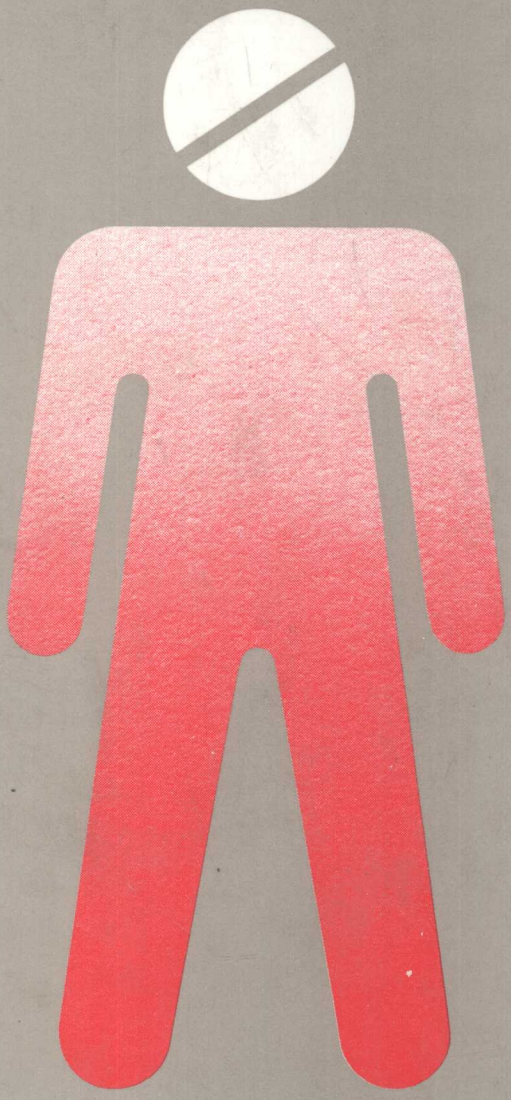
# DRUG METABOLISM AND DISPOSITION:

## Considerations in Clinical Pharmacology



Edited by G.R.Wilkinson & D.M. Rawlins

# DRUG METABOLISM AND DISPOSITION: CONSIDERATIONS IN CLINICAL PHARMACOLOGY



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# DRUG METABOLISM AND DISPOSITION: CONSIDERATIONS IN CLINICAL PHARMACOLOGY

# PREFACE

The last decade has seen increased awareness that many individual patients have inappropriate responses to usual doses of therapeutic agents. Such differences in drug responsiveness frequently arise because of interindividual differences in drug disposition, i.e. absorption, distribution, metabolism and excretion. A considerable body of knowledge has developed of the often large number of factors that contribute to this variability, which generally may be characterized as environmental and disease-induced changes superimposed on the genetic constitution of an individual. The ultimate goal of such studies is the application of the derived information and knowledge to optimization of drug therapy in the individual patient.

In science, advances in understanding and concept are gradual and slowly established, and this is particularly true in clinical research. However, there eventually comes a time when sufficient progress has been made to evaluate the broad significance and contribution of a particular area of research. This allows recognition of interesting but 'blind alleys' of endeavour, deficiencies in current knowledge and, hopefully, the identification of potentially new avenues for exploration and application. It was this philosophy upon which the concept of this book was based following oral presentations by several of the authors at the First World Conference of Clinical Pharmacology.

This book, therefore, reviews the existing state of knowledge in a number of areas of drug disposition with particular reference to their relevance to clinical pharmacology and improved rational drug therapy. The influence of development on drug handling continues to be a major area of concern at both extremes of age. The knowledge base, however, still remains small because of the difficulties associated with studying the unique patient populations. Increasing interest in novel drug delivery systems and routes of administration other than enteral necessitates that attention be directed towards possible metabolic degradation at sites other than the liver. In certain instances, such extrahepatic metabolism may have important qualitative and quan-

