Furosemide (Frusemide)
A Pharmacokinetic/Pharmacodynamic Review (Part I) \(^1\)

Laura L. Boles Ponto and Ronald D. Schoenwald

Colleges of Medicine and Pharmacy, University of Iowa, Iowa City, Iowa, USA

Summary

Furosemide (frusemide) is a potent loop diuretic used in the treatment of oedematous states associated with cardiac, renal and hepatic failure, and for the treatment of hypertension. Therapy is frequently complicated by apparently erratic systemic availability from the oral route and from unpredictable responses to a given dosage. The exact mechanism of action is not fully understood, but furosemide is believed to act at the luminal surface of the ascending limb of the loop of Henle by inhibiting the active reabsorption of chloride. The response to a given dosage is modulated by the fluid and electrolyte balance of the individual. Acute and delayed tolerance has been demonstrated both in animals and in man, and is postulated to be due to the intervention of homeostatic mechanisms influencing fluid and electrolyte balances. Furosemide is delivered to its site of action by active secretion via the nonspecific organic acid pump. Comparisons between the observed diuresis/saluresis and plasma furosemide concentrations, urinary excretion rates and renal clearance found either negative or no correlations with plasma drug concentration but significant correlations with urine measurements. Response is related to the concentration of the drug in urine rather than in plasma. The most common adverse reactions attributable to furosemide therapy are essentially extensions of the therapeutic effects (i.e. fluid and electrolyte disturbances).

The pharmacokinetic behaviour of furosemide is marked by a large degree of vari-

---

\(^1\) A complete reference list will appear in Part II of this article in the following issue of the Journal.
ability, derived from differences within and between both subjects and study protocols. Part of this variability can be attributed to differences in organ function, which is important in view of the types of patients treated with furosemide. On the other hand, a large proportion remains as inter- and intrasubject variation.

The bioavailability of furosemide from oral dosage forms is highly variable. The poor bioavailability has been hypothesised to be due to the poor solubility of the compound, site-specific absorption, presystemic metabolism and/or other unknown mechanisms. Furosemide is highly bound to plasma proteins, almost exclusively to albumin. Although the drug is insoluble in water and favours partitioning into fatty tissue, the high degree of plasma protein binding restricts the apparent volume of distribution at steady-state to values within a multiple of 2 to 5 times the plasma volume. Furosemide has two documented metabolites – furosemide glucuronide and saluamine (CSA). The first is an accepted metabolite product, whereas the status of CSA as a metabolite is highly controversial. The half-life reported for furosemide in normal subjects generally falls in the range of 30 to 120 minutes, but is influenced by underlying disease processes: for example, in patients with end-stage renal disease without other organ impairment it averages 9.7 hours.

Since the site of action of furosemide is the luminal surface of the ascending limb of the loop of Henle, the fraction of the dosage excreted unchanged in the urine represents the fraction which is potentially available for pharmacological action. Approximately one-half to two-thirds of an intravenous dosage or a quarter to one-third of an oral dosage will actually be available at the site of action. This general finding is altered by factors which alter the bioavailability and/or urinary delivery of the drug. Clinical nonresponders tend to have decreased excretion percentages.

The dose-response relationship of furosemide entails a linear pharmacokinetic relationship superimposed on a nonlinear pharmacodynamic relationship, and the mathematical model deemed most appropriate for the characterisation of the observed pharmacodynamic behaviour is a 4-parameter logistic function.

Clinically, furosemide is used by large numbers of diseased patients on a long term basis. The majority of the knowledge that is currently available on its pharmacodynamics is based on the investigation of healthy, drug-free subjects receiving single doses and undergoing concurrent rehydration. This information is useful in delineating the impact of a variety of factors which influence the dose-response relationship, but does not provide the clinician with the answers to important questions regarding the specifics of the therapeutic application of furosemide in diseased populations.

The extensive literature on furosemide (frusemide) reviewed here is an accumulation of information which is often confusing and variable, and sometimes conflicting.

1. Physical Properties

Furosemide, 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid or 5-(amino-sulfonyl)-4-chloro-2[(2-furanylmethyl)amino] benzoic acid, is an anthranilic acid derivative with a molecular weight equal to 330.74 g/mole (Hoechst-Roussel Pharmaceuticals Inc. 1988; Osol et al. 1975; United States Pharmacopeia 1990) [fig. 1].

![Fig. 1. Chemical structure of furosemide (frusemide).](image)

The white to slightly yellow crystalline powder is odourless and practically tasteless, and melts at between 203° and 205°C with decomposition. The compound is unstable to light but stable to air. Furosemide absorbs ultraviolet light at 275 and 345nm and fluoresces at 405 to 417nm. The fluorescence