Effect of Misoprostol on the Pharmacokinetics of Sustained Release Diclofenac in Myanmar Healthy Male Volunteers

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ABSTRACT

Background: Sustained release diclofenac (diclofenac SR) is the commonly used non-steroidal anti-inflammatory drug for chronic inflammatory conditions such as rheumatoid arthritis. Misoprostol, prostaglandin analogue, is the agent that enhances gastrointestinal mucosal defense. Concomitant administration of misoprostol with diclofenac SR can prevent the gastrointestinal side effects of diclofenac SR.

Objective: The purpose of the study was to explore the effect of misoprostol on the pharmacokinetics of diclofenac SR in healthy volunteers.

Methods: Crossover study was evaluated in 14 male volunteers. Single oral dose of 100 mg diclofenac SR was concomitantly administered with 200 µg misoprostol with one-week wash out period. Plasma concentrations at 0, 0.5, 1, 1.5, 2, 3, 6 and 10 hrs were determined by high performance liquid chromatography (HPLC). Pharmacokinetic parameters such as area under concentration-time curve ($AUC_{0-\alpha}$), peak plasma concentration (C_{max}), time to achieve peak plasma concentration (T_{max}), absorption half-life ($T_{½(ab)}$), elimination half-life ($T_{1/2(el)}$), absorption rate constant (K_{ab}), and elimination rate constant (K_{el}) were determined.

Results: With misoprostol, the mean $AUC_{0-\alpha}$ of diclofenac SR was significantly reduced from 12.11±5.25µg/mL×hr to 4.17±2.72µg/mL×hr ($p<0.001$). The mean C_{max} was also significantly decreased from 1.43±0.46 µg/mL to 0.98±0.48 µg/mL ($p<0.05$). The mean T_{max} was decreased from 1.61±0.53hr to 1.46±0.41hr ($p>0.05$). The mean $T_{½(ab)}$ was decreased from 0.56±0.23hr to 0.54±0.19hr ($p>0.05$). The mean K_{ab} were almost the same 1.43±0.54hr^{-1} and 1.43±0.48hr^{-1}. The mean $T_{1/2(el)}$ was decreased from 3.68±1.64hr to 3.03±1.08hr ($p>0.05$). The mean K_{el} was increased from 0.21±0.09hr^{-1} to 0.25±0.09hr^{-1} ($p>0.05$).

Conclusion: There was a significant reduction in the extent of absorption of diclofenac SR when concomitantly administered with misoprostol. Therefore, the dose of diclofenac SR may need to be increased to avoid therapeutic failure of diclofenac SR or concurrent use with misoprostol may need to be changed to other gastroprotective agents.

Keywords: Diclofenac SR; misoprostol; pharmacokinetics (Siriraj Med J 2017;69: 75-79)

INTRODUCTION

The goal of a drug therapy is to optimize the therapeutic effect and to minimize the toxicity and adverse effects of the drug. The concurrent administration of two or more drugs can alter the responses of the drugs. Drug interactions are important and may often cause unexpected clinical outcomes and treatment failure.

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for various types of pain and inflammation in the form of different preparations. Among them, diclofenac is the commonly used NSAID due to its adequate efficacy, reasonable price, better accumulation in synovial fluid and longer action in joints. It is one of the commonly used NSAIDs in the world, including

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Myanmar. Among different formulations of diclofenac, sustained release form of diclofenac is more useful for chronic painful inflammatory conditions such as chronic arthritis (e.g., rheumatoid arthritis and osteoarthritis).[1]

The most common adverse effect of diclofenac is its gastrointestinal (GI) side effects. To prevent these common gastrointestinal side effects, many effective measures have been established. These measures include usage of enteric coated diclofenac and co-prescription of gastroprotective agents such as proton pump inhibitors (PPIs), prostaglandin analogue (e.g., misoprostol), sucralfate or antacids.[2]

On prescribing diclofenac, clinicians concurrently use gastroprotective agents, including prostaglandin analogue, misoprostol to prevent the gastrointestinal side effects of diclofenac as much as possible. In Myanmar also, diclofenac is prescribed together with misoprostol, as a gastroprotective agent.