titative consequences different from those customarily associated with hepatic biotransformation. In a similar fashion, the disposition and pharmacological effects of optimal isomers of chiral drugs may differ considerably. Accordingly, administration of a racemic mixture, which is frequently the clinically available form, is equivalent to giving two separate and distinct drugs. Pharmacokinetics is the major tool by which quantitative differences in disposition are assessed, and while essentially descriptive in nature, there has been increased understanding of how biological determinants of the processes of disposition manifest themselves in, for example, a plasma concentration/time profile. A clearer understanding of the role of 'reactive' intermediate metabolites in the mechanism of drug induced toxicity has also developed over the last decade of intensive research. Much still remains to be elucidated at the molecular mechanistic level, but the difficulties and experimental limitations are now much more apparent. Finally, the direct problems of individualizing drug therapy in patients is considered. Can practically feasible tests be used to characterize a patient's ability to metabolize a drug and, if not, what other approaches are potentially available to aid in the optimization process?

G. R. Wilkinson

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# CONTENTS

# 1

# DRUG METABOLISM AND DISPOSITION IN NEONATES AND INFANCY

**ANDERS RANE**

The object of pharmacotherapy is to obtain a specific pharmacologic response with as little risk of adverse effects as possible. This goal is best achieved by selecting the correct drug for the specific disease, and choosing the correct dose and dosage regimen. The latter is hampered by interindividual variability with respect to both drug response (pharmacodynamics) and disposition (pharmacokinetics), as well as the disease state and age. There are reasons to believe that interindividual age-dependent and genetic variability in drug response is less pronounced than the variability in drug kinetics. In addition, the age-dependent variation in drug kinetics is larger than the genetic variation for most drugs, if one includes the neonatal period of life. The well-known therapeutic disasters with sulphonamides (Silverman *et al.*, 1956), and chloramphenicol (Weiss *et al.*, 1960), involving toxic effects after administration of the same (body weight related) doses as to adults are historical examples of the therapeutic consequences of altered drug disposition in the young. These events have contributed to the dogma that the developing infant has an augmented response to drugs, but this is not always the case.

The functional maturation of the liver and the kidneys has a pronounced effect on the kinetics and hence the response to many drugs. Drug kinetics may also be influenced by the age-dependent variation in plasma protein binding, in tissue distribution and in the absorption.

The purpose of this chapter is to review the principles behind the developmental changes in drug metabolism and disposition during the neonatal period and infancy. It is beyond its scope to give a complete

review of all knowledge in this area. Rather, general principles will be illustrated by examples of single drugs or drug groups.

## DRUG METABOLISM AS REFLECTED BY PHARMACOKINETIC DATA

The drug eliminating processes are essential defence mechanisms against accumulation and toxicity of foreign compounds entering the organism. They include excretion (usually via the kidneys) with, or without, preceding chemical alteration of the drug which may be enzymatic or non-enzymatic. The combined efficacy of these processes is quantitated by the total body clearance ($Cl_{iv}$) of the drug which, by definition, is the volume of blood or plasma that is irreversibly cleared of drug per unit time. The $Cl_{iv}$ may be calculated from the i.v. dose (D) and the area under the plasma concentration versus time curve ($AUC_{iv}$) according to equation (1):

$$Cl_{iv} = \frac{D}{AUC_{iv}} . \qquad (1)$$

The contribution of renal excretory processes to the $Cl_{iv}$ can be estimated if the urinary excretion of the drug is measured. Thus, $Cl_{iv}$ is the sum of hepatic ($Cl_H$), renal ($Cl_R$) and other ($Cl_X$) clearance mechanisms:

$$Cl_{iv} = Cl_H + Cl_R + Cl_X. \qquad (2)$$

If the drug is administered orally the plasma clearance ($Cl_o$) must be corrected for by the fraction of the oral dose that reaches the systemic circulation (F):

$$Cl_o = \frac{F \cdot D}{AUC_o} . \qquad (3)$$

By definition, $(1 - F)$ is the fraction of the absorbed oral dose that is metabolized in the liver and/or gut wall during the passage from the gut to the systemic circulation. This is called the 'first pass elimination' (FPE). If all of the drug in the gut is absorbed into the portal vein, then

$$1 - F = E \qquad (4)$$

where E is the hepatic extraction ratio. E is defined as the fraction of the dose entering the liver that is eliminated during one passage through the liver.

