Pharmacokinetics and Psychopharmacological Research

The Significance of Pharmacokinetic Basic Data for Research of Psychopharmaca on Human Behaviour

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Psychopharmaca belong to the most dangerous classes of drugs presently available. The psychiatrist makes use of psychopharmaca in extensive amounts but often without the basic knowledge which is needed in order to perform an adequate therapy. Psychopharmaca have been a great help in resocialization of the mental patient. But it is also not surprising that many patients get into a deplorable condition because of psychopharmacotherapy.

Because of the creeping character of the overdosage (excessive therapy) with psychopharmacological agents, iatrogenic diseases are often not discovered until it is too late for the patient. Especially elderly patients are apt to end their lives in an institution for the dement aged where they vegetate, as a result of wrong treatment with psychopharmaca.

We might expect that psychological research of psychopharmaca in patients is done by using the necessary basic data of the drugs. However, this appears not to be the case. Basic data are either not known to the investigators or they do not exist. As a consequence many double-blind studies with psychopharmaca have very limited or no meaning at all.

(1) ACTION OF PSYCHOPHARMACOLOGICAL AGENTS ON THE CENTRAL NERVOUS SYSTEM

Psychopharmaca are classified, according to their main or required action, in neuroleptics, tranquilizers, antidepressants, psychomotor stimulants, etc. Each drug has a variety of behavioral effects which may be based on interaction with a particular type of receptor in various areas of the brain, interaction with different types of receptors and also on the formation of active metabolites which have a different spectrum of action as parent compound.

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Thus, neuroleptics act by blocking dopamine receptors in the brain, but these are localized in the neostriatum. The infundibular tract and the area postrema influence on motor function have endocrine effects and are anti-emetics.

The various amphetamines interact to a different extent on the dopamine system, the noradrenaline system and the 5-hydroxytryptamine system so that a large variety of central stimulant and other effects may be encountered. Diazepam is metabolized into desmethyldiazepam and oxazepam which have a spectrum of action different from the parent drug.

The intensity of the behavioral effects induced by psychopharmacological agents and their metabolites depends on the concentration of such substances in the brain area where they find their locus of action. The concentration in discrete areas of the brain is related to the concentration in the blood plasma which in turn depends on the dose, the way of administration, the rate of absorption, distribution and elimination. In other words the drug concentration in the brain will not be constant unless special precautions have been taken. Even if the concentration would remain constant, adaptation to the effects of the drug occurs so that the drug-induced change in behavior does not remain constant.

Furthermore, the behavioral pattern and the intensity of the various behavioral items strongly depend on past experience, conditioning, culture, religion, the type of psychological tests performed, etc. It may therefore be relatively easy to observe

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![Graph](image)

**Fig. 1.** A: Isoconcentration curve of haloperidol following administration of different doses. The minima in the curve show at what time after injection the indicated concentration is reached with the minimum dose capable of giving such a level. The equi-effective dose curve representing ED$_{50}$ values of the anti-amphetamine response at various times. The equi-effective dose curve parallels the iso-concentration curve. (Reproduced from Lewi *et al.* 16, with permission of the authors and *Arzneimittel Forschung.*)
drug-induced changes in human behavior, but it is difficult to evaluate dose-dependent studies.

Despite of the inherent difficulties of drug-induced behavioral studies, results have been obtained which indicate a reasonable correlation between brain content and neuroleptic action of haloperidol (Fig. 1a) and between plasma concentrations and behavioral changes induced by LSD (Fig. 1b).

Since it is important to have some knowledge of the plasma concentration as a function of time after administration, basic information on pharmacokinetics is necessary in order to do fruitful research on drug-induced behavior.

**2) Basic Pharmacokinetic Parameters**

In pharmacotherapy one does not only use knowledge of the action of the drug on the body (pharmacodynamics), but also information regarding the action of the body on the drug (pharmacokinetics). If a drug is taken orally, absorption in the gastrointestinal tract takes place followed by distribution over the various tissues of the body and elimination by means of metabolism and excretion. In general, the elimination is proportional to the quantity of the drug in the body. This implies that after intravenous administration, at first elimination is rapid but progressively slows down when the drug content in the body decreases (see Fig. 2). The elimination either by metabolism or excretion may be considered as a clearance process. This process is analogous to the situation in which a substance is cleared from a vessel by means of a fresh water flow. The rate of elimination and therefore the rate of decrease of the concentration in the vessel is proportional to the fresh water flow and inversely proportional to the volume of the vessel. Under such simplified conditions the body may be regarded as a vessel, a so-called single compartment, with a certain volume of distribution and a certain elimination clearance constant. Under such conditions the elimination rate may be characterized by the biological half-life.
The biological half-life is then directly proportional to the volume of distribution and inversely proportional to the clearance constant.

\[ t_\frac{1}{2} = 0.69 \frac{V_d}{k_e} \]

Various drugs which belong to the same pharmacological class may differ considerably with respect to the biological half-life and consequently in the volume of distribution.

