8

Assessment of Pharmacokinetics and Drug Activity: Isolated Organ Systems and the Membrane Transporter Family

Kevin R. Sweeney
Pfizer Global Research, Groton, Connecticut, U.S.A.
David R. Taft
Long Island University, Brooklyn, New York, U.S.A.

1. INTRODUCTION

The relationship between pharmacokinetics and drug activity is well established. Clearance, the most important determinant of drug disposition, dictates the amount of drug that must be administered to maintain therapeutic effectiveness. Likewise, the ability of a medication to distribute to the biophase will influence its efficacy and/or toxicity. Each of these processes depends on drug transport across organs and tissues in the body.

Membrane transporters perform a central function in drug disposition and activity. Significant advances in experimental methodology have resulted in the identification of transporters in the liver, gastrointestinal (GI) tract, kidney, and central nervous system (CNS). Together with the metabolizing enzymes (e.g., cytochrome P-450), membrane transporters form a primary defense mechanism against the potential toxic effects of xenobiotics (1). Knowledge of the transporter(s) responsible for the elimination of a compound allows for the elucidation of potential drug interactions (drug–drug, drug–disease) and the identification of possible mechanisms of