The Phenomenon and Cause of the Dose-Dependent Oral Absorption of Chlorothiazide in Rats: Extrapolation to Human Data Based on the Body Surface Area Concept

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The reported incomplete and dose-dependent absorption of chlorothiazide in humans was demonstrated in six rats after five oral solutions at doses of 0.93, 2.55, 9.23, 25.6, and 70.2 mg/kg. Mean 48-hr urinary recoveries of intact drug were 52.3, 50.4, 36.7, 22.8, and 15.3%, respectively. A similar degree of dose dependency in absorption was found in rat, dog, and human when the doses were related to unit body surface area (BSA) but not on unit body weight, indicating similar interspecies absorptive capacity in terms of unit BSA. This finding may be partly rationalized by marked similarities in the reported solution transit time (2–3 hr) in the small intestine as well as in the calculated gross surface area of the small intestine per unit BSA (0.163 for rat and 0.132 for human). Contrary to the previous postulation of a specific absorption site, the drug was absorbed from different regions of the GI tract with apparent 1-hr absorption rates, studied by the in situ closed-loop method, in the following rank order: jejunum (34.6%) > duodenum (32.7%) > large intestine (20.1%) > ileum (18.0%) > stomach (12.4%). Different from the commonly assumed first-order absorption process, the intestinal loop absorption was concentration-dependent, suggesting a saturable mechanism. For example, the absorption rate at 0.008 mg/mL was higher than that at 0.2 mg/mL in ileal loops (61%, p < 0.01) and jejunal loops (22%, p < 0.1). In addition, the absorption rates at pH 6 and 7.4 were statistically identical, indicating a lack of ionization effect that is important in the passive absorption process. The solubility-limited absorption could probably be ruled out at doses below 2.55 mg/kg for rat and 125 mg for human in view of higher aqueous solubilities at 37°C (e.g., 1.3 mg/mL at pH 7) found in the present study. Contrary to the previous hypothesis of low membrane permeability as a limiting factor for absorption, the "intrinsic" partition coefficient in 1-octanol/aqueous buffer was moderate, 0.6. Furthermore, the

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absorption in ileal and jejunal loops was enhanced by an apparent increase in mesenteric blood flow by caffeine. The existence of prolonged oral absorption in rats and humans is discussed.

KEY WORDS: dose-dependent oral absorption; chlorothiazide; intestinal absorption; body surface area; interspecies correlation in pharmacokinetics.

INTRODUCTION

Oral absorption of chlorothiazide in humans from both solution and solid dosage forms has been shown to be incomplete and dose-dependent (1-12). For example, the mean 72-hr urinary recoveries of intact drug fell from 35 to 16% (6) and from 56 to 33% (10) as doses were increased from 125 to 500 mg and from 50 to 250 mg, respectively. Bioavailability was reduced to only 9% when a 1-g dose was given (12). In most previous studies (1-12), cumulative urinary excretion of chlorothiazide was used as a measure for the extent of oral absorption since essentially all of the intravenous dose could be recovered unchanged in urine (1,12-14).

The exact cause for the above interesting absorption property is still unknown. For example, this has been attributed to (i) a specific absorption site or window for absorption (1,5,10,11); (ii) an active or saturable absorption process (5,6,10,11); (iii) low gastrointestinal (GI) membrane permeability (1,15); and (iv) low water solubility (1,2,15). The last hypothesis apparently was based on solubility data obtained at room temperature (13,16-18); no solubility profile at body temperature in the pH range of the intestine has been considered. Furthermore, the solubility factor alone apparently cannot explain the observed poor bioavailability (approximately 50%) (10) when only a dose of 50 mg in solution was administered because the aqueous solubility at pH 7 obtained in our laboratory (to be discussed later) is about 1.3 mg/mL at 37 C; only 38.5 mL may be needed to prevent precipitation in such fluid.

More recently, based on a good agreement between reported experimental data and theoretical absorption profiles constructed according to a two-tank perfect-mixing tank model for GI absorption, it was concluded (15) that the physical characteristics of chlorothiazide (especially its limited aqueous solubility and low ionization constant, $pK_a$ being 6.7), rather than a saturable transport mechanism at the intestinal wall, may be responsible for the dose-dependent absorption found for this drug. One complicating factor in that simulation (15) is that the solubility used (0.65 mg at pH 7) was apparently based on the value obtained at room temperature.

Oral absorption in rats following a 9.5-mg dose of chlorothiazide powder has been reported recently (19). Plasma data were fitted successfully to a one-compartment model with first-order absorption and elimination. Bioavailability was markedly enhanced when the GI transit time of the drug