The absorption of sustained release diclofenac mainly depends on its intestinal transit time.[3] The transit time is affected by age, gender, body mass index and the state of health of the individual as well as his emotional state and composition of meals. In addition, drugs affecting gastric motility, such as opioid analgesics or metoclopramide or misoprostol, have to be taken into account.[4] The orocecal transit time is consistently and significantly shorter after misoprostol therapy. Therefore, administration of misoprostol together with sustained release diclofenac may disturb the intestinal absorption of sustained release diclofenac as a result of shorter transit time.[5]

The purpose of this study was to find out the effect of misoprostol on the pharmacokinetics of sustained release diclofenac orally administered in Myanmar healthy male volunteers.

MATERIALS AND METHODS

A crossover study design was employed in the study. Healthy male subjects between 18-50 years of age with no clinical evidences of renal, hepatic, gastrointestinal and cardiac diseases, generally determined by clinical examination, history taking and laboratory investigations such as blood for CP, LFT, creatinine and urine RE, who gave written formal consent after explanation of detailed experimental procedure were allowed to include in the study.

The present study was approved by Ethical committee of University of Medicine (2). Fourteen normal healthy male volunteers with inclusion criteria were chosen. Healthy male subjects between 18-50 years of age with no history of allergic reactions to diclofenac and misoprostol and no other medications recently within one week who gave written formal consent after explanation of detailed experimental procedure were allowed to include in the study. The volunteers were allowed to withdraw from the study on their requests. Non-compliance subjects and subjects suffering any allergic reactions to diclofenac and misoprostol during the study were withdrawn from the study. The procedure was shown in Fig 1. The pharmacokinetic parameters of sustained release diclofenac alone and sustained release diclofenac with misoprostol were statistically compared.

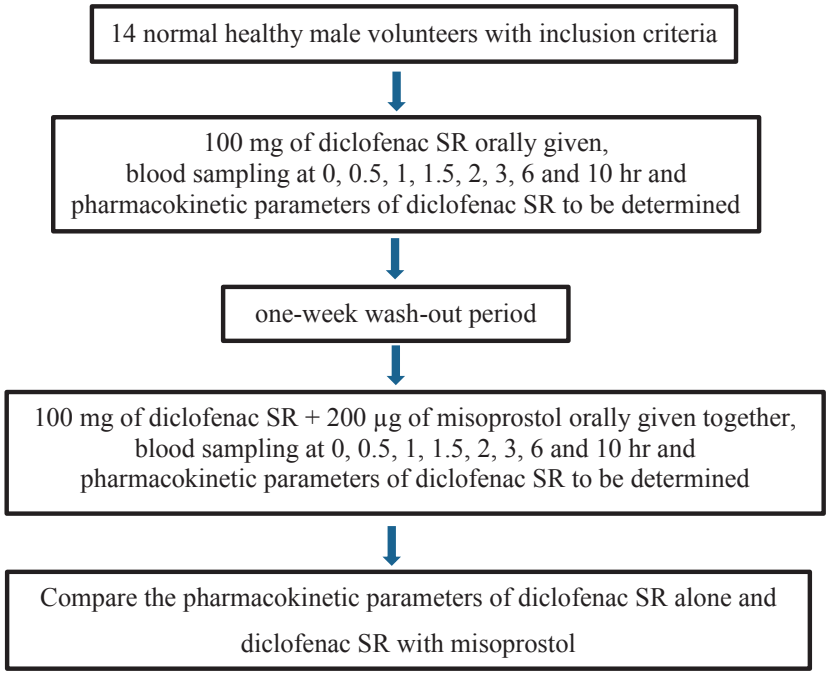

Fig 1. Flow chart of procedure

Blood samples were centrifuged at 1,000 rpm for 15 minutes to attain plasma. The samples were centrifuged within 1 hr after collection. Plasma samples were labeled and stored carefully in polyethylene tubes at -20°C.

