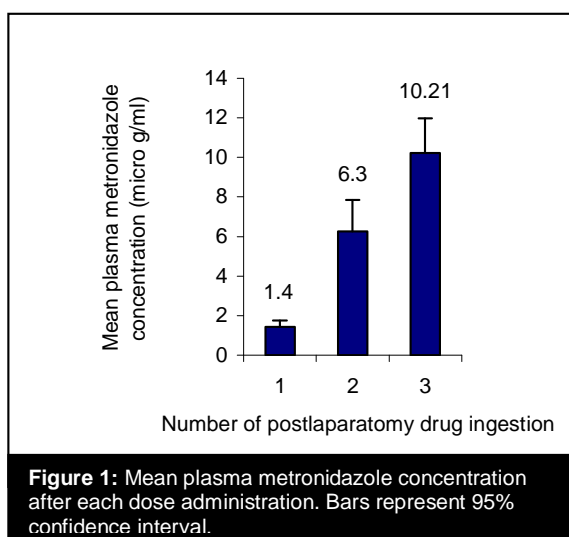
Discussion

Many patients undergoing laparotomy for different reasons, especially for generalized peritonitis, biliary tract infections, pelvic inflammatory disease and/or colorectal surgery, require anti-anaerobic coverage.⁵⁻⁹ Although metronidazole is, undoubtedly, one of the most suitable drugs for this purpose, the parenteral preparation is relatively expensive, so that most of the patients are unable to afford it in developing countries. Despite the acceptable bioavailability of OM in ordinary conditions and in various enteric diseases including ulcerative colitis, Crohn's and celiac disease, it is not used in the early post-operative period.^{3,4,15}

Graber, *et al.* showed that in monkey the duration and pattern of post-operative ileus was independent of the site, extent and time of the operation. According to that study, the gastric antrum requires about 3.4±1.4 hrs after laparotomy in order to obtain its normal contraction frequency, followed by the small bowel (6.5±2.5 hrs).¹⁶ Ingram, *et al.* also showed that gastric emptying following cholecystectomy was not related to

age, plasma potassium, the duration of operation or anesthesia.¹⁷ Similarly, in our series, blood concentrations of metronidazole did not show any correlation to the type and time of operation. Nonetheless, there is a report about a significant correlation between gastric emptying and some drugs, particularly opiates, administered during the perioperative period.¹⁷ Therefore, the inadequate blood level immediately following laparotomy, is probably secondary to gastric stasis and draining of the administered drug, caused by declamping of the N/G tube (or sometimes vomiting) (Table 1).

Fifteen minutes to 4 hrs, following the intake of a single 500 mg OM by normal adult volunteer, the peak serum concentration reaches to approximately 10 µg/ml (one hour in average)^{3,4,18,19} However, the drug level at 8 hrs would be about 5-7 µg/ml, which is still near, or in excess of MBC. Moreover, following multiple doses at intervals of 6-12 hrs, higher concentrations, due to the accumulation of the drug, are obtained.¹⁸ Comparatively, the majority of our patients (84%) showed a level around or higher than MBC after the third dose, while it was nil and then 36% after the first and second doses, respectively (p<0.00001). Furthermore, if the lowest bacteriostatic drug level (MIC) is taken into consideration, most patients (92% and 96%) obtained such a concentration following the second and third doses as compared to 4% after the first dose (p<0.00001, Table 1). This important finding indicates that disturbance in the absorption of OM after elective laparotomy is temporary and for only a short period. In other words, the bioavailability of OM will be above MIC in almost all, and equal to or higher than MBC in the majority of patients in less than 24 hours (following the third dose) after laparotomy, provided that proper dosage of the drug is taken regularly and not vomited (Table and Fig.1).



A significant rise in the drug blood level after successive doses is due to the accumulative property of metronidazole (Fig.1).¹⁹ This property lasts for 3 days, after which its concentration reaches a plateau.¹⁹ Thus, mean blood levels would be even higher, should one determine the plasma concentration after a few more doses.

Conclusively, because of an inadequate blood level in nearly all patients after the first dose and still less than MBC in about 64% of patients following the second dose, it is recommended to give parenteral metronidazole, if it is mandatory, only during the first 24 hours after laparotomy. In other words, owing to the acceptable blood levels relatively soon after abdominal operations, administration of OM is safe, commencing with the second post-operative day

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