CHAPTER I

INTRODUCTION

Background and Rationale

More than 90% of Thailand's drug consumption is imported, either in form of finished pharmaceutical product or in form of raw materials, which later will be formulated to the required dosage form by local drug manufacturers.

The absense of pharmaceutical drug patent law in Thailand, results in at least 25,000 finished pharmaceutical products in the market (1). This high competition causes the manufacturers to lower the price of their products and, may be, the efficacy of them too. In order to ensure drug efficacy, the regulatory agencies try to monitor in vitro quality such as amount of active ingredient, disintegration, dissolution, and stability according to accepted standard in Pharmacopia. However, it is well-known that a drug passing all in vitro testing, may not reach the expected therapeutic response. The best way to measure drug effectiveness and drug formulation is to test in human, e.g.,bioavailability studies.

Furosemide is one of a loop diuretics which is frequently used in the treatment of edema associated with congestive heart failure, hypertension, and renal failure (2).

At present, more than 13 different generic brands of 40-mg furosemide tablets are available in the market. One is a well-known original brand and the others are various local brands. Although it has been used for many years, there appears to be little information about its bioavailability and pharmacokinetics characteristics (3-9), especially in Thailand. Hence, an extensive study was designed to compare the relative bioavailability of different commercially furosemide tablets and to investigate the pharmacokinetics of furosemide after oral administration to healthy volunteers.

Objectives:

1. To compare the bioavailability of commercial furosemide tablets marketed in Thailand.

2. To investigate the pharmacokinetics of furosemide after single oral administration of furosemide tablets in Thai healthy volunteers.

3. To correlate relative in vivo bioavailability of different tablets with their in vitro disintegration time and dissolution rate.

Significance of the Study:

1. This study will provide significantly an information about the bioavailability of furosemide tablets.

2. This study will provide an useful information about the pharmacokinetics of furosemide in Thai healthy adult volunteers.

3. From the pharmacokinetics parameters obtained from different brands, we shall be able to justify whether the local manufactured brand of furosemide tablets are equivalent to that of the original brand. It also enables us to select the economical products which produce equivalently therapeutic effect.

Review of Furosemide

In the early 1960's, Siedel and colleagues (10) in Germany investigated the biological activities of a large number of sulphonamide derivative of anthranilic (2-aminobenzoic) acid and discovered the unusual high ceiling properties of furosemide. Furosemide or frusemide is one of the most potent diuretics, loop diuretics or high-ceiling diuretics. Other diuretics in this group are ethacrynic acid, bumetanide, piretanide, etc.

1. Physicochemical Properties (11,12)

Furosemide is a 4 - chloro - N - furfuryl - 5 - sulfamoyl anthranilic acid compound with a pKa of 3.8. (Figure 1)

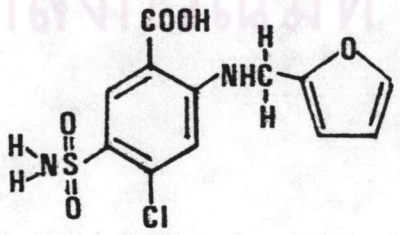

Figure 1 Structural formula of furosemide

Empirical formula : $C_{12} H_{11} Cl N_2 O_5 S$

Molecular weight : 330.74

Description : A white or slightly yellow, odourless, almost tasteless, crystalline powder

Solubility : Practically insoluble in water and chloroform; soluble in alcohol (1.33 g/100 ml), ether (0.118g/100 ml) and acetone (6.67 g/100 ml); freely soluble in dimethylformamide and solutions of alkali hydroxides; soluble in methyl alcohol

Stability : Exposure to light may cause discoloration and degradation to its metabolite, 2-amino-4-chloro-5-sulphomoyl anthranilic acid (CSA). Solution of furosemide should not be mix with other acidic solution.

Melting point: 206° C (with decomposition)

2. Mechanism of Action

After oral administration, furosemide evokes a rapid saluretic response which peaks within 20 to 30 miniutes and the major effect of the drug is completedwithin 3 to 4 hr.

The major renal target for furosemide is salt reabsorption in the thick ascending limb of Henle's loop (10). Microperfusion of isolated segments of rabbit renal tubule have shown that furosemide acts from within the tubular lumen to inhibit active chloride transport. Because of its physicochemical properfiles, furosemide gains access to its site of action by being transported through the

nonspecific secretory pathway for organic acids in the proximal tubule.

Homeida et al (13) found a close relationship between tubular secretion of furosemide and the magnitude of the saluretic response. That finding shows that a diuretic response of furosemide depends on the amount of unchanged drug delivery by the proximal secretory pathway to the tubular lumen of the kidney. Transportation of furosemide through this pathway could be significantly modified by changes in the capacity of the system in conditions such as uremia as well as in the presence of other organic acid (14,15,16) which could compete for active transport. Either condition could importantly change the relationship of the dose of furosemide to its diuretic effect.

