PHARMACOKINETIC STUDIES IN MAN

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Additional Notes	**This note for guidance concerns the application of Part 4, section D, 2 of the Annex to Directive 75/318/EEC as amended with a view to the granting of a marketing authorisation for a medicinal product. It is intended to assist applicants in the interpretation of the Directive with respect to the specific problems of pharmacokinetic studies, including metabolism, in healthy volunteers and patients.**

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GENERAL

This note for guidance is designed to provide guidance on, and assist applicants in the interpretation of, preclinical and clinical pharmacokinetic investigations of a new medicinal product, irrespective of the nature, mode of action or route of administration.

It should be read in the light of the Directive 75/318/EEC as amended and is intended solely to assist applicants in the interpretation of the latter with respect to the specific problems of pharmacokinetic studies, including metabolism, in healthy volunteers and patients.

This note only considers general rules; all the points mentioned do not necessarily apply to each substance; therefore each study should be planned and designed taking into account the properties and indications of the substance concerned.

The relation between dose, plasma concentrations and therapeutic or toxic effects, where this is feasible, should be studied. Pharmacokinetic studies are as a rule necessary in order to employ substances under the best conditions of efficacy and safety. They are essential to establish therapeutic schedules, to evaluate their relevance or to proceed to dosage adjustments in particular patients. This particularly applies to medicinal products with a narrow therapeutic range and to those for which a close relation between plasma concentrations and therapeutic and/or toxic effects can be demonstrated or expected.

In some instances, pharmacokinetic studies may be impossible or limited, e.g. where their provision raises insuperable difficulties or would create risks for test subjects; in these cases, the use of medicinal product is partly or completely based upon pharmacodynamic and clinical studies.

This note consists of two sections:

I. Pharmacokinetic factors to be studied which deal with:

1. absorption,
2. distribution,
3. elimination,

as well as with interactions and adverse reactions, and

II. Methodology and conditions of study which deals with:

1. choice of administration (route, dosage, dosage intervals),
2. choice of subject (healthy volunteers, patients with relevant disorders, patients with other interfering conditions),
3. choice of methodology (sampling and analysis, data processing and statistics).

I. PHARMACOKINETIC FACTORS TO BE STUDIED

1. ABSORPTION

Both the rate and extent to which the active substance or therapeutic moiety are absorbed should be known.

Data on bioavailability, which is referred to in the note for guidance on *Investigation of Bioavailability and Bioequivalence*, should be provided.

a) Substances intended to produce systemic effects

Whatever the route of administration (e.g. buccal, sublingual, parenteral, rectal, percutaneous, pulmonary), direct or indirect data on the extent of absorption should be submitted; whenever possible, comparison with an intravenous dose should be made. Preferably a precise pharmacokinetic analysis of the entire plasma profile, including absorption, distribution and elimination, should be given since these various steps may be interrelated to a great extent. This applies particularly to special dosage forms for which delayed release of the active substance or a prolonged duration of action is claimed. Failing this, at least data on substance concentration at peak (C_{max}), time to reach peak (t_{max}) and area under the concentration/time curve (AUC) should be provided.

If there is reason to suspect that certain physiological or pathological factors, such as the presence of food or certain food constituents (e.g. dairy products) in the stomach, or certain functional or anatomical disorders of the gastrointestinal tract might substantially alter absorption, separate pharmacokinetic studies in suitable volunteers or patients should be performed.

b) Substances not intended to produce systemic effects

In the case of substances with a high intrinsic activity (i.e. topical corticosteroids, some aerosols for respiratory disease), it is often desirable to study the passage into the circulation, since pronounced systemic effects can be produced. The same principle holds good for topical application of medicinal products in patients suffering from disorders of the skin or mucous membranes. Data on systemic effects should therefore be submitted or direct pharmacokinetic data otherwise.

2. DISTRIBUTION

Data on adequate mathematical analysis (descriptive and/or interpretative analysis or models) including data on model independent parameters should be provided.

The percentage and characteristics of binding to serum proteins should be studied using appropriate ex vivo or in vitro methods. Particularly in the case of substances or their active metabolites of which a high percentage is bound to plasma proteins, factors which might alter protein binding and so alter therapeutic response should be studied. Binding to red blood cells and other blood components should also be known.

