CHAPTER I

INTRODUCTION

The treatment of peptic ulceration and hypersecretory status have been revolutionized in recent years by the introduction of two histamine H_2-receptor antagonists, cimetidine and ranitidine. The principal pharmacological action of H_2-blocking agents is that of reducing gastric acid secretion stimulated by all three endogenous secretagogues, histamine, acetylcholine and gastrin (1). Since the discovery in 1979 that cimetidine inhibits microsomal drug metabolism in rats (2), the drug has been reported to alter the disposition of at least 23 other drugs in human (3). Cimetidine-induced inhibition of drug oxidation may be related to the presence of an imidazole ring in the structure (Figure 1B). Many imidazole-containing drugs, including cimetidine, bind tightly to hepatic cytochrome P-450 the mixed-function oxidative enzyme system whose activity is closely related to the oxidative biotransformation of many drugs (4, 5, 6).Ranitidine, with a furan ring structure instead (Figure 1A), has been shown to be five to eight times more potent as a specific competitive H_2-blocking agent than cimetidine (7, 8) but binds cytochrome P-450 with a much lower affinity (10 times) and in a different fashion than does cimetidine (8). Because of the advantages of more potency and fewer side effects, ranitidine appears to be more available use in the treatment

of peptic ulcer and allied diseases and has been substituted for cimetidine in patients intolerant of cimetidine.

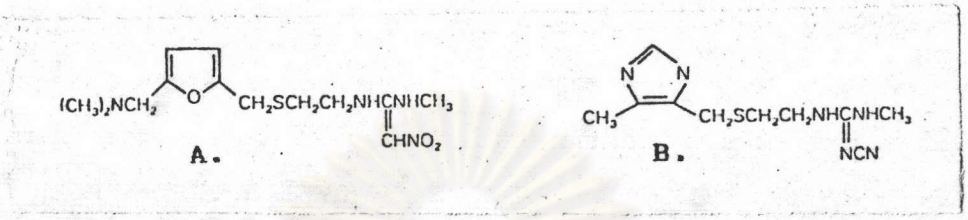

Figure 1 Structural formula of ranitidine (A) and cimetidine (B)

Ranitidine is available in both tablet and injection dosage form. In Thailand, there are 5 brands of 150 mg ranitidine tablets in the market. One is the innovator's product, with higher retail price, and the others are locally manufactured. As the formulation and production of the drug may markedly affect its bioavailability, the bioequivalence of these products should be evaluated (9). Hence, the present study was conducted to provide the absolute and relative bioavailabilities of different brands of ranitidine tablets available in Thailand. Additionally, there is a relationship between dosage and peak plasma concentration of ranitidine and also a relationship between the plasma concentration and the degree of acid suppression (10, 11, 12, 13). Therefore, the information on ranitidine pharmacokinetics after oral and intravenous administration in healthy volunteers could be useful in determining an optimum concentration of ranitidine in plasma.

Objectives

1. To determine the absolute bioavailability of ranitidine tablets commercially available in Thailand.

2. To compare the bioavailability of ranitidine tablets commercially available in Thailand.

3. To investigate the pharmacokinetics of ranitidine after single oral and intravenous administration of ranitidine tablets and injections in Thai healthy male volunteers.

4. To investigate the correlation of disintegration, dissolution of tablets and principal pharmacokinetic parameters.

Significance of the Study

1. This study will provide significantly an information about absolute and relative bioavailability of ranitidine tablets.

2. This study will provide the pharmacokinetics of ranitidine in Thai-healthy volunteers. The information obtained will be compared with previously studies conducted in other countries.

3. The information on ranitidine kinetic and bioavailability would be very useful in selecting the cheapest product, which is bioequivalent to the innovator's product, and determining an optimum dosage regimen.