The perfusion-limited model (Rowland *et al.*, 1973; Wilkinson and Shand, 1975) for drug clearance in the liver defines the relation between

$Cl_H$, the blood flow (Q) and the total intrinsic hepatic clearance ($Cl_i$) according to equation (5):

$$Cl_H = Q \cdot E = Q \left[ \frac{Cl_i}{Q + Cl_i} \right]. \quad (5)$$

The $Cl_i$ is defined as the maximum capacity to remove drug from the blood in the absence of flow limitations. From this equation it is obvious that *changes in liver blood flow* will preferentially affect the clearance of drugs with high values of $Cl_i$, which may be observed as changes in plasma half-life ($T_{\frac{1}{2}}$). In contrast, *changes in enzymatic activity* will affect the $T_{\frac{1}{2}}$ only of drugs with low values of $Cl_i$. In addition such changes affect the AUC after both oral and intravenous administration, such that the AUC is decreased when the enzyme activity increases.

The hepatic clearance is also dependent on drug binding in the blood by modification of equation (5):

$$Cl_H = Q \left[ \frac{f_B \cdot Cl_i'}{Q + f_B \cdot Cl_i'} \right]. \quad (6)$$

In equation (6), $f_B$ denotes the unbound fraction in blood and $Cl_i'$ is the intrinsic hepatic clearance of unbound drug. This equation indicates that drug binding in blood has little importance for E and $Cl_H$ if $Cl_i'$ is high. In contrast, it may influence the $Cl_H$ if the value of $Cl_i'$ is low (Wilkinson and Shand, 1975).

As a consequence of these pharmacokinetic considerations, caution must be exercised in the interpretation of age-dependent differences in the $T_{\frac{1}{2}}$ and/or AUC of a drug which is eliminated by metabolism; do they reflect differences in metabolic drug clearance or in blood flow of the drug metabolizing organ, notably the liver? This obviously depends on the magnitude of $Cl_i$ and only a few drugs have been classified according to this system. In the discussion of drug kinetics in the growing infant and child it is thus essential to differentiate between 'low clearance' and 'high clearance' drugs. Too little attention has been paid to this issue in paediatric pharmacology.

After repeated oral administration, the steady-state concentration ($C_{ss}$) is determined only by F, $Cl_H$, the dose and the dosing interval ($\tau$). In equation (7) the drug is assumed to be eliminated only by hepatic metabolism:

$$C_{ss} = \frac{F \cdot D}{Cl_H \cdot \tau}. \quad (7)$$

Substitution for F and clearance yields:

$$C_{ss} = \frac{D}{f_B \cdot Cl_i' \cdot \tau}. \quad (8)$$

This equation shows that $Cl_i'$ and the binding are the only biological determinants of the steady-state concentration of a drug, given orally and metabolized only by the liver. Hence, the blood flow may be excluded as a determining factor for the $C_{ss}$. For the further discussion about the oral steady-state kinetics any concern about Q is, therefore, superfluous.

There are at least two clinically realistic ways to estimate hepatic drug metabolizing capacity in a patient or subject. If the drug is completely absorbed, and metabolized only by the liver, the apparent oral clearance ($Cl_o$) of the drug is equivalent to the intrinsic hepatic clearance. Determination of $Cl_o$ requires repeated blood samples after an oral dose and has not often been applied since so far only a few drugs are known to fulfil the above criteria. The plasma half-life ($T_{\frac{1}{2}}$) of a drug may serve as an estimate of the drug metabolizing capacity under certain circumstances. Since the $T_{\frac{1}{2}}$ is dependent not only on $Cl_H$ (for drugs metabolized only by the liver) but also on the apparent volume of distribution ($V_d$)

$$T_{\frac{1}{2}} = \frac{0{\cdot}693 \cdot V_d}{Cl_H} \tag{9}$$

it is necessary for the latter to be the same when comparison of $T_{\frac{1}{2}}$ is made between different age groups or between infants and adults. The $V_d$ is often unknown and therefore the value of the $T_{\frac{1}{2}}$ gives little information about the drug eliminating capacity.