Some disease states may significantly alter the distribution pattern of a substance. If such changes (e.g. decreased volume of distribution in renal insufficiency, changes in penetration of antibiotics into cerebrospinal fluid in meningitis, changes in the

concentrations of individual proteins to which a substance is bound, etc.) could lead to alterations in dosage schemes or indications, they should be studied in suitable patients.

In so far as relevant to the claims, distribution to accessible body fluids (cerebrospinal fluid, synovial fluid) should be investigated.

Actual substance concentrations in tissues can rarely be measured; nevertheless, such data should be submitted when they are particularly desirable or even necessary to solve some important problems related to efficacy or safety and when such measurements are feasible.

3. ELIMINATION

The elimination rate for the parent compound (e.g. total body clearance, elimination half-life) should be studied in volunteers with normal elimination mechanisms, and whenever possible also in patients with functional disturbances of these elimination mechanisms. The nature of the main routes of elimination and their relative importance in regard to total elimination should be known.

a) Metabolism

With a few exceptions substances are to a greater or lesser extent subject to metabolic breakdown within the human body. Pharmacokinetic studies should indicate whether the rate of biotransformation may be substantially modified in case of genetic enzymatic deficiency and whether within the dosage levels normally used, saturation of metabolism may occur, thereby inducing non-linear kinetics. The possibility of enzymatic induction should also be studied if metabolic clearance as a fraction of the systemic clearance is relatively high. If there is an indication that pharmacologically active metabolites (the qualitative activity of which may also occasionally differ from that of the parent substance) are formed, this should be ascertained and, if there is reason to suspect that they contribute to a significant extent to the therapeutic activity and/or adverse reactions in man, they should be examined in suitable animal models or if necessary in appropriate human clinical-pharmacological studies. The pharmacokinetic data on such metabolites, the rate of their formation and elimination and their distribution and clearance characteristics should be known.

b) Excretion

The urinary excretion should be defined by parameters such as:

– total cumulated amounts of unchanged and metabolised substance found in the urine following a single dose;

– renal clearance of the substance.

The excretion half-life and the extent of variation between individuals should be determined. In substances which show a high renal clearance or form pharmacologically active metabolites to a significant level with a predominantly renal clearance and are liable to be used in patients with renal insufficiency, the elimination and accumulation characteristics in patients with varying degrees of reduction of glomerular filtration rate should, when possible, be examined. Further quantitative data on the relation between the elimination rate constant and the glomerular filtration rate should be provided, or evidence be presented that such data can be derived from the measurement of the fraction of the

absorbed dose excreted in unchanged form in the urine of patients or healthy volunteers with normal renal function.

If renal clearance constitutes a substantial proportion of systemic clearance (e.g. more than 30%), the existence of tubular secretion and/or reabsorption and pH dependency of secretion should be investigated. In so far as relevant to the claims (i.e. prolonged duration of action caused by enterohepatic recirculation), other routes of excretion (bile, milk) should be investigated. It may be useful to know if the substance is dialysable and/or can be removed by haemoperfusion.

4. INTERACTIONS AND ADVERSE REACTIONS

Pharmacokinetic interactions may occur during the absorption phase, as well as during the distribution and the elimination phase. If such interactions are suspected on the basis of animal data, expected on the basis of the physico-chemical or pharmacological properties of the substance or similar compounds (i.e. protein binding, enzyme induction), or observed during (pre)clinical studies, the pharmacokinetic changes due to such interactions should be measured and, whenever possible, the mechanisms elucidated (e.g. enzyme induction, competition for renal elimination sites, etc.).

Certain types of adverse reactions are due to unusual genetic pharmacokinetic variations; though it will rarely be possible to study such aberrant behaviour in a prospective manner every effort must be put into elucidating the pharmacokinetic mechanism(s) if there is any reason to suspect that the adverse reaction is caused by the altered pharmacokinetics of the substance.

II. METHODOLOGY AND CONDITION STUDY

1. SCHEME OF ADMINISTRATION

Both single-dose and multiple-dose studies should be performed within the recommended dose range and dose intervals.

