Eur. J. Pediatr. 131, 85—91 (1979)

European Journal of
Pediatrics

Review

The Importance of Pharmacokinetics for Paediatrics

E. Gladtke

Children's Hospital, University of Cologne, Joseph-Stelzmann-Str. 9, D-5000 Cologne 41, Federal Republic of Germany

Key word: Pharmacokinetics.

Introduction

Pharmacokinetics has been defined as the theory of quantitative interaction between the organism and the drug administered. In this sense the organism has to be regarded as an open system in a state of equilibrium which it tries to regain after any disturbance.

This behaviour can be elucidated by dose–time curves obtained after incorporation of exogenous or endogenous substances. These curves permit calculation of parameters of distribution and metabolism, which in turn supply the basis for dosage regimes, and which can also disclose the functional performance of different organs.

Knowledge of pharmacokinetic data is of particular importance to pediatricians since their patients show great variations in body dimensions, and their metabolic functions differ in their degree of maturity, above all in very early life. It therefore does not come as a surprise that so many pediatricians are actively engaged in this field. The concept of pharmacokinetics was established in 1953 by the pediatrician F. H. Dost who developed this new branch of science on the basis of his own data, data from the literature, and also from his work on renal clearance. He also coined the name for this new field of science which has now become common usage all over the world.

Some terms from the field of pharmacokinetics are presented and discussed below, largely without mathematical equations, so as to be generally understood, and without claiming completeness.

Distribution Volume

After incorporation each and every endogenous substance will always reach the blood first and distribute there. After enteral absorption a few substances are immediately taken up by the liver where they are catabolized or eliminated directly without reaching major concentrations in the blood. This process is called the 'first pass effect.'

Substances staying in the intravascular space can be used to determine its parameters by introducing the simple expression $V=\frac{D}{c}$ (V=Volume of distribution, D=Dose, c=concentration; example: I-131-albumin, Evans blue, iron preparations, labelled red cells and others). On the other hand if the distribution volume is known or can be taken from tables and the desired concentration c is also known, the required dose can be calculated from the same equation written in the following form: $D=\frac{V}{c}$.

This relationship will also apply if the distribution volume extends over a larger space, for example if the extracellular fluid compartment (saccharose, glucose, inulin, thiosulfate, and many drugs) or even total body fluid (ethanol, antipyrin) act as the distribution volume. If diffusion and back diffusion to and from these compartments take place quickly and at nearly the same rate, evaluation of the concentration curves is easy. If we also assume that the concentration in the distribution volume and the concentration at the site of action are in good correlation, the dosage regime can be determined by this method.

Quite frequently the distribution volume does not correspond to one of the known compartments. However it supplies reproducible values if biological parameters are applied. The distribution volume must therefore be regarded as a hypothetical parameter which, like all other standard metabolic parameters, is well suited for this type of work. The hypothetical distribution volume can even exceed the body volume, if for example a compound is deposited in certain structures.

The volume of the known compartments, such as the extracellular fluid compartment and total body fluid, are also subject to age-dependent variations in relation to body weight. In young infants the extracellular fluid compartment amounts to 40% of body weight, compared to approximately 20% in adults. The dosage of drugs administered in relation to body weight must therefore be twice as high in young infants as in older children or adults if the same concentration is to be reached. Variations in total body fluid are not of the same order, since its share of body weight falls from approximately 75% to 60% (Fig. 1).

Since for most compounds the extracellular fluid compartment is part of the distribution volume or constitutes the distribution volume itself, age-dependent variation of its volume must be taken into account in therapy.

Elimination

Each incorporation of an exogenous or endogenous substance must be looked upon as a disturbance which must be corrected. Elimination can be effected via the kidneys, liver, or lung in unchanged form or after chemical modification, but also after metabolism and introduction into the endogenous metabolism. Over certain ranges elimination is proportional to concentration. Recognition of this fact leads to the classical concept of clearance: A certain quantity of blood is

