Pharmacokinetics of Sulfaethidole in the Rat: Nonlinear Multicompartment Solution

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Received January 4, 1980—Final August 8, 1981

Sulfaethidole distribution and elimination in the rat was studied over a 90-fold dose range. This experimental design produced marked nonlinearity in the binding of sulfaethidole to proteins in both interstitial fluid and plasma. Using a multicompartmental model consisting of binding of sulfaethidole to plasma and interstitial fluid proteins, sulfaethidole distribution in the body could be simulated. Urinary and biliary elimination of sulfaethidole depended on the unbound drug mass in the plasma and urine flow. The results confirm the central role of the unbound species in the distribution and elimination of drugs with marked binding to plasma proteins.

KEY WORDS: pharmacokinetics; models; plasma protein binding; nonlinear processes; sulfaethidole.

INTRODUCTION

Nonlinear processes have been considered for more than a decade to play a significant role in the pharmacokinetics of many drugs. Systematic theoretical work in this field has been carried out by Krüger-Thiemer and his associates (1–3). More recently, additional formulations of the problem (4–6) and practical solutions for many drugs (6–10) have widened our understanding of nonlinear pharmacokinetics.

We have earlier studied the role of plasma and interstitial fluid proteins in producing nonlinearities in the distribution of warfarin, a drug with marked plasma protein binding (11,12). The assumption of nonlinear binding of the drug to both plasma and interstitial fluid proteins was used to facilitate the multicompartment solution of warfarin pharmacokinetics.

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In addition, fixed volumes were used for the two extracellular compartments with the same aim in mind (12).

In the present paper, we have adopted this same analytical approach using sulfaethidole (approximately 84–97% bound to bovine albumin; ref. 13) as a reference drug. After some technical revisions and modifications to the model, it has now been possible to simulate the whole set of plasma curves, including the initial phase of distribution. Direct analyses of renal and biliary elimination of sulfaethidole were also performed and confirmed the central role of the unbound drug in the model.

**MATERIALS AND METHODS**

Male Sprague-Dawley rats, weighing 297±21 (SD) g in series I, 356±12 (SD) g in series II, and 220±12 (SD) g in series III, were fasted for 15–18 h but allowed water ad libitum. The rats in series I and II weighed more because of sampling difficulties, which were met by using smaller animals. The rats were anesthetized with 1.2 g/kg ethyl carbamate (Riedel-De Haen, AG, Scelze, Hannover), intraperitoneally. The study was carried out as three separate experiments to obtain data on the plasma protein binding of sulfaethidole (series I), the elimination of the drug into urine and bile (series II), and a set of sulfaethidole plasma concentration curves to furnish data for multicompartmental analysis of sulfaethidole pharmacokinetics (series III). Sulfaethidole (Shering AG, Berlin) was dissolved in aqueous sodium hydroxide and the solutions neutralized to pH 7.0–7.4 with hydrochloric acid. The injected volume was 2 ml/kg.

**Series I**

The plasma protein binding of sulfaethidole was studied by the polyacrylamide gel batch method (11). In this study, blood samples for the drug concentration measurements were obtained after injecting a dose in the range 0.95–85.32 mg/kg and killing the animals for sampling. The purpose was to preserve identical circumstances in the plasma protein binding of the drug as in series III. The highest sulfaethidole concentration was 556 μg/ml in series III and 624 μg/ml in series I. Minor deviations at all six concentration points were unavoidable (Fig. 2), but these did not affect the analysis significantly. The data were used in a nonlinear three-compartment model and analyzed, using a digital computer, to obtain functional values for the sulfaethidole binding to plasma and interstitial fluid proteins (11).

¹A nomenclature section appears at the end of the article.