## Low clearance drugs. Clinical data in paediatric patients

Many antiepileptic drugs which are frequently used in infants belong to the group of drugs with low clearance. Their $T_{\frac{1}{2}}$ is predominantly dependent on the drug metabolizing enzyme activity and their $C_{ss}$ (as for all drugs) is determined by the hepatic enzyme activity and by the drug binding in blood (equation 8). Inasmuch as $V_d$ and $f_B$ are similar in the compared patient groups, the $T_{\frac{1}{2}}$ and the $C_{ss}$ may serve as rough estimates of the capacity to metabolize a particular drug. Table 1 lists some of those drugs that have been studied both in newborns and adults.

It may be noted that carbamazepine and phenytoin had similar $T_{\frac{1}{2}}$ in newborns and adults which may be due to intrauterine induction. For phenytoin it has been shown (Loughnan *et al.*, 1976) that the $V_d$ is almost the same in newborn and older infants ($0{\cdot}8\,l \times kg^{-1}$) as in adults ($0{\cdot}6-0{\cdot}7\,l \times kg^{-1}$) and the $T_{\frac{1}{2}}$ values indicate that the capacity to metabolize the drug is well developed at birth.

There is also evidence that the capacity to oxidize phenytoin decreases with age (Chiba *et al.*, 1980) and a significantly higher $V_{max}$ in

**Table 1 Half-lives (hours) of drugs known or suspected to be *poorly* extracted by the human liver in newborns and adults**

| *Drug* | $T_{\frac{1}{2}}$ *in newborns* | $T_{\frac{1}{2}}$ *in adults* | *Reference* |
|---|---|---|---|
| Amylobarbitone | 17–60 | 12–27 | Krauer *et al.*, 1973 |
| Caffeine | 103 | 6 | Aranda *et al.*, 1979; Parsons and Neims, 1978 |
| Carbamazepine | 8–28 | 21–36 | Rane *et al.*, 1975 |
| Diazepam | 25–100 | 15–25 | Morselli *et al.*, 1973 |
| Mepivacaine | 8·7 | 3·2 | Moore *et al.*, 1978 |
| Phenobarbitone | 21–100 | 52–120* | Garrettson and Dayton, 1970; Heinze and Kampffmeyer, 1971; Jalling, 1976; Wilson and Wilkinson, 1973; Minigawa *et al.*, 1981; Butler *et al.*, 1954*; Lous, 1954* |
| Phenytoin | 21 | 11–29 | Rane *et al.*, 1974 |
| Theophylline | 24–36 | 3–9 | Aranda *et al.*, 1976 |
| Tolbutamide | 10–40 | 4·4–9 | Nitowsky *et al.*, 1966 |

children, than in adults, was also found by Eadie *et al.* (1976). The clinical tradition to use higher weight-related doses of many antiepileptics for children than for adults is consonant with their higher drug oxidizing activity (*see* below).

## High clearance drugs. Clinical data in paediatric patients

The best-known drugs which are subjected to high clearance i.e. many β-adrenoceptor blocking agents, some local anaesthetics, most of the narcotic analgesics and tricyclic antidepressants are rarely used in young patients. Nevertheless, some data on the kinetics of these drugs have been published and are included in Table 2. For these agents,

**Table 2 Half-lives (hours) of drugs known or suspected to be *highly* extracted by the human liver in newborns and adults**

| *Drug* | $T_{\frac{1}{2}}$ *in newborns* | $T_{\frac{1}{2}}$ *in adults* | *Reference* |
|---|---|---|---|
| Bromosulphophthalein | 0·16 