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OPTIMALIZATION OF PHARMACOKINETICS - AN ESSENTIAL ASPECT OF DRUG DEVELOPMENT - BY "METABOLIC STABILIZATION"

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1) INTRODUCTION

Generally speaking, the chemical properties and hence the chemical structure of a compound definitely determine the way in which it participates in the various part-processes involved in biological action. A structure-action relationship (SAR), therefore, has to be a fundamental characteristic of bioactive agents. The apparent absence of such a relationship can only be due to deficient methods of investigation and to the multiplicity and complexity of the process as a whole. Although the various part-processes are biochemical and physicochemical in nature, they differ greatly. Totally different SAR patterns may be expected for, for instance, the rate of absorption, the mode of distribution, the renal excretion, the various types of metabolic conversion, and the capacity of the agent to activate the molecular sites of action (the receptors) in the target tissue - the structure-action relationship in a strict sense. Absorption, distribution and excretion, which are mainly based on passive diffusion processes, will largely depend on partition coefficients. Metabolic conversion will depend mainly on the presence in the molecule of particular groups that are open to attack by enzymes. These groups as a rule have little or nothing to do with the chemical characteristics which are essential for the induction of the effect. Whether an agent is hydrolysed by esterases, for instance, depends mainly on the presence of a suitable ester group in the molecule. The ester group, however, has little or nothing to do with the question whether the agent has a curariform, an anticholinergic, a local anesthetic action, is an insecticide, a herbicide, a plasticizer, or some toxon. Whether an agent is capable of inducing a particular type of biological effect is usually dependent on various specific chemical characteristics in the molecule.

SAR will emerge most clearly if it is studied for particular part-processes such as those involved in absorption, distribution or excretion, where passage of membranes is essential, those involved in drug metabolism, where SAR will depend on the particular enzyme, and SAR for the final step of action, the induction of the effect. In a comparison of the quantitative dose-effect relationship for a

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group of compounds the in vivo-SAR is the resultant of the integrated contribution of SAR for the various part-processes.

2) THE MAIN PHASES IN BIOLOGICAL ACTION

The complex of processes involved in biological action can be split up in three phases (Fig. 1) (ref. 1, 2).

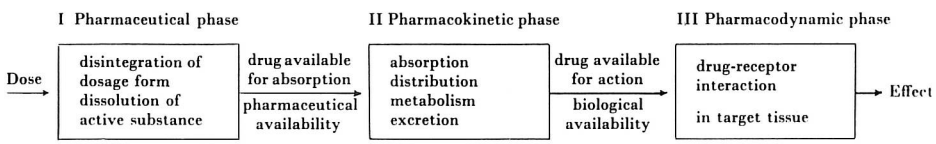

Fig. 1.

I. The pharmaceutical phase

This phase comprises the processes that are determinant for the efficacy of the application. Here the disintegration of the dosage form, tablets, capsules, etc., in such a way that the active agent becomes available in a molecular dispersed form suitable for absorption, and avoidance of chemical or enzymatic activation of the active agent before absorption, e.g. in the intestinal tract, count. In general, for the absorption - which implies passage of biological membranes - the lipid/water solubility and therewith the partition coefficient is determinant. For weak bases and acids also the degree of ionization and therewith the pK_A of the compound and the pH at the site of absorption count. The fraction of the dose available for absorption is indicated as the "pharmaceutical availability". The time course of the events has to be taken into account, too, and results in the "pharmaceutical availability profile".

II. The pharmacokinetic phase

This phase comprises the processes involved in absorption, distribution, excretion and metabolic conversion of the agent after absorption. The fraction of the dose that reaches the general circulation is indicated as the "biological (systemic) availability". Also here the time course represented in the "biological availability profile" is of particular significance. The concentration of the active agent in the target tissue as a function of time is represented by the "pharmacological availability profile". In the pharmacokinetic phase, besides the lipid/water solubility and degree of ionization of the agent, particularly its sensitivity to various enzymes counts. The presence in the molecule of vulnerable moieties accessible to enzymatic attack plays a predominant role. In this respect, like in the case of active, carrier-related transport, the charge distribution of the agent and its steric properties are determinant factors. The metabolic conversion of the agent applied may result in its bioinactivation (biodetoxification) or bioactivation

(biotoxification).