Measurement of diclofenac sodium in plasma was carried out by HPLC-UV detection. Acetonitrile and sodium acetate (40:60 V/V) was used as mobile phase. It was adjusted to pH 6.2 by using glacial acetic acid. The column type used was reverse phase C 18 column (5 µm x 25 cm x 4.6 mm). The retention time of diclofenac was 8.4 min at the flow rate of 1.2 mL/min. The UV detection wave length was 278 nm and the inlet pressure was 1,700 psi. The plasma extraction procedure was done as follow. 500 µL of a 2.5 Mortho-phosphoric acid solution was added to 225 µL of plasma and the tube will be vigorously shaken on a vortex mixer for 20 s. After agitation, 1.5 mL of hexane-isopropyl alcohol (80:20) was added to the mixture, which had to be shaken on a vortex mixer for 2.5 min and then centrifuged for 10 min at 3,000 rpm at room temperature. The organic layer was transferred to a 10 mL culture tube and evaporated to dryness under a stream of dry Nitrogen at 37°C. The residue was reconstituted in 350 µL of mobile phase. 20 µL aliquot was then injected directly into the loop injector of HPLC.[6,7]

Assay validation of HPLC-UV method for the determination of sustained release diclofenac was done. Concentration time curve was plotted for each individual run and pharmacokinetic parameters such as maximal plasma concentration (C_{max}), area under concentration-time curve from time zero to α($AUC_{0-\alpha}$), time at which C_{max} is reached (T_{max}), absorption half-life ($T_{1/2(ab)}$), elimination half-life ($T_{1/2(el)}$), absorption rate constant (K_{ab}) and elimination rate contant (K_{el}) were calculated. The pharmacokinetic parameters of diclofenac SR alone were compared with diclofenac SR with misoprostol and statistical significance of pharmacokinetic parameters was determined by using Paired sample 't' test (SPSS Version 22).

RESULTS

Plasma drug concentrations of diclofenac SR and diclofenac SR with misoprostol were shown in Table 1 and comparison of plasma log concentration-time curves between diclofenac SR alone and diclofenac SR with misoprostol was shown in Fig 2. Comparison of pharmacokinetic parameters of diclofenac SR and diclofenac SR with misoprostol was shown in Table 2.

The mean C_{max} of sustained release diclofenac was reduced from 1.43 ± 0.46 µg/mL to 0.98 ± 0.48 µg/mL with misoprostol ($p < 0.05$). The mean T_{max} of sustained release diclofenac was reduced from 1.61 ± 0.53 hr to 1.46 ± 0.41 hr with misoprostol ($p = 0.336$). The mean $AUC_{0-\alpha}$ of sustained release diclofenac alone was 12.11 ± 5.25 µg/mL× hr and that of sustained release diclofenac with misoprostol was 4.17 ± 2.72 µg/mL×hr ($p < 0.001$). The mean K_{ab} were almost the same, 1.43 ± 0.59 hr^{-1} in sustained release diclofenac alone and 1.43 ± 0.48 hr^{-1} in sustained release diclofenac with misoprostol ($p = 1$). The mean absorption half-life of sustained release diclofenac alone was 0.56 ± 0.23 hr and sustained release diclofenac with misoprostol was 0.54 ± 0.19 hr ($p = 0.81$). The mean elimination rate constant of sustained release diclofenac alone was 0.21 ± 0.09 hr^{-1} and sustained release diclofenac with misoprostol was 0.25 ± 0.09 hr^{-1}. The mean K_{el} was slightly increased, but not statistically significant ($p = 0.92$). The mean elimination half-life of sustained release diclofenac alone was 3.68 ± 1.64 hr and sustained release diclofenac with misoprostol was 3.03 ± 1.08 hr ($p = 0.87$).

TABLE 1. Plasma concentrations diclofenac SR at different times in diclofenac SR alone and diclofenac SR with misoprostol.