Fig. 2. A: Plasma concentration decay curves of dimethylamphetamine following oral administration of 35 mg in a solution to a human test subject. The experimental data agree very well with the lines calculated for first order elimination of the drug from a single compartment. Note a rapid decrease initially, while as the concentration drops the disappearance rate decreases. B: The plasma decay curve is straight in a semilogarithmic plot. The biological half-life has been calculated from this straight line. (Reproduced from Vree (25) with permission of the author.)

Fig. 3. Biphasic plasma decay curves of diazepam and thiopental. There is a rapid decay initially followed by a slower exponential decay later on. This is more pronounced after i.v. administration (thiopental) than after oral administration. It is also evident that the rate of absorption will greatly affect the initial peak after oral administration. The initial peak may be responsible for a short effect after a single dose, while the slow phase is important for accumulation following chronic medication. The curve for diazepam has been calculated from data by Van der Kleijn et al., (14). The curve for thiopental has been calculated from data by Brodie et al., (7).
TABLE 1

BIOLOGICAL HALF-LIFE TIMES OF PSYCHOPHARMACOLOGICAL AGENTS

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug</th>
<th>Half-Life (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Psychomotor stimulant drugs and anorectic agents</td>
<td>ephedrine</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>amfepramone</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>pipradrol</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>fenfluramine</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>dexamphetamine</td>
<td>8–13</td>
</tr>
<tr>
<td></td>
<td>methamphetamine</td>
<td>8–15</td>
</tr>
<tr>
<td></td>
<td>phentermine</td>
<td>10–12</td>
</tr>
<tr>
<td></td>
<td>chlorphentermine</td>
<td>2–3</td>
</tr>
<tr>
<td>B. Antidepressant drugs</td>
<td>imipramine</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>desipramine</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>nortriptyline</td>
<td>20–60</td>
</tr>
<tr>
<td>C. Hypnotics</td>
<td>glutethimide</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>methaqualone</td>
<td>2–3</td>
</tr>
<tr>
<td></td>
<td>butobarbital</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>hexobarbital</td>
<td>10–12</td>
</tr>
<tr>
<td></td>
<td>cyclobarbital</td>
<td>20–24</td>
</tr>
<tr>
<td>D. Tranquillizers and sedatives</td>
<td>meprobamate</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>chlor Diazepoxide</td>
<td>7–15</td>
</tr>
<tr>
<td></td>
<td>diazepam</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>demoxapam</td>
<td>15–50</td>
</tr>
<tr>
<td></td>
<td>barbital</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>phenobarbital</td>
<td>50–70</td>
</tr>
<tr>
<td>E. Narcotic analgesics</td>
<td>meperidine</td>
<td>5–6</td>
</tr>
<tr>
<td></td>
<td>pentazocine</td>
<td>3–6</td>
</tr>
<tr>
<td></td>
<td>methadone</td>
<td>6.5–7.5</td>
</tr>
<tr>
<td></td>
<td>morphine</td>
<td>2–3</td>
</tr>
<tr>
<td>F. Antipyretic analgesics</td>
<td>acetosal</td>
<td>20 min</td>
</tr>
<tr>
<td></td>
<td>salicylic acid</td>
<td>4–6</td>
</tr>
<tr>
<td></td>
<td>paracetamol</td>
<td>1.5–2.5</td>
</tr>
<tr>
<td></td>
<td>phenacetine</td>
<td>1–1.5</td>
</tr>
<tr>
<td></td>
<td>phenazon</td>
<td>10–12</td>
</tr>
<tr>
<td></td>
<td>aminophenazon</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>propyphenazon</td>
<td>2</td>
</tr>
<tr>
<td>G. Antiparkinson agents</td>
<td>amantadine</td>
<td>9–15</td>
</tr>
<tr>
<td></td>
<td>orphenadrine</td>
<td>10–12</td>
</tr>
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Distribution and the clearance constant. This is, for instance, the case for the hypnotic agents, the antidepressant drugs, the tranquillizers and other groups of psychopharmacological agents (see Table 1). It must be realized that for a number of psycho-
pharmacological agents the biological half-life is not known while for most drugs the
volume of distribution and the clearance constant is not known. In addition, for
many pharmacological agents the body may not be regarded as a single compartment
system. This implies that elimination does not proceed \textit{via} a single exponential decay
(see Fig. 3). This holds in general for psychopharmacological agents. In any case, the
concept of a clearance as well as the volume of distribution also holds in the more
complicated situation. The clearance constant can always be calculated from the
plasma decay curve in which often more than one biological half-life can be dis-
tinguished.