The involvement of various metabolites greatly complicates pharmacokinetics. Metabolic conversion usually increases hydrophilicity thus facilitating renal excretion.

III. The pharmacodynamic phase

This phase comprises the processes involved in the interaction between the bioactive compounds and their molecular sites of action, receptors, enzymes, etc. Pharmacon-receptor interaction results in the induction of a stimulus which initiates a sequence of biochemical and biophysical events which finally lead to the effect observed.

3) PHARMACON METABOLISM, A NATURAL DEFENCE AGAINST INTRUSION OF CHEMICALS (XENOBIOTICS), INCLUDING DRUGS

Although one might get the impression that the toxicological risks involved in the exposure to chemicals, including drugs, are generated by the evolvement of chemical and pharmaceutical industries and thus are of recent origin, this is definitely not the case. Already since the very beginning of evolution living systems have been exposed to chemicals. This especially holds true for the heterotrophic organisms (in general, animal life) which are to a large extent dependent on the consumption of autotrophic organisms (mainly plant material) and are exposed, therefore, to a great variety of potentially toxic chemicals of plant origin. These plant products are xenobiotic to the animal concerned. The term "biogenic xenobiotics" is appropriate here.

As long as life was limited to the oceans, the problems were relatively small, since there was a tremendous water compartment available for the disposal of undesired body-foreign chemicals, even if these were rather lipid-soluble. The "affinity" thereof for the relatively lipophilic biomass was counterbalanced by the tremendous volume of the disposal compartment. Photodegradation and oxidation in the surface layers of the waters largely took care of chemical degradation. By the time animal life switched from water to land, this opportunity got lost. Water became relatively scarce and only a small volume became available for disposal (for man about 1 liter a day). This increased the danger of accumulation of lipophilic, poorly water-soluble agents in the biomass. In the line of evolution an answer was found in the development of enzyme systems which take care of the conversion of relatively lipophilic compounds into highly water soluble end-products suitable for renal excretion (table 1). This conversion occurs in two steps: a first predominantly oxidative step and a second predominantly conjugational step (Fig. 2). Simultaneously, a strong increase in the concentration of plasma albumin took place (table 1), important for osmotic regulation but serving as well as a temporary sink, a kind of parking lot, for lipophilic xenobiotics. Such agents would easily pass the various membranes in the body and so enter tissues and cells where damage

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TABLE 1. EVOLUTIONARY ASPECTS OF PLASMA PROTEIN AND DRUG METABOLISM (ref. 3).

Species	*Plasma protein* %	*Oxidative N-demethylation*[c]	*Phenol glucuronidation*[d]	*Species*
man	6.5	19 ± 2	21 ± 3	mouse
dog	6.1–6.7	15 ± 2	46 ± 13	rat
turtle	4.8	26 ± 8	85 ± 22	pigeon
crocodile	3.69	4 ± 0.6	8.9 ± 2.3	lizard
frog	1.5–4.3	1.6 ± 0.45	1.26 ± 0.47	frog
skate	2.4–3.1	1.1 ± 0.30	1.72 ± 0.25	trout
menhaden	0.72–2.9	0.71 ± 0.28	1.9 ± 0.33	goldenorfe
goosefish	1.4–2.2	0.86 ± 0.23	2.68 ± 0.65	carp

[c] µmoles formaldehyde formed per gram fresh liver tissue/hour.

[d] µmoles p-nitrophenol glucuronidation per gram fresh liver tissue/hour.

Note the increases at the switch from water to land animals.

