

## Research Article

## Pharmacokinetic Interaction of Metronidazole with Husk

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### ABSTRACT

The effect of Psyllium husk on the pharmacokinetic of metronidazole was studied using rabbits in a crossover study method. The relevance of this study borders on the wide use of Psyllium husk for culinary and phytotherapeutic purposes, and metronidazole that is commonly used for every gastrointestinal complain in our communities without prescription. Psyllium husk significantly increased the absorption and plasma half-life, and significantly decreased the elimination rate constant and clearance of metronidazole ( $P < 0.05$ ).

**Keywords:** Metronidazole, Psyllium husk, herb-drug interaction, pharmacokinetics.

### INTRODUCTION

A natural remedy for constipation, regulates bowel functions by stimulating nutritional program of digestive system. It contains natural fibers which are part of healthy regimen and has ability to decrease symptoms of fatigue loss of energy and other severe health problems. It helps to reduce risk of heart attack by decreasing serum cholesterol through proper excretion of bile acids. Also helps in eliminating accumulated toxic, chemicals and excessive waste products from the body.

Psyllium husk is derived from the seed of the *Plantago ovata* plant. Besides *Plantago ovata*, psyllium is also known as *Ispaghula* and *Isapgol*. *Plantago ovata* is an annual herb native to Asia, the Mediterranean region, and North Africa. Psyllium grows in sandy and silty soils. Psyllium has a long history of use throughout the world. Psyllium has been used in traditional medicine in the US, Europe, India, and China. Some of the uses of psyllium in traditional medicine are as laxative, emollient, demulcent, and diuretic.

Metronidazole is a potent protozoicidal and trichomonocidal agent and has good activity against intestinal amebiasis<sup>1,2</sup> and many gastrointestinal complaints<sup>3,4</sup>. Its effective plasma concentration is 10 µg/ml<sup>1,5</sup>, which occurs within 1 to 2 h post administration orally after a single 400 mg dose.

The use of complementary or alternative remedies is on the increase globally because most people believe that the natural agents are safer than the conventional therapeutic agents.

Psyllium husk is known to improve blood circulation and bioavailability of other herbs.<sup>1-8</sup> when concurrently administered or co-formulated. In India, the indiscriminate use of unprescribed metronidazole for diverse gastrointestinal problems is high. Given that Psyllium husk is also widely used by a vast majority of the populace for various ailments including gastrointestinal, there is a high probability of concomitant consumption of Psyllium husk and metronidazole.

### MATERIAL AND METHOD

Our present study therefore attempts at elucidating the possible herb-drug interaction between metronidazole and Psyllium husk viz-a-viz the effect of on the pharmacokinetics of metronidazole. Metronidazole tablets (Flagyl-200 mg) were purchased from a registered pharmacy in Meerut, metronidazole pure powder was a gift from Asuhaj Pharmaceutical Ahamdabad, Gujrat, India. Sulphuric acid (CDH) and methanol (CDH) were analytical grade. Five healthy locally bred white rabbits (1.0-1.8 kg) of 3 females and 2 males were used for the study. They were also separated into cages according to gender to avoid conception before and during the study. They were fasted for 12 h before the commencement of the study but had access to water *ad libitum*. The animals were handled according to internationally and locally approved protocol for handling animal based experiment. Fresh Psyllium husk purchased from Meerut market and 1g weighed out and administered 1

g/kg orally. Drug-food interaction study design consisted of two-phase or crossover study method.

## EXPERIMENT

In phase one, the five healthy local strain rabbits were each given 3 mg/kg per oral metronidazole and 0.5 ml blood sample from their marginal veins were withdrawn over 24 h (0, 1, 2, 4, 8 and 24 h). The withdrawn blood samples were analyzed immediately. The animals were allowed a washout period of 2 weeks. In the phase two, all the five rabbits were given 1 g/kg of Psyllium husk extract per oral daily for 3 days and immediately given 3 mg/kg metronidazole per oral on the third day. Blood samples, 0.5 ml, were collected at the same time intervals of 0, 1, 2, 4, 8 and 24 h, and the samples analyzed immediately.