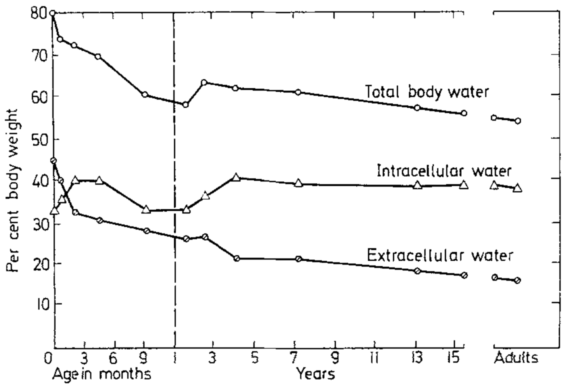

Fig. 1. Change of body water compartments with age

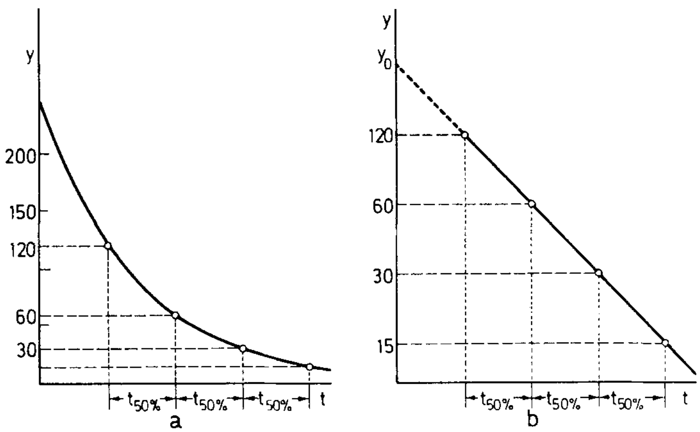

Fig. 2a and b. First order kinetic of elimination. **a)** in a linear plot, **b)** in a semilogarithmic plot

totally freed or cleared of a foreign substance in a unit of time. This means that during a unit of time the fraction of a compound eliminated is always the same. Clearance is expressed as volume clearance e.g. in ml/min and is corrected to the average adult body surface area of $1.73\,m^2$.

Elimination proportional to concentration can also be expressed as a time clearance, e.g. as the elimination half-life of the compound, which is defined as the time within which the concentration falls to half the initial value. In mathematical terms this is an exponential function which in a semilogarithmic plot results in a straight line, the slope of which shows the rate of elimination. As already mentioned, this can be represented as the elimination half-life (t_{50}) or as the elimination constant ($k_2 = \frac{\ln 2}{t_{50}}$) (Fig. 2). These values are independent of body weight, height, and surface area, and are thus better suited for comparative purposes in paediatrics than volume clearance. Transformation to standardized body surface is unnecessary.

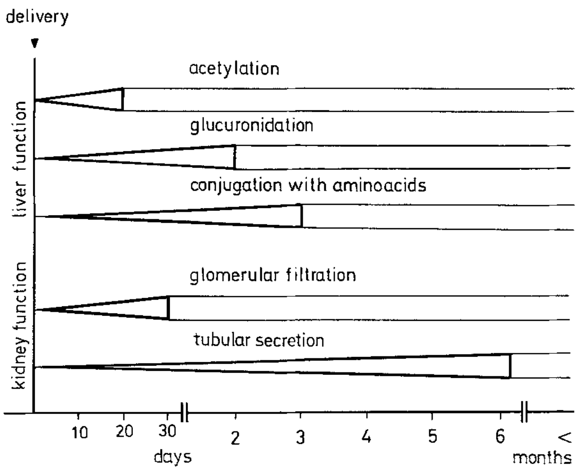

Fig. 3. Age depending development of eliminating functions

If curves are plotted after rapid intravenous injection, often several sections of the curve called the alpha-, beta-, and gamma-slopes can be observed. In most cases the first section corresponds to the distribution phase (e.g. distribution from the blood into the central compartment). The second sections depicts the elimination from the central compartment. If there are major deep compartments from which back-diffusion into the central compartment is slower than the diffusion rate, the gamma-slope shows very delayed elimination. Only by using sophisticated analyses allowing exact measurement of very low concentrations has it recently become possible to elucidate these processes, although Dost had already postulated the basic method of calculation.

The elimination rate also shows age-dependent variations. Elimination of all known substances is clearly delayed in neonates, as compared to older children (Fig. 3). This fact must always be born in mind with repeated doses to avoid accumulation of the compound.

The concentrations for some substances may reach the limit or go beyond the capacity for elimination. With increasing dose or rising concentration, the phenomenon of saturation kinetics can be observed. Eventually elimination will no longer be proportional to concentration, but the same fraction of substance will be continuously eliminated during each unit of time and the curve will no longer follow a first-order function, but become a zero-order function giving a straight line in the linear plot (e.g., ethanol).

Compartments

The simplest pharmacokinetic model consists of only one compartment which the drug enters and from which it irreversibly disappears. The circulatory volume and extracellular fluid compartment can also give the impression of a uniform compartment in case of fast metabolism. In a multicompartment model, the course of the curves and calculation of the pharmacokinetic parameters can become more complicated. These problems can, however, be solved by computer programs, if a suitable model is available.

Protein Binding

Numerous substances are bound to protein to a greater or lesser extent. According to the law of mass action an equilibrium between the bound and free fraction of the substance will occur not only in the blood or plasma, but also for example in the cerebrospinal fluid, which may lead to a higher total concentration of the substance as a result of the higher CSF protein content caused by inflammation.