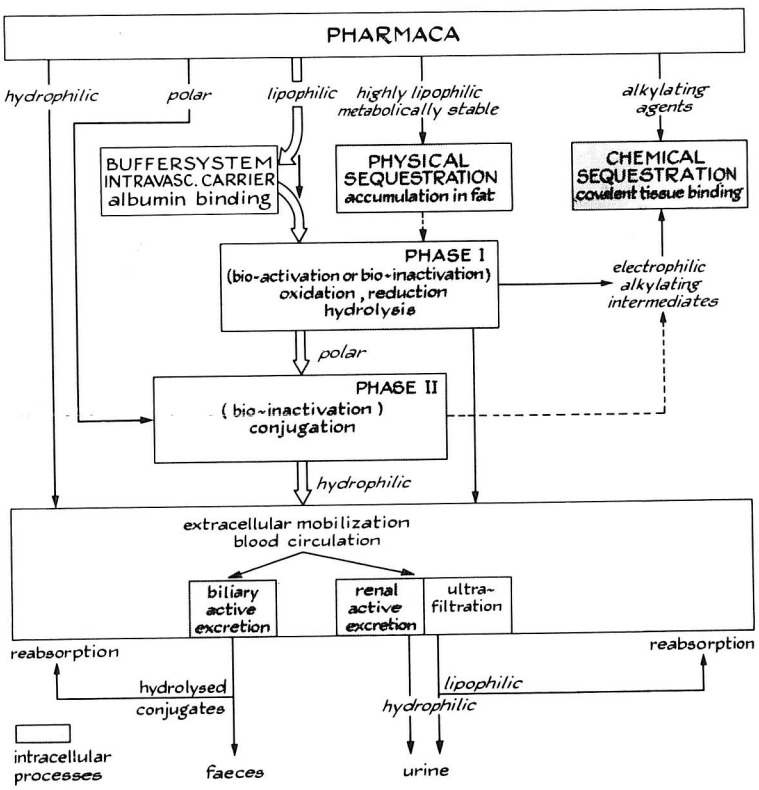

Fig. 2. Schematic representation of the main steps in drug metabolism and elimination.

might be done. Binding to albumin implies lowering of the free concentration in plasma and therewith lowering of the effective concentration to which cells and tissues are exposed. The agents involved are temporarily stored on the albumin in the circulation, where they are available for the enzymes, particularly in the liver, that especially take care of biochemical conversion to products that are suitable for renal excretion (ref. 3).

In short, by the time chemical and pharmaceutical industry came to development, animal and man were more or less prepared for dealing with - in fact for defence against - exposure to the products of these industries, "synthetic xenobiotics", including drugs, thanks to their experience with "biogenic xenobiotics".

4) DRUG METABOLISM - DETOXIFICATION AND TOXIFICATION

In the early days of studies on this subject, drug metabolism was put more or less synonymous with detoxification as indicated, for instance, by the classic book entitled "Detoxication Mechanisms" by R.T. Williams, 1959 (ref. 4). In the case the metabolic elimination of xenobiotics concerns the application of drugs as therapeutics, the action is considered, at least by the prescribing physician, as desirable, although some components in the action still may count as undesirable, i.e. as side-effects. In fact in drug metabolism two classes of undesirable aspects can be distinguished:

1) the generation of toxic metabolites, still xenobiotic in nature, biotoxification;
2) the untimely elimination of the drug and complication of pharmacokinetics with as a consequence blurring of the dose-effect relationship due to drug metabolism.

5) BIOTOXIFICATION

Drug metabolites may be biologically active and in some cases are fully responsible for the action of the drug, which then in fact must be considered as a prodrug. With regard to the bioactive metabolites, distinctions can be made between:

a) Stable metabolites, active in a pharmacological sense, producing effects mostly related to that of the mother compound. This type of bioactivation which depending on the circumstances may be considered positive or negative will not be discussed in further detail here.

b) Chemically highly reactive, electrophilic, biologically alkylating intermediate products with a very short half-life time, formed in the course of the metabolic conversion - particularly oxidation, but also conjugation reactions. These intermediates act under covalent binding with nucleophilic groups on biological macromolecules such as nucleic acids and proteins. The resulting "chemical lesions" may have serious consequences such as:

a) carcinogenesis, involving chemical lesions in chromosomal DNA
b) mutagenesis, also involving chemical lesions in chromosomal DNA
c) possibly accelerated aging, caused by an increase in the error frequency in-

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duced in chromosomal DNA,
d) teratogenesis, caused by disturbed cell proliferation due to chemical lesions during embryogenesis,
e) allergic sensitization, due to chemical lesions in proteins that cause them to act as allergens,
f) cell degeneration and necrosis, due to chemical damage to the membranes of lysosomes or to essential enzymes,
g) photosensitization, involving formation of reactive products by radiation of the drug or its metabolite(s), thus causing local chemical lesions, or formation of allergens.