Extraction of metronidazole from the blood samples was carried out following the method described by.<sup>7</sup> Blood samples (0.5 ml) were mixed with 5 ml of 0.1 N H<sub>2</sub>SO<sub>4</sub> in methanol and centrifuged for 15 min at 3000g. The supernatants were separated and analyzed spectrophotometrically at 323 nm for metronidazole against plasma blank containing no drug.

For the generated data on metronidazole and Psyllium husk interaction to be analyzed, we assumed that the kinetics of metronidazole elimination was linear. The data was represented in a plasma level-time curve from where the area under time curve (AUC<sub>0-24h</sub>) was calculated using Trapezoid rule. The maximum concentration (C<sub>max</sub>) and maximum time (T<sub>max</sub>) were obtained directly from generated data. The elimination constant (K) and half-life (t<sub>1/2</sub>) were determined from the semi-log plot of the data. The clearance (CL) and apparent volume of distribution (V<sub>d</sub>) of the drug in the animals were calculated from the equations,

$$CL = (0.7 \times V_d) / t_{1/2} \dots 1, V_d = D_b^0 / C_p^0 \dots \dots 2$$

$$AUC_{\infty} = AUC_{0-24h} + C_{24h} / k \dots \dots \dots 3,$$

where, D<sub>b</sub><sup>0</sup> is the administered dose of drug; C<sub>p</sub><sup>0</sup> is the initial plasma concentration of drug obtained at intercept of semi log plot of plasma drug sample and C<sub>24hour</sub> is the plasma drug concentration at 24<sup>th</sup> h.

## RESULT AND DISCUSSION

The results were analyzed statistically using analysis of variance (ANOVA) and the student's t-test. Means that differed significantly were identified using the least square difference (LSD) post-hoc test at 95% confidence interval (p<0.05). The mean plasma concentration-time curve for metronidazole (3 mg/kg) alone and metronidazole after once a day administration of oral Psyllium husk for 3 days (1 g/kg) was shown in **Fig.1**. The study was done for 24 h since the half-life of metronidazole is 8 h<sup>5</sup>. The pharmacokinetic parameters were shown in **Tab. 1**.

The T<sub>max</sub> and C<sub>max</sub>, AUC<sub>0-24h</sub> and AUC<sub>∞</sub> showed significant difference (p<0.05) between the metronidazole alone and metronidazole plus Psyllium husk treated groups. The peak (C<sub>max</sub>) in the plasma concentration-time curve of metronidazole plus Psyllium husk occurred at about 4 h while the metronidazole alone was 2 h post administration, indicating that Psyllium husk may have caused delay in the rate of absorption of oral metronidazole but enhanced the extent of absorption considering the significant difference between the AUC<sub>0-24h</sub> of metronidazole alone and metronidazole plus Psyllium husk group. This is shown in the relatively prolonged T<sub>1/2</sub> (h) from 8.8 h to 12.7 h while that of human has been reported to be about 8 h.<sup>5</sup> The metronidazole clearance was reduced from 1.648 to 0.558 ml/kg.h (p<0.05) and the elimination rate was also reduced from 0.079 to 0.054 h<sup>-1</sup> (p<0.05).

The observations from our data showed that Psyllium husk, has definite and significant effects on the absorption kinetics of metronidazole. Since the peak plasma concentration of metronidazole when co administered with ginger occurred at about two hours later than that of metronidazole alone, its an indication that ginger may have caused delay in the rate of absorption of oral metronidazole but enhanced the extent of absorption considering the significant difference between the AUC<sub>0-24h</sub> of metronidazole alone and metronidazole plus Psyllium husk group. Psyllium husk is known to improve blood circulation and bioavailability of some herbs<sup>8,9</sup> when concurrently administered or co-formulated. It has also been reported to have spasmolytic effect and do cause smooth muscles relaxation.<sup>10</sup> These effects may have caused a reduction in gastric emptying, gastrointestinal motility and increased the blood circulation to the gastrointestinal tract thereby

facilitating the increased absorption of metronidazole.

The elimination rate constant ( $k_{el}$ ) and clearance of a drug indicates the proportion of that drug that is removed from the body<sup>8</sup> and half-life is a reciprocal function of these. As the co administration of Psyllium husk and metronidazole reduced the elimination rate constant and the clearance of the drug especially in linear kinetic, it invariably caused prolongation of the half-life. The liver is the main site of metabolism of metronidazole and about 50% of the drug is cleared from the systemic circulation by the liver<sup>3</sup>; since Psyllium husk decreased the clearance of the drug, it may be that ginger altered the metabolism of the drug by the liver.