	Plasma concentration (Mean ± SD) (µg/mL)		
Time	**Diclofenac SR alone**	**Diclofenac SR + Misoprostol**	***p* value**
0.5 hr	0.75 ± 0.26	0.68 ± 0.29	> 0.05
1 hr	1.04 ± 0.23	0.84 ± 0.41	> 0.05
1.5 hr	1.15 ± 0.41	0.85 ± 0.40	< 0.05
2 hr	1.32 ± 0.58	0.70 ± 0.47	< 0.01
3 hr	1.02 ± 0.40	0.43 ± 0.35	< 0.01
6 hr	0.78 ± 0.28	0.24 ± 0.18	< 0.001
10 hr	0.60 ± 0.27	0.17 ± 0.10	< 0.001

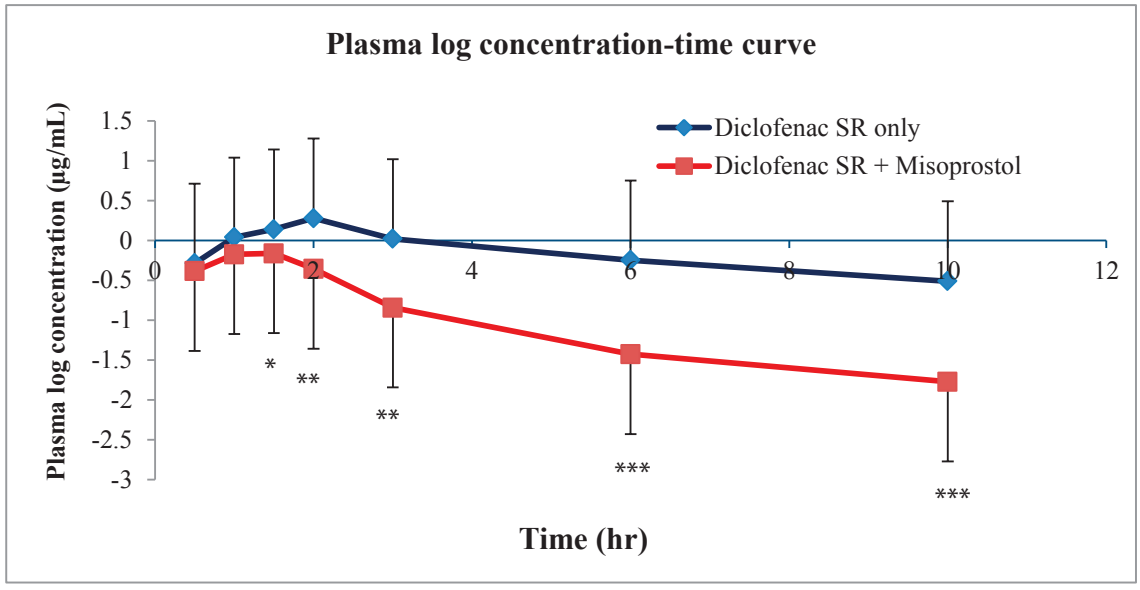

Fig 2. Comparison of plasma log concentration-time curves between diclofenac SR alone and diclofenac SR with misoprostol (n = 14)
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

TABLE 2. Comparison of pharmacokinetic parameters of diclofenac SR between diclofenac SR alone and diclofenac SR with misoprostol

	C_{max} (µg/mL)	T_{max} (hr)	$AUC_{0\text{-}\alpha\ hr}$ (µg/mL×hr)	K_{ab} (hr^{-1})	$T_{1/2(ab)}$ (hr)	K_{el} (hr^{-1})	$T_{1/2(el)}$ (hr)
Diclofenac SR alone	1.43 ± 0.46	1.61 ± 0.53	12.11 ± 5.25	1.43 ± 0.59	0.56 ± 0.23	0.21 ± 0.09	3.68 ± 1.64
Diclofenac SR + Misoprostol	0.98 ± 0.48	1.46 ± 0.41	4.17 ± 2.72	1.43 ± 0.48	0.54 ± 0.19	0.25 ± 0.09	3.03 ± 1.08
p value	< 0.05	0.336	< 0.001	1	0.81	0.92	0.87

DISCUSSION

Diclofenac is one of the commonly used NSAIDs in the world, including Myanmar. Sustained release form of diclofenac is more useful for chronic painful inflammatory conditions such as chronic arthritis.[1] The most common adverse effect of diclofenac is its action on the stomach, resulting in dyspepsia, gastric and duodenal erosions, occult bleeding, and haemorrhage. To prevent these common GI side effects, gastroprotective agents, including prostaglandin analogue, misoprostol, are co-prescribed in clinical routine.[2]

Misoprostol is the agent that enhances GI mucosal defense. It is a prostaglandin analogue. Misoprostol is used to locally replace prostaglandins the formation of which is inhibited by NSAIDs. Misoprostol prevents NSAID-induced GI damage: gastric ulceration is found to be significantly reduced in both acute and chronic NSAID treatment.The effect of misoprostol on the pharmacokinetics of sustained release diclofenac was explored in this study.