As a matter of fact, toxic effects such as the ones just mentioned may also be induced by directly alkylating agents, such as some cytostatics used in the chemotherapy of cancer. Particularly troublesome with regard to the carcinogenesis and mutagenesis is the latency, the long lag-time between exposure to the agent and the appearance of the effect. This is partly due to the irreversible nature of the chemical lesions, which implies an accumulation of the effect. Like in the case of exposure to ionizing radiation, in fact each dose, how small it may be, counts and contributes to the effect. The total lifetime exposure constitutes the dose. Further, especially for lesions in chromosomal DNA, "syncarcinogenesis" due to various agents has to be taken into account. The chemical lesions in proteins are reversible to a certain extent on the basis of de novo synthesis of proteins. If the damage is limited, it may be largely reversible. This is not the case for protein damage resulting in allergic sensitization where the immunological memory of the lymphocytes is involved. In the case of damage to DNA, to a certain extent, especially short term, repair mechanisms may eliminate part of the chemical lesions.

Metabolic systems protecting against biochemical lesions

In the line of evolution, nature not only developed biochemical clearance systems for xenobiotics, but also systems to control the risks thereof, namely those involved in the formation of reactive intermediate metabolites. The major protecting systems are: the glutathione transferase system, coupling glutathione to the chemically reactive, biologically alkylating metabolic intermediate, under the formation of conjugation products that appear in the urine as water soluble mercapturic acid derivatives (Fig. 3) and methylthiolation which implies the coupling of a methylthio ($-SCH_3$) group to the chemically reactive, electrophilic group in the alkylating metabolic intermediate, which thus is detoxicated. Further there is the epoxide hydratase system taking care of the hydrolysis of alkylating epoxides under the formation of diols which appear in the urine mostly as water-soluble phenol sulphate conjugates (Fig. 3) (ref. 1, 2, 5, 6).

Conjugation products such as those formed by acetylation or sulphate conjugation as

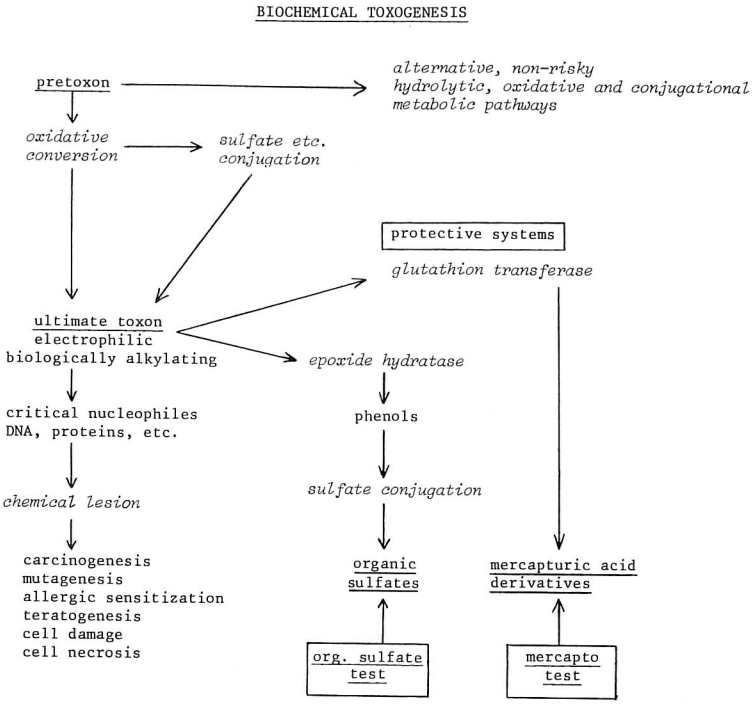

Fig. 3.

a rule are considered as harmless final detoxification products. However, although exceptionally, also such conjugation products, may be chemically reactive, biologically alkylating, and thus toxic. Also here the glutathione transferase system has a protective function.

