Nonlinear Relationship Between Plasma and Red Blood Cell Pharmacokinetics of Chlorthalidone in Man

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Plasma concentrations, red blood cell concentrations, and urinary excretion of chlorthalidone were measured after oral administration of single doses of 100 or 200 mg to ten human subjects. The decay of red blood cell concentrations showed a much longer elimination half-life than the terminal plasma decay curve. The in vitro distribution of chlorthalidone between plasma and erythrocytes was similar to the in vivo distribution curve obtained from patients who were in a steady-state concentration range. A pharmacokinetic model was developed including nonlinear binding of chlorthalidone by the red blood cells, which in detail accounted for the observed time courses of drug in plasma and erythrocytes simultaneously.

KEY WORDS: chlorthalidone pharmacokinetics in man; oral administration; plasma concentrations; red blood cell concentrations; nonlinear distribution; pharmacokinetic model.

INTRODUCTION

The compartment models employed in current pharmacokinetic literature are mathematical descriptions of the plasma, serum, or blood decay curves based on a continuous first-order exchange between the central compartment (generally the sampling compartment, e.g., plasma) and the peripheral compartments (tissues) (1-4). The factors which can be used to relate the concentrations in the different compartments are distribution rate

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constants (e.g., hour$^{-1}$) or transfer clearance constants (e.g., liters/hour). In this way, hypothetical amounts of drug in tissues or tissue concentrations can be simulated, provided that the plasma concentrations are known. The use of the ratio of the transfer clearance constants of entry into and release from such compartment $k_{c,\text{in}}/k_{c,\text{out}}$ has the advantage of giving directly the ratio of the eventual tissue and plasma concentrations, provided that the state of equilibrium after absorption and distribution phases has been reached.

An implication of this description by linear differential equations is that if the decay curves of plasma and tissue concentrations vs. time are compared, they always appear to become parallel to each other independently of how fast the equilibrium is reached (linear pharmacokinetics). This is shown in Fig. 1, in which we brought about variations in the transfer rates of entry into and release from a peripheral compartment and kept the ratio between them constant. The upper curves represent tissue compartments to which the drug is transferred preferentially compared with the central compartments. If the numerical value $k_{c,\text{out}}$ is lower, it takes more time to reach the point where the tissue concentration is maximal. For those drugs that to an appreciable amount accumulate in the erythrocytes, the erythrocytes may be considered as a separate compartment that belongs to either the central or the peripheral compartment depending on the rate of drug exchange between plasma and erythrocytes.

Chlorthalidone is a diuretic with a long duration of action that strongly binds to erythrocytes (5–8). While the plasma is part of the central compartment, the erythrocytes may be considered as a tissue compartment that is easily accessible, allowing the analysis of the kinetics of drugs exhibiting tissue binding.

From preliminary experiments, it became evident that the decay curves of chlorthalidone in plasma and in the erythrocytes are not parallel (6), suggesting that binding of this diuretic to constituents in the erythrocytes may be responsible for this nonlinear kinetic behavior (6). Such nonlinear behavior may have important consequences for therapy with this drug, especially because its longer half-life in the erythrocytes may result in considerable accumulation in this tissue in the clinical situation.

We therefore analyzed the pharmacokinetics of chlorthalidone simultaneously in plasma and erythrocytes in experimental subjects receiving a single dose of chlorthalidone and measured steady-state concentrations in patients receiving repetitive doses over long periods of time.

**MATERIALS AND METHODS**

Chlorthalidone was given in doses of 100 or 200 mg to ten young, healthy male subjects ranging in age from 22 to 25 years. The drug was