(3) THE CONCENTRATION AND THE LOCUS OF ACTION IN RELATION
TO THE PLASMA CONCENTRATION

Psychopharmacological agents have the locus of action in the central nervous system.
In most cases more than one particular structure is involved. For instance, neuro-
leptic drugs interact at least at the level of the neostriatum, the ventral hypothalamus
and the midbrain chemoreceptor trigger zone. They do so by blocking dopamine
receptors which are found to play a role in these structures. It is therefore evident
that neuroleptic drugs may cause changes in motor performance, as for instance
hypokinesia, endocrine effects, as for instance lactorrhoea, but also inhibit vomiting.
All these effects are inherent in the dopamine receptor blocking action. Nevertheless,
certain neuroleptic drugs may be selective by affinity to some structures rather than
to others. Following i.v. administration of psychopharmacological agents certain
structures take up the drug more rapidly than others depending on the degree of
vascularization of these structures and the physicochemical properties of the drug.
Therefore, differences in effect may occur following i.v. and oral administration.
Since the drug is leaving the body by means of a clearance process, in no instance
can a true equilibrium be reached between the plasma concentration and the con-
centration in certain areas in the brain. If a drug, however, is slowly eliminated, a
steady state condition may occur some time after administration when absorption
and distribution are complete. Drugs leaving the body very rapidly may not reach
a steady state with respect to the diffusion between blood and brain. It is evident
that following i.v. administration, depending on physical properties of the drug,
initially the concentration in all areas of the brain is low while the concentration of
the plasma immediately after injection is high. Therefore the concentration in the
highly vascularized areas increases rapidly provided that the drug passes the barrier
rapidly enough and may be retained in the brain as a result of the binding properties
of the drug to certain brain structures. The relation between the concentration in
plasma and the concentration in the brain may therefore be very complicated. An
unambiguous relationship, however, always occurs. It is obvious that one cannot
expect to find the same relationships between the psychopharmacological effect and
the plasma concentration for the same drug in different situations (see Fig. 4). The way
of administration and the speed of injection is of importance. The relation between
Fig. 4. Theoretical curves representing drug concentration in plasma, and tissue rapidly equilibrating with plasma, the brain and the other tissues of the body. In fact three compartment kinetics are applied. The elimination clearance is kept constant at 86.8 ml/min, while only the clearance constant governing entry in the brain is varied from 60 l/hr to 2 l/hr. A: The clearance plasma–brain is 60 l/hr or 1000 ml/min. As a result the brain concentration rises rapidly and remains higher than the plasma concentration and the fictive volume of distribution is 47 l.

B: The plasma–brain clearance is 10 l/hr or 167 ml/min. As a result plasma and brain concentrations are practically equal and the fictive volume of distribution is 37 l.

C: The plasma–brain clearance is 2 l/hr or 33 ml/min. As a result the brain concentration is always very low and the fictive volume of distribution is 35.5 l.

It may be concluded that the same effect corresponds well with an isoconcentration curve. In animals, the relation between plasma and brain concentration can be in-
vestigated but in man one may only guess. In man, correlations can be found at the best between effects and the plasma decay curve. The picture is further complicated by the rate of biotransformation of the psychopharmacological agent into one or more active metabolites which may have a similar or an entirely different spectrum of psychopharmacological action.

(4) KINETICS OF METABOLISM OF DRUGS

If only one active metabolite is formed, it may be that the metabolite is cleared from the body more rapidly than the parent compound. One would expect then a lower concentration in the blood for the metabolites than for the parent drug (see Fig. 5). The plasma decay curve for metabolite and parent compound in the steady state conditions is of equal shape. The plasma concentration of the metabolites, however, may be relatively high if the volume of distribution of the metabolite is much smaller than that of parent compound. Thus, from the relative concentrations of metabolites and parent compounds not very much can be concluded unless additional information on volume and distribution is available.

Fig. 5. Pharmacokinetics of metabolism. Theory: A: The metabolite is eliminated more rapidly than the parent drug. B: The parent drug disappears more rapidly than the metabolite. Experimental: C: Chlordiazepoxide is eliminated more rapidly than one of its metabolites desmethylchlordiazepoxide (subject 4). From data by Schwartz et al. (22). D: Flurazepam is eliminated less rapidly than its metabolites. From data by De Silva and Strojny (10).
It is also possible that the metabolite leaves the body less rapidly than the parent compound; in such case the plasma decay curve of the metabolite is flatter than that of the parent compound. Then the half-life — if we may speak of one half-life — of the metabolite is longer than that of the parent compound, whereas in the previously mentioned case both substances seemed to have equal half-lives. It is known, for instance, that diazepam is metabolized to a desmethyl compound and further metabolized to oxazepam. Both metabolites are biologically active although they have a different spectrum of action than diazepam. The metabolites of diazepam remain in the body much longer than the parent compound. This implies that initially after i.v. administration, the action is mainly due to the spectrum of action of diazepam. After oral administration the active metabolites may contribute to a large extent to the action of the drug. This will be more so after chronic administration when the metabolites accumulate much more than the parent compound (see Fig. 5).

