Compartmental Study on the Pharmacokinetics of D-Penicillamine

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Received March 17, 1973

Summary. An eight-compartment model was developed for the pharmacokinetics of D-penicillamine. The analysis shows that a simpler model, based on the assumption of one chemical form of penicillamine only, fails and that the concept of two different forms of penicillamine must be introduced. Most probably, it concerns the disulfide of penicillamine and its mixed disulfide with cysteine. The primary distribution volume for both compounds is the extracellular fluid. Binding to plasma proteins has no essential effect on the overall kinetics. The two disulfides are handled by the kidneys in a different manner.

Introduction

D-penicillamine (Pa) has gained increasing significance in medicine during the last decade. Beside its unique efficacy in the treatment of the hepatolenticular degeneration Pa has antidotal properties in heavy-metal intoxication (Hg, Pb, Co) and has yielded promising therapeutic results in rheumatoid arthritis, cystinuria and other pathological conditions. Until quite recently, however, our knowledge of its pharmacokinetics was scanty. The synthesis of labeled D-penicillamine-2-14C [5] enabled us to perform detailed experiments on its pharmacokinetics in the rat [18]. The present study aims at a compartmental analysis of the experimental results. The actual data subject to analysis will be particularized in the following analysis; here it should be sufficient to outline a few pertinent points: Pa is mainly excreted with urine, whereas the faecal route can be neglected. In keeping with other authors [9, 11], there is no evidence that Pa is subject to a noteworthy metabolic degradation. In particular, it does not undergo glucuronide conjugation [19] which is at variance with the behaviour of the dithiol 2,3-dimercaptopropanol. Finally, one must take into account that Pa is bound by plasma albumin, and it is possible that the binding is due, as in the case of cysteine [12, 13], to mixed disulfide formation. Another binding mechanism, the formation of a ternary complex with Cu as a linking metal ion [22], can be neglected because of the low concentration of albumin-bound Cu ($\sim 10^{-6}$ M).

Analysis

The pharmacokinetics of Pa intravenously injected in the rat shows the following basic features:

1. The dynamic behaviour of Pa in all relevant tissues is virtually identical with the exception of the liver and the kidneys.
2. The bulk of Pa is retained by the skin and muscles.

3. The curves describing the time dependence of the fractional Pa content of the different organs show no initial rise.

Statement (1) allows a substantial simplification for the construction of a compartmental model: If the time dependence of the concentration of various peripheral compartments in a mamillary system is parallel on a semilog scale, these compartments can be treated as one homogeneous compartment without altering the kinetics of the other parts of the system. Thus, the fractional contents of the skin, muscles, skeleton and liver were lumped into one compartment depicted as "tissues". The incorporation of the liver into the lumped tissue compartment does not introduce a substantial error, since the dynamic behaviour of this compartment, according to statement (2), is mainly determined by the skin and muscles. Statement (3) means that diffusion through the various membranes reaches a quasi-steady state within a rather short time. The assumption of rapid mixing justifies also to lump the different fluid spaces into one compartment.

As a first approach we took into consideration a corresponding four-compartment model comprising the drug-protein complex, fluids, tissues and kidneys; linear kinetics and only one chemical form of Pa with well defined flow rate constants were assumed (Fig. 1). Drug binding by proteins is a function of the binding capacity of the protein molecule and the stability of the complex. As a rule it is reversible and can be described by the law of mass action [1]. In accordance with similar analyses on the influence of protein binding on drug distribution [3, 16,17], the kinetics may be represented as the following simple scheme:

\[ D + P \xrightleftharpoons[k_2]{k_1} DP. \]

\( k_1, k_2 \) are the rate constants, \( P \) and \( D \) stand for the protein and the drug molecule, respectively, and \( DP \) is the resulting complex. This scheme, expressed in computational form, is:

\[ \frac{d}{dt} [DP] = k_1 [D] [P] - k_2 [DP]. \]  

(1)

For the following analysis it will be favourable to use fractions of total activity \( (q) \) instead of concentrations.

Therefore by definition:

\[ q_0 = \frac{V_P[D]}{M_0}; \quad q_1 = \frac{V_D[DP]}{M_0} \]

\[ V_P = a_1 V_D \]

where \( V_P, V_D \) mean the plasma volume and total distribution volume, respectively. \( M_0 \) is the total amount of Pa. In principle, the total distribution volume \( V_D \) is determined if \( a_1 \) is known. Insertion of the definitions of \( q_0 \) and \( q_1 \) into Eq. (1) leads to

\[ \frac{dq_1}{dt} = a_1 k_1 q_0 - k_2 q_1; \quad k_1' = k_1[P]. \]

As can be seen from Fig. 2, chemical equilibrium of the binding process is attained approximately after 1 h; strictly speaking, the slope of the curve for the protein-