Oxidation products formed in the course of drug metabolism may also lead to peroxides and oxidation products with a toxic character with regard to redox systems. An example of the damage caused is the formation of methemoglobin from hemoglobin. The latter type of action is well known for aniline derivatives. Again, glutathione has a protecting action since it contributes to the regeneration of hemoglobin from methemoglobin.

Early detection of biotoxification

It will be clear from the foregoing that considerations on drug metabolism and its consequences such as biotoxification are essential already in an early phase, if possible on the drawing table, of drug design. Reasoning on the relationship between chemical structure and action in this respect implies recognition in the

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structures of chemical groups potentially open to metabolic conversion. One has to differentiate between moieties leading to non-risky conversion - being particularly significant for the bioavailability and duration of action, i.e. the pharmacokinetics - and to risky conversion via reactive, alkylating intermediates particularly significant for toxicity. Moieties determining the lipophilicity of the compound are especially important in absorption, distribution and excretion and thus for pharmacokinetics (ref. 1, 2).

Remarkably, up to now, very little attention has been paid to the relationship between chemical structure and pharmacon metabolism. There is no doubt that such a relationship exists and even that in many cases, for instance in the case of particular enzymatic conversion, the relationships are relatively clear and simple. In vivo, however, often multiple metabolic pathways and a sequence of different metabolic steps are involved. Avoidance in the chemical structure of moieties potentially involved in biotoxification is advisable. Once compounds have been synthesized, a testing on mutagenic and carcinogenic action is advisable, in order to select or at least incorporate in the groups of compounds to be studied, the agents with a reduced risk with respect to the causation of chemical lesions. The use of the Ames-test, or better a properly chosen set of such in vitro tests, gives a reasonable indication of the risk for a mutagenic and carcinogenic action (ref. 7, 8, 9). By the way, one has to be well aware that even, although there is not a 100% correlation between mutagenic action as detected by such in vitro tests and the carcinogenic action in vivo, mutagenesis as such - for which the bill will be paid by future generations - , should be taken at least as serious as carcinogenesis.

A covalent binding of the toxon to biopolymers has as a consequence that the toxon cannot be extracted from the tissues anymore with hydrophilic or lipophilic solvents. A chemical sequestration is involved, to be distinguished from a physical sequestration where the compound, due to its metabolic stability combined with high lipophilicity, is kept back in the organism, predominantly by dissolution in the body fat. In balance studies, relating the dose to the quantity of the agent excreted, the fraction missing in that balance is important, even if it may be small, especially if chemical sequestration is involved (ref. 10).

The final inevitable step in the testing of a new drug, before its release for practical use, is the study of its carcinogenic potential in animal species. This still does not present a 100% safeguarding. Even after the agent has been released for application to the patient it has to be monitored in a toxicological sense. Introduction in a number of steps, comprising larger and larger groups of individuals, for drugs widely used for minor ailments numbering many thousands of individuals, is advisable.

6) BLURRING OF PHARMACOKINETICS AND THUS OF THE DOSE-EFFECT RELATIONSHIP BY DRUG METABOLISM

Therapeuticals usually are metabolized and eliminated at the time that the action is still wanted; thus sequential dosages have to be supplied. This in fact means a drug waste. Also other aspects of drug metabolism count as negative, e.g. the first-pass losses, due to metabolic conversion in the intestinal wall and the liver, the patient-to-patient and intra-patient variations in metabolic capacity with as a result a highly variable bioavailability, and the drug interactions related to drug metabolism. A highly variable relationship between dose and plasma level due to drug metabolism makes expensive therapeutic monitoring on basis of plasma level measurements, especially of drugs with a small therapeutic margin, necessary. Species differences, mostly related to differences in drug metabolism make extrapolation of animal data to the human situation difficult. An answer to the problems inherent in drug metabolism may be the development of drugs resisting drug metabolism, metabolic stabilization (ref. 1, 2, 11).

If short or ultrashort action is required or at local application, systemic action has to be avoided, introduction of suitable, safe, vulnerable moieties may be required. The same holds true in the case that the prodrug principle is to be applied. In general, however, avoidance of drug metabolism or reduction of it to the possible minimum will be advantageous.