These pharmacokinetic effects of Psyllium husk are must be cautiously considered if the

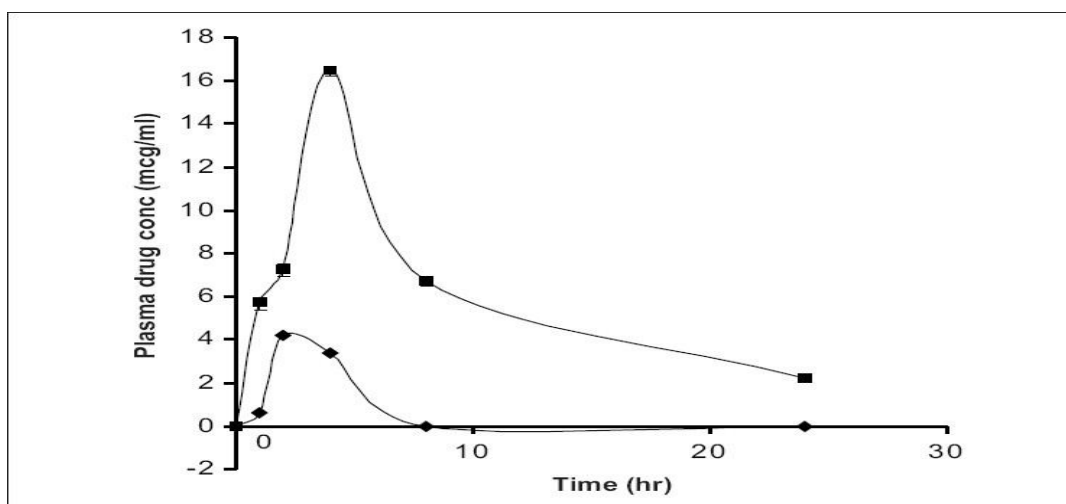
metronidazole must be used by a patient that consumes ginger in whatever form as the peak plasma concentrations of approximately 5 to 10  $\mu\text{g/ml}$  are achieved within 1-3 hours after single doses of 250 and 500 mg of oral metronidazole<sup>7</sup>, and the co administration of ginger and metronidazole at 3 mg/kg increased the peak plasma concentration from 4.23 to 16.50  $\mu\text{g/ml}$ , which is about four folds.

In conclusion, this study revealed that Psyllium husk could cause increase in the bioavailability and half-life, and decrease in the clearance and elimination rate constant of metronidazole per oral. This may pose a negative implication in clinical practice as toxicity of metronidazole may easily be reached especially during multiple dosing because of the possibility of drug accumulation.

**Table 1: Pharmacokinetic parameters of metronidazole on coadministered with Psyllium husk**

S.No.	PARAMETER	MTZ	MTZ+ PSYLLIUM HUSK
1-	$C_{max}(\mu\text{g/ml})$	4.23 $\pm$ 0.41	16.50 $\pm$ 1.02*
2-	$T_{max}(\text{hr})$	2.0 $\pm$ 0.08	4.0 $\pm$ 0.23*
3-	$AUC_{0-24\text{h}}(\mu\text{g/h.ml})$	17.16 $\pm$ 2.02	151.1 $\pm$ 3.17*
4-	$AUC_{\infty}(\mu\text{g/h.ml})$	17.16 $\pm$ 1.08	192.0 $\pm$ 12.04*
5-	$K_e(\text{h}^{-1})$	0.078 $\pm$ 0.002	0.054 $\pm$ 0.001
6-	$CL(\text{ml/kg.h})$	1.648 $\pm$ 0.43	0.558 $\pm$ 0.10
7-	$t^{1/2}(\text{h})$	8.6 $\pm$ 0.76	12.7 $\pm$ 1.04*
8-	$V_d(\text{ml/kg}^{-1})$	20.48 $\pm$ 2.04	10.23 $\pm$ 2.12

\* $P \leq 0.05$  significant to the parameter of MTZ.



**Fig. 1: Effects of Psyllium husk on plasma metronidazole concentration**

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