For many drugs such data are not available but one must realize the possibility, if one studies the psychopharmacological effect certain time after administration. The constantly changing concentration of drug and its metabolites hardly allows a proper estimation of the pharmacological activity. At what time after administration should a psychological test be performed? At the plasma peak? But what is the contribution of the metabolites? Depending on the rate of elimination after the peak concentration, there is a more or less rapid decrease and, consequently, an ever changing brain concentration. If one knows the plasma concentration but does not know the biological half-life, what value can we attach to psychopharmacological data? Furthermore, in therapy the drugs are given chronically which may lead to a completely different picture.

(5) CHRONIC MEDICATION AND ACCUMULATION

In therapy with psychopharmaca a certain dosage regimen is established, for instance that the patient takes the drug every 8 hr. If in the dosage interval $\Delta t$ a substantial amount of the drug remains in the body the next dose will be added on top, leading to accumulation (see Fig. 6). Since elimination is in general proportional to the plasma concentration, as a result of accumulation the rate of elimination increases so that accumulation slows down. Finally a plateau is reached. Then the input of drug equals the output and a steady state situation is reached not only with regard to the plasma but also with regard to the concentration in brain and other tissues. It takes about 4 times the half-life to reach the plateau. E.g., desipramine with a half-life of approx. 36 hr will reach a plateau after almost a week. For bromide with a half-life of 10 days, it will take more than a month to reach the plateau. Cessation of administration may result in a slow plasma decay curve. This means that the drug remains in the body much longer than was expected from the plasma curve of a single dose (see Fig. 6b).
Fig. 6. Pharmacokinetics of accumulation. A: Theory: A dose of 1 mmole of a drug with a half-life of 24 hr given orally 3 dd (every 8 hr). Within 4 days a plateau is reached. B: Plasma levels of diazepam and metabolite following chronic medication of 10 mg 3 dd for 15 days. In agreement with the long half-life the drug disappears slowly after cessation of therapy. This is more pronounced for the metabolite which reaches a plateau after more than one week. (Reproduced from Van der Kleijn et al., 14, with permission of the authors and the *Acta Pharmacologica et Toxicologica.*)

(6) CHRONIC ADMINISTRATION OF PSYCHOPHARMACA AND PLATEAU LEVELS

Repetitive administration of drugs over sufficiently long periods of time has the advantage that plateau levels are reached. This implies that the blood concentration is relatively constant at a fixed level provided that the elimination rate is not too rapid. Depending on the dosage interval and the pharmacokinetic parameters a certain degree of oscillation occurs. If the dosage interval is short and the various half-lives are relatively long, the blood concentration in the plateau may be regarded as constant.

If the blood concentration can be kept constant also the drug concentration in the different areas of the brain will be constant (steady state). The same holds for the level of possible metabolites formed from the parent psychopharmacological agent. It is then much easier to perform psychological tests. A disadvantage of chronic dosing is adaptation of the brain systems. The action produced by the drug or metabolite may be counteracted by adaptive mechanism. It is well known that a single dose of 200 mg phenobarbital causes drowsiness in most patients. After chronic therapy with 30 mg 3 dd, a higher plasma concentration will be reached but drowsiness is not apparent.
CONSTANT CONCENTRATIONS BY SUSTAINED RELEASE MEDICINES

Unless the time constants are larger than the dosage interval, substantial variation in the plateau concentration may occur. A better constancy may be acquired by injection of sustained release preparations. From such preparations as for instance perphenazine enanthate, flupentixol decanoate or fluperazine enanthate constant plasma and tissue levels may be obtained. Consequently toxic side-effects are reduced to a minimum.

Another possibility is the development of psychopharmaca that have strong affinity towards target tissues as for instance pimozide that binds to the neostriatum over prolonged periods of time. These drugs are of great help in therapy especially when the patients do not take the drugs regularly, as the case may be for chronic schizophrenics.

Such forms of drug taking may also help the investigator in the study of drug-induced behavior.

CONCLUSION

Superficial studies of drug-induced behavior can be done easily but it is very difficult to study adequate dose-dependent behavioral effects and to interpret their significance. The correct applications of pharmacokinetic knowledge is a prerequisite for such an understanding. The estimation of blood levels of parent drug and active metabolites is also necessary for such an understanding.

The use of dosage regimens or drug administration measures which ensure constant steady state blood levels and thereby constant tissue levels facilitates the usefulness of behavioral studies and limits the number of blood level estimations.

REFERENCES