For metabolically stable agents pharmacokinetics (absorption, distribution and excretion) are mainly determined by the balance between lipid and water solubility as expressed by the partition coefficient which in its turn is related to the pK_A-value. An exception has to be made for active transport processes. A modulation of pharmacokinetics on the basis of adaptation in the partition coefficient will usually be much simpler than adaptation in the metabolic pathways and the rates of conversion. Often various metabolic pathways and a sequence of different metabolic conversions are involved in the processing of one drug.

With regard to metabolic stabilization two aspects have to be taken into account:
1) Metabolic stabilization in general, predominantly aimed at the simplification and control of pharmacokinetics. In this case a reduction of the fraction of the dose metabolized counts.
2) Metabolic stabilization, particularly concerned with those moieties in the molecule that can be converted to electrophilic, alkylating groups. The aim is to control biotoxification. In this case a reduction in the absolute quantity of reactive intermediates counts.

7) METABOLIC STABILIZATION TO CONTROL PHARMACOKINETICS

Metabolic stabilization implies a longer half-life time and therewith less drug waste, less exposure to unnecessary quantities of the drug in repeated application, and simpler dosage regimens and therewith a better patient compliance.

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Metabolic stabilization contributes to a reduction in drug interactions which in many cases are generated on the drug metabolic level.

Metabolic stabilization reduces the patient-to-patient and the intra-patient variability in the relationship between dose and effect, since this variability is largely based on differences and variations in the drug metabolic capacity.

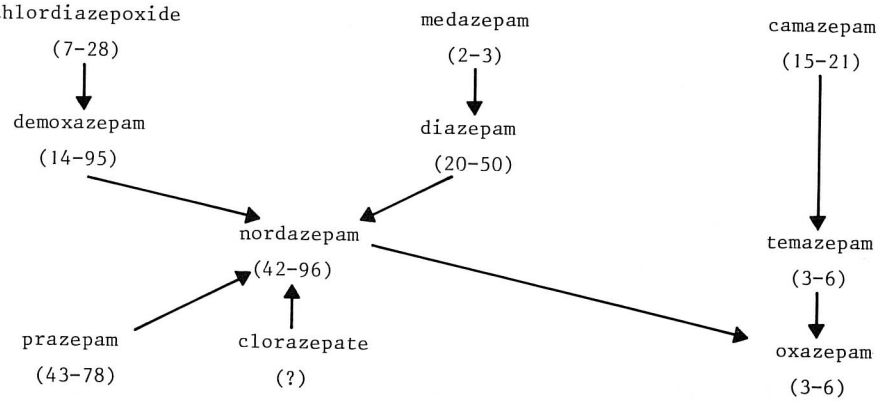
Metabolic stabilization will reduce the variability in the relationship between dose and plasma concentration. This will reduce or eliminate the need for expensive therapeutic monitoring via plasma drug concentration measurements for drugs with a relatively small therapeutic margin. The uncertainty in the dose-effect relationship which enforces plasma level monitoring is largely related to the variability in drug metabolism. Therapeutics that require therapeutic monitoring should be replaced as soon as possible by analogously acting new drugs which are pharmacokinetically better controlled, an aim which may be realized by metabolic stabilization. Such new drugs definitely cannot be regarded as "me-too" drugs, but in fact are badly needed revisions in the therapeutic arsenal (ref. 12, 13, 14).

Metabolic stabilization implies a reduction in species differences which are largely related to species differences in metabolic capacities. It will make the now highly uncertain transfer of animal data to man more reliable.

Metabolic stabilization will greatly reduce the number and significance of possibly active metabolites, which implies a fargoing reduction of elaborate and expensive studies on drug metabolites on both the preclinical and clinical level.