The free and protein-bound fractions of the compound must be regarded as two compartments although they are present in the same physiological space. The influence on pharmacokinetic parameters can often be neglected, since no major shifts occur in the therapeutic concentration range. Mutual displacement from the binding protein plays a role in the interaction between drugs and is of importance for the pediatrician as bilirubin may be displaced from its binding to albumin and cause damage.

Enzyme Induction

In the hepatocytes numerous substances produce a reactive increase of enzymes capable of metabolizing foreign substances. Subsequently these compounds and other substances metabolized in the same manner are eliminated more rapidly after some days of therapy. We take this phenomenon into account by slowly increasing the dose of an anticonvulsant agent to the final dosage level, accepting transitory central sedation and we are always being surprised by the liveliness of the child under fairly high doses of sedatives.

The elimination half-life of both the inducing drug and other drugs can be considerably shortened and the duration of the effect of the substance will be shorter. Under long-term therapy either the dose must be increased or the dosage interval shortened. After discontinuation of the inducing substance accumulation or excessive concentrations of another drug, may occur if the dose is not reduced.

Interaction

Although enzyme induction has already been mentioned as the major cause of drug interaction, several other factors which could be called interaction must be discussed. It will only be mentioned in passing that among these are enzyme inhibition, displacement from the protein binding, formation of insoluble complexes in the intestine, the influence of acidosis and alkalosis on the elimination rate, clearance depression, disorders of the enterohepatic circulation, and many other factors which are of major concern to clinical pharmacology since these processes may influence pharmacokinetic parameters.

Enteral Absorption

Enteral absorption is an extremely complex process which can be regarded as concentration dependent in the first instance. The interval between oral intake and onset of absorption causes a delay in the course of the curve which may be called the lag time. Drug-induced or pathological changes of transit time may lead to delayed or accelerated absorption, or even to incomplete absorption.

Last but not least, the absorption rate for all substances studied so far is slower in young infants than in older children or adults. As a result the maximum concentration is not reached as rapidly as in older children and with equivalent doses the concentrations reached are not equally high. Thus in young infants either the first dose must be increased or the drug administered parenterally (Fig. 4).

Long-Term Medication

The conditions described in the previous paragraphs lead to a number of conclusions concerning long-term medication. For rapid action parenteral administration is required in young infants, at least at the beginning of therapy. Since young infants have a high distribution volume related to body weight they require a higher initial dose than older children. A good correlation exists between body surface and dose, or extracellular fluid compartment and dose, and the recommended doses are also listed in Table 1, according to von Harnack (1965).

The low elimination rate in young infants makes it necessary to prolong the dosage interval or reduce subsequent doses. One must, however, be aware that depending on the route of elimination, the elimination rate is significantly prolonged only in the first three weeks to four months of life.

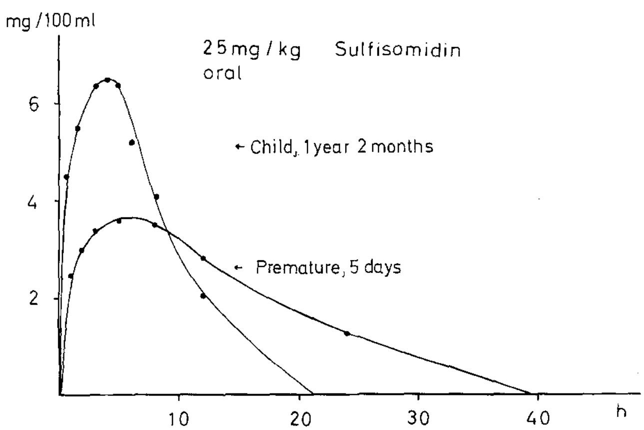

Fig. 4. Concentration of Sulfisomidin after oral administration

Table 1. Extracellular fluid space, body surface and recommended dose in relation to age

Age (years)	ECF	Surface	Share of dose of adults
	in proportion to adult		
2/12	2.0	2.0	1/6
6/12	1.8	1.8	1/5
1	1.6	1.6	1/4
3	1.4	1.6	1/3
7	1.4	1.4	1/2
12	1.2	1.2	2/3
Adult	1.0	1.0	1

Closing Remarks

As mentioned in the introduction, pharmacokinetics is an important aspect of drug therapy and the diagnosis of organ function.

If a rough estimate of the changes influencing therapy is made, drugs with a wide therapeutic range will not cause any damage. For drugs with a narrow therapeutic range, concentration checks and possibly correction of the therapy regime are recommended, particularly if side effects occur when the toxic limit is exceeded.

Unfortunately, fear of toxic side effects sometimes induces the clinician to use too low a dose. It is a matter of experience that inefficacy is the most frequent side effect.

Today, pharmacokinetics is a major tool of clinical pharmacology, and thus ultimately an aid for every physician. However, knowledge of pharmacokinetics is of particular importance to the pediatrician.

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Received December 18, 1978