Multiple-dose studies should be, whenever possible, continued long enough to establish steady-state concentrations of the substance, and for such steady-state levels, their dose dependence and variability should be determined. Accumulation kinetics of the substance predicted from the kinetic constants obtained from single-dose studies should be verified experimentally: different doses should be included in one study to determine dose dependence and to decide whether changes from linearity to non-linearity occur at dosage levels which are normally used. After discontinuation of a prolonged treatment, the possibility of a very slow terminal decrease in plasma concentrations, which can reflect the existence of a deep compartment, should be investigated. This might explain the discrepancy between the long action of the substance and the apparent short elimination half-life as measured after a single-dose administration.

Though these principles should normally be followed in detail, it is acknowledged that this is not always feasible.

2. SUBJECTS

a) Initial studies

Initial studies are generally performed in a restricted number of fasting, healthy, adult volunteers, in well-defined and controlled conditions. When the substance carries too serious a risk to healthy volunteers (e.g. cytostatics), they are conducted in patients suffering from diseases for which the substance is considered to be indicated.

b) Further studies in patients

Further studies should be conducted in patients suffering from diseases for which the substance is claimed to be indicated. The relation between dose, plasma concentration and therapeutic effect, where this is feasible, should be studied. Particularly, it should be established that the pharmacokinetic behaviour of the substance in patients corresponds to that in healthy subjects. The full range of kinetic studies need only be repeated in patients if studies indicate that the pharmacokinetics in this group differ from those in healthy volunteers.

c) Influence of various patho-physiological states

It is very useful to know the kinetics of substances in a very large number of patho-physiological situations; however, it is clear that this knowledge requires multiple, long and expensive studies which cannot all be performed before authorisation.

Therefore, the only studies which should be reasonably submitted before marketing are those which seem to be necessary in regard to the properties, indications, contra-indications, routes of elimination, scheme of administration of the substance and which are required to define the necessary dosage changes which cannot be calculated from the pharmacokinetic parameters available from volunteers under standardised conditions and in patients without functional disturbances of the systems of absorption, distribution or elimination.

In so far as the indications render this relevant, kinetics should be studied in patients of extremes of age (infants, children and the elderly). For medicinal products intended to be orally administered, it is important to study the effects of food on absorption. Other factors like body weight, time of the day, environmental factors, genetic differences, alcohol, smoking habits, concomitant medication, sex, may markedly interfere, and if there is particular reason to believe that these may markedly influence the results and the interpretation of later clinical studies, kinetic studies should be extended accordingly.

3. METHODOLOGY

The quality of pharmacokinetic analysis can be no better than the quality of the experimental data that serve as input for such analyses. The following principles should therefore be kept in mind:

a) Sampling

The number of blood samples should be large enough and the timing appropriate to allow an adequate determination of the absorption and/or distribution and elimination phases. Plasma concentrations in the post-absorptive phase should, whenever possible, be determined over at least two or three half-lives to avoid confusion between distribution, and elimination half-lives. If there is any evidence for a very long terminal half-life, plasma concentrations should be followed for a much longer time. If urinary data are obtained, the urine should be

collected until there is no further detectable excretion of parent substance or metabolites within the limits of the method used.

b) Stability

The stability of the substance during sampling and storage requires careful attention.

c) Analytical procedures

Specificity, precision (sensitivity and reproducibility) and accuracy (e.g. as regards recovery) of the methods should be mentioned. Both for reasons of safety and for technical reasons, cold analytical methods are often to be preferred to tracer radioactive techniques. If radioactive isotopes are used the tracer dose should always be combined with a quantity of non-labelled substance within the therapeutic dose range. However, in most cases it will be necessary to develop suitable cold analytical methods to separate and assay quantitatively the metabolites and/or the parent compound.

d) Interpretation of data

The mathematical methods used (graphical representation, computer analysis, pharmacokinetic formulas) should be stated, including the confidence limits.

e) Presentation and evaluation of the results

In summarising data obtained from more than one subject, it is usually preferable to analyse individual data and at a later stage to average the pharmacokinetic constants so obtained.

Proper statistical analysis of the data obtained should be made and the inter- and intra-individual variations estimated, in at least some of the studies where the number of subjects is large enough.