Metabolic stabilization will reduce the chance that the drug applied in fact is a prodrug or the situation that, besides the active agent applied, a number of more or less similarly active, but pharmacokinetically different metabolites complicate the picture. These situations which occur incidentally should in no way be regarded as advantageous. In the given circumstances it is advisable to consider (one of) the active metabolite(s) as a potential drug. Clearcut examples of this situation are found among the benzodiazepines (table 2). Various benzodiazepines on the market are in fact benzodiazepine metabolites. The use of the therapeutically active metabolites as such, especially the ones in the most advanced oxidized state, will automatically reduce the impact of metabolic conversion and thus reduce both the metabolic toxicological risks and the complexity of pharmacokinetics. If so required , the metabolite can be presented as a prodrug - e.g. to enhance absorption of the usually more hydrophilic metabolite. This has as a matter of fact to be based on a safe metabolic handle for bioactivation. As such,hydrolytic cleavage is to be preferred,but also oxidation of a saturated alkyl side-chain may be considered. Unsaturated alkyl side-chains may lead to risky epoxides. Similar reasonings hold true if a vulnerable moiety has to be introduced into the molecule in order to obtain an ultrashort or short action or to avoid systemic action after local application.

TABLE 2



Flow scheme of benzodiazepine metabolism.
All substances (half-life in hours) are in use as drugs.

8) METABOLIC STABILIZATION AND CONTROL OF BIOTOXIFICATION

The aim is a reduction in the absolute quantity of reactive intermediates formed. There are two approaches here:

a) reduction in the dose of the drug required;

b) metabolic stabilization.

A reduction in the quantity of reactive, potentially carcinogenic, mutagenic, etc. intermediate products is to a certain extent a natural consequence of the development of highly potent agents. Only low dosages are required then, which implies the reduction of the quantity of metabolites anyway and therewith a reduction in the risk of induction of chemical lesions.

An increase in potency, as far as related to the process in the pharmacodynamic phase - that is to the induction of the effect on specific sites of action, and not to, for instance,reduction in first pass loss - implies that lower plasma and tissue concentrations are needed for the induction of the effect desired. If the therapeutic effect and side-effect are induced on different target molecules (receptors, enzymes, etc.), an increase in the affinity to the sites involved in the therapeutic action only under particular circumstances will go hand in hand with a comparable increase in the affinity to the sites on which the side-effects are induced. An exception has to be made for those cases in which the higher therapeutic potency is related to accumulation of the agent in a phase (e.g. a lipophilic phase), in which both the sites for therapeutic effect and side-effect are located. In those cases that the increase in therapeutic potency is related to a higher degree of complementarity of the active agent to the molecular sites for therapeutic action, as a rule, this

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tends to enhance selectivity and thus to reduce side-effects. Besides this the lowering of the dose required also implies a smaller metabolic turnover and thus a reduction in the quantity of potentially toxic reactive intermediate products.

Metabolic stabilization aimed at a control of pharmacokinetics also implies a reduction of the dose required and therewith a reduction in the risky metabolic turnover as well as a reduction in the formation of metabolic products causing pharmacological side-effects. If stabilization of risky metabolic handles, chemical groups open to conversion to electrophilic, alkylating moieties, is involved, biotoxification is brought under control even more effectively. An alternative to metabolic stabilization of risky metabolic handles, is introduction into the molecule of safe metabolic handles offering a preferred alternative route of conversion. An example is toluene as compared to benzene (see fig. 4).

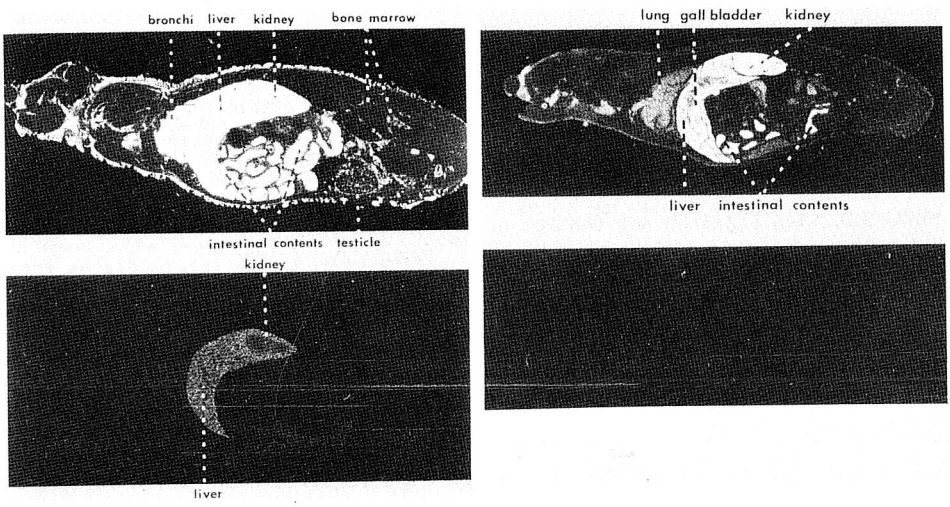
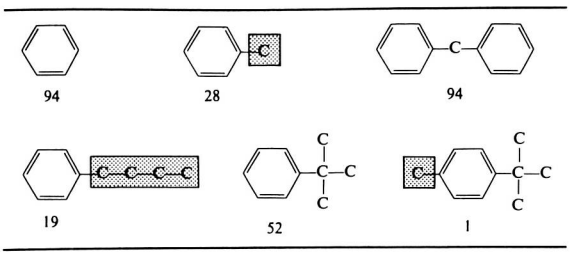


