The Role of the Kidney in the Elimination of Cephapirin in Man

B. E. Cabana, 1,3 D. R. Van Harken, 1,5 G. H. Hottendorf, 1
J. T. Doluisio, 2,4 W. O. Griffen, Jr., 2 D. W. A. Bourne, 2 and
L. W. Dittert 2

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A pharmacokinetic model was developed to describe the absorption, distribution, metabolism, and excretion of cephapirin and its major metabolite, desacetylcephapirin, following intravenous and intramuscular administration of cephapirin in healthy adult subjects. The model involved a two-compartment open model for cephapirin in plasma and extravascular tissues and included metabolism of cephapirin to desacetylcephapirin in both the plasma compartment and the kidney. Renal metabolism of cephapirin was followed by excretion of the desacetylcephapirin into the urine. Clearance calculations and digital computer simulation supported these features of the model.

KEY WORDS: cephapirin; desacetylcephapirin; cephalosporin; renal clearance calculations; renal metabolism.

INTRODUCTION

The primary function of the kidney in drug elimination is generally thought to be excretion of drugs and metabolites, while the liver, rich in drug-metabolizing enzymes, is considered to be the major site of drug metabolism (1,2). However, appreciable amounts of drug-metabolizing enzymes have been shown to be present in blood cells as well as in gastrointestinal, kidney, lung, and brain tissues (3,4), and significant extrahepatic
metabolism has been demonstrated for a variety of drugs (4-10). In several cases, extrahepatic metabolism occurred in the kidney (6-10). A review by Rennick (11) strongly suggests that the renal metabolism of many drugs may be an integral part of the renal tubular transport system for these drugs. Often the renal metabolism involves production of conjugates such as hippurates, glucuronides, and ethereal sulfates (6-11), and the reactions which produce these metabolites are catalyzed by transferases (3).

Cabana et al. (12-15) reported that the metabolism of cephapirin in laboratory animals and man was similar to that reported for cephalothin (16,17). Both cephalosporins were deacetylated to a bioactive desacetyl metabolite by esterase enzymes, and both the parent compound and the desacetyl metabolite were excreted by the kidney. However, evidence was presented to suggest that in rat, dog, and man the kidneys performed a role not only in excretion but also in the metabolism of cephapirin to desacetylcephapirin (12,15). In man, the apparent renal clearance of desacetylcephapirin exceeded renal plasma flow, suggesting that metabolism of cephapirin to desacetylcephapirin must occur to some extent within the kidneys (14,15).

A preliminary report of a kinetic model for cephapirin in man in which the kidney functions as a distinct metabolic site has been presented by Cabana et al. (13). In this report, we develop a detailed kinetic analysis of the absorption, distribution, and elimination of cephapirin in man with emphasis on the role of the kidney in the deacetylation as well as the excretion of the drug.

EXPERIMENTAL

Since the potential of cephapirin to produce hypersensitivity in humans had not been unequivocally established in the early stages of clinical evaluation, the intravenous and intramuscular studies were conducted with parallel groups of eight subjects each instead of a crossover design to avoid exposing the volunteers to any unnecessary risk. Because of the parallel study design, every effort was made to match the subject groups as closely as possible with regard to weight (see Table I), but the 8% difference in mean weights of the two groups was unavoidable. Two groups of eight healthy adult male volunteers ranging in age from 21 to 35 years and weighing between 150 and 186 lbs (68-84.5 kg) were studied. The first group of volunteers (mean weight 73.3 kg) was administered a 1.0-kg dose of cephapirin (sodium salt, lot 71L29, biopotency 950 µg/mg, dissolved in 20 ml of normal saline) intravenously in the back of the right hand over a 5-min period by means of a constant-rate infusion pump. Experimental timing was begun at the beginning of the infusion period. The second group of volunteers (mean weight 79.5 kg) was