3. Adverse Reactions and Precautions (12,17)

Therapy with furosemide must be administered cautiously because it is a potent drug. Dosage should be individualized to avoid excessive diuresis. Overdosage therapy can cause volume depletion, hypotension, and marked hypokalemic and hypochloremic alkalosis. Transient deafness has occurred following rapid intravenous administration of large doses and occasionally after administration of small doses and/or during oral therapy. When furosemide is used for long-term therapy of edematous conditions, rapid withdrawal may cause rebound edema.

4. Pharmacokinetics Studies

4.1 Absorption, Metabolism and Excretion

Some of the earlier studies on the biological fate of furosemide were limited by the sensitivities of the assay methods available. This may account for some differences in results reported by various invertigators (2).

Approximately 60 to 70 % of an oral dose of furosemide is absorbed. Food may slow the rate of absorption but does not alter the total amount of drug absorbed (18). Absorption is also slowed in patient with decompensated congestive heart failure (17). Onset of action after oral administration is about 30 to 60 minutes and about 5 minutes after intravenous administration.

Furosemide is 91 to 99 % bound to serum albumin, but protein binding is reduced in those with uremia and nephrosis (17). The half-lives of furosemide are in wide variation among individuals. In normal, half-lives are between 0.5 to 1 hr. In patients with both renal and hepatic insufficiency, half-lives of 11 to 20 hr have been reported. A time to peak effect is 1 to 2 hr after oral dose and the diuretic action will last for 6 to 8 hr.

The data available concerning the metabolism of furosemide are controversial. Hajdu and Häussler (19) reported that 2-amino-4-chloro-5-sulfamoylanthranillic acid (CSA) was the only metabolite of furosemide after the analysis of urine from subjects

administered unlabeled furosemide but Calessnick et.al.(19) found no evidence of other compounds in urine following [^{35}S] furosemide administration to healthy volunteers. In the other hand, Beerman et. al.(20) reported that the major excretory route for furosemide is via a kidney where the main urinary metabolite isolated in man has been the glucuronide. Recovery of about 10% of intravenously administered ^{35}S-furosemide in the feces implies biliary and probably also direct intestinal excretion of the drug.

4.2 Pharmacokinetics Studies in Normals

Culter et.al. (21) described furosemide kinetics in four normal volunteers each at three different dose levels. They found that furosemide essentially followed a one-compartment model and the average half-life for elimination was 29.5 minutes. Kelly et. al. (22) studied furosemide kinetics following intravenous dosing in four additional normals and found that data appeared to follow two-compartment kinetics in two of these individuals and one compartment kinetics in the other two. However, the terminal half-life for this group averaged 26 minutes.

Beerman et.al.(20) reported furosemide kinetics after intravenous administration of a radiolabeled compound to two normals. Half-lives estimated from plasma between 0.5 and 4 hr yielded an average of 50 mintes, a value very similar to that observed by Rupp and Hajdu (19) and almost twice as great as that of Cutler et.al. (21) and Kelly et.al.(22). Beerman et.al. (23) again studied furosemide kinetics following intravenous administration to five healthy

volunteers and found that plasma half-lives averaged 47 minutes. An average terminal half-life from the study of Rane et. al. (23) after both intravenous and oral administration of furosemide to six normal subjects was 51±4 minutes.

The difference of terminal half-lives of furosemide from many studies described above implies that there are wide variation of half-lives among individuals. They also showed that most pharmacokinetics studies were performed after intravenous dosing.

4.3 Bioavailability Studies

There is a little information about bioavailability studies of furosemide. Kelly et. al. (22) reported the absolute bioavailability of tablets and oral aqueous solution of furosemide to be 65% and 69% respectively. Branch et. al. (25), in a study with six volunteers, found that absolute bioavailability of oral furosemide (dosage form not identified) was 49%. Eleven normal volunteers were studied by Tilstone and Fine (26) and they found that tablet and solution preparations were determined to be 69% bioavailable.

Absolute bioavailability of solution and tablet of furosemide were also determined by Waller et al. (4) using both plasma and urine data. They found that plasma time curves of several subjects revealed secondary maxima which indicated enterohepatic cycling. In a comparative bioavailability study of two furosemide formulations by Martin et. al. (6), the generic tablets was inequivalent to the brand-name tablets. The same result was found in the study of Meyer et.al. (7).

4.4 Therapeutic Uses

Furosemide is usually preferred to ethacrynic acid (17) because it (1) has a broader dose-response curve; (2) is less ototoxic; (3) causes fewer gastrointestinal side effects; (4) is more convenient for intravenous use; (5) may be less likely to cause alkalosis; and (6) is available as an oral solution.

Furosemide is useful in the treatment of edema associated with congestive heart failure. It may be effective in some patients who have become refractory to other diuretics. Orally administered furosemide may be used in mild to moderate hypertension, either alone or in combination with other hypotensive agents (27).