Fig. 4 a-b. Autoradiograms of mice 1 h after inhalation for 10 minutes of 5 µl ^{14}C-benzene (a) and 10 µl ^{14}C-toluene (b). Preparation: dried and evaporated (upper), additionally extracted (lower). Note: benzene metabolites are irreversibly bound in kidney cortex and liver (a); all toluene metabolites are completely extractable (b) After Bergman (ref.10).

The oxidative attack on the benzene ring leads to the formation of an epoxide as toxic reactive intermediate. In toluene the methyl group serves as a safe metabolic handle preferably attacked by the mixed function oxidases leading to benzoic acid as an end product. This principle is further elucidated in fig. 5.

The objection that metabolically stable agents, lipophilic enough to penetrate the central nervous system, would not be eliminated by renal excretion can be rejected for a number of reasons. Centrally active compounds excreted to a large extent unmetabolized exist. Examples are anorectic agents, such as phentermine and derivatives and phenphluramine, which still have relatively short half-life times

Fig. 5. AVOIDANCE OF RISKY AROMATIC RING OXIDATION (PHENOL FORMATION) BY INTRODUCTION OF ALTERNATIVE SAFER METABOLIC HANDLES.



The figures indicate the organic (phenolic) sulphate as a fraction of the total sulphate excretion in the urine (rat). High values imply ring oxidation, low values imply attack along safer metabolic pathway. The low value 1 for the last compound - which implies nearly complete ring oxidation - results from the combination of blockade in the ring (tertiary butyl group) and alternative pathway (methyl group). Based on data from H.W. Gerarde. "Toxicology and Biochemistry of Aromatic Hydrocarbons." Elsevier, Amsterdam 1960 (ref. 15).

in the order of 10 to 30 hours (ref. 16). Metabolically stable agents are not necessarily highly lipophilic. On the other hand, prolonged half-life times in the order of 48 hours or even longer may allow for simple dosage regimens. If so required, the drugs, as far as tertiary amines, mostly weak bases, or weak acids are involved, - many centrally acting drugs belong to these categories - can be driven out by acidifying or alkalinizing the urine by means of, for instance, ammonium chloride or sodium bicarbonate, respectively.

Although our insight in the relationship between structure and metabolic conversion is still scanty, a number of principles applicable in metabolic stabilization or, if required so, metabolic destabilization, have been worked out and proven effective. As such can be mentioned the principle of "packing" of the vulnerable moiety thus sterically or otherwise hindering the enzymatic attack on the group concerned and blocking of vulnerable positions in the drug molecule, for instance by substitution of hydrogen by fluorine or possibly deuterium. For examples the reader is referred to various reviews in the literature (1, 2, 11, 21, 22).

In conclusion, drug metabolism should be regarded as acceptable only if it has a particular, well defined purpose, such as: realization of short or ultrashort action; solely local action under the avoidance of systemic action; prodrug formation aimed at, for instance, facilitation of absorption; avoidance of local irritation; protection against first-pass loss; selective bioactivation, e.g. in the target tissue; increase in water solubility for intravenous application; increase in lipophilicity to obtain depot preparations, etc. These are areas for the "soft drug approach" (ref. 17, 18, 19, 20).

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