Plasma drug concentrations at 0.5, 1, 1.5, 2, 3, 6 and 10 hr were also reduced when sustained release diclofenac was taken together with misoprostol. This meant that the plasma concentration of diclofenac SR was decreased at any moment when co-administered with misoprostol.

The mean $AUC_{(0\text{-}\alpha)}$ of sustained release diclofenac was significantly reduced from 12.11 ± 5.25 µg/mL×hr to 4.17 ± 2.72 µg/mL×hr ($p < 0.001$) when it was co-administered with misoprostol. This implied that less

diclofenac SR remained in the blood stream. The change in AUC might be due to reduced absorption or increased elimination or both.

The change in AUC as well as plasma concentrations at any moment, including C_{max}, were a resultant of change in absorption, distribution and/or elimination of the administered drug due to some reasons.

Regarding distribution, since same drug was administered to the same subjects as control, volume of distribution of sustained release diclofenac can be assumed as the same with misoprostol co-administration. Therefore, the changes in AUC and C_{max} might not be due to changes in distribution.

Regarding elimination, the elimination rate constant (K_{el}) of diclofenac SR was slightly increased from 0.21 ± 0.09 hr^{-1} to 0.25 ± 0.09 hr^{-1} ($p > 0.05$) and its elimination half-life was a little bit decreased from 3.68 ± 1.64 hr to 3.03 ± 1.08 hr ($p > 0.05$) when it was given together with misoprostol. Therefore, the significant reduction in AUC and C_{max} were less likely due to changes in elimination process.

Regarding absorption, the absorption rate constant (K_{ab}) of diclofenac SR alone was the same as that of diclofenac SR with misoprostol ($p > 0.05$). The absorption half-lives of diclofenac SR alone and diclofenac SR with misoprostol were also nearly the same, 0.56 ± 0.23 hr and 0.54 ± 0.19 hr respectively.

Absorption of a drug with sustained release formulation may vary according to an average GI transit time.[3] The transit time is affected by age, gender, BMI, and the state of health of the individuals as well as his emotional state and composition of meals. In addition, drugs affecting GI motility, such as opioid analgesic, misoprostol or metoclopramide, have to be taken into account.[4] The key point of the numerous sustained release drug delivery systems is that they have to be absorbed well throughout the whole GI tract.

Generally, the absorption of an oral sustained release drug delivery system depends on the variable nature of gastric emptying process.[8] The relatively brief gastric emptying time through the stomach or upper part of the intestine (major absorption site), can result in incomplete drug release from the drug delivery system, leading to diminished absorption of the administered dose.

Variable factors such as age, sex, BMI, meal pattern, hepatic and renal functions and baseline laboratory parameters and interaction with other medications were fixed as much as possible among 14 male volunteers.

In this study, misoprostol is co-administered as a gastroprotective agent, together with sustained release diclofenac. Misoprostol has rapid onset of action.[9] Orocecal transit time was consistently and significantly shorter after misoprostol treatment.[5] Quicker passage of a drug with sustained release formulation may probably lead to its incomplete absorption since the extent of absorption and plasma concentration of a sustained release drug mainly depends on the GI transit time. The longer the GI transit time, the more complete the absorption of the sustained release drug is. Therefore, administration of misoprostol together with sustained release diclofenac may disturb the intestinal absorption of sustained release diclofenac as a result of shorter transit time.

CONCLUSION

The effect of misoprostol on the pharmacokinetics of sustained release diclofenac in healthy Myanmar male volunteers was explored in this study. The significant decrease in AUC and Cmax of sustained release diclofenac might probably be due to the disturbance in the extent of absorption of sustained release diclofenac as a result of its shorter GI transit time by misoprostol. This effect may be clinically significant, resulting in the reduction of analgesic and anti-inflammatory efficacy of sustained release diclofenac if it is co-administered with misoprostol as a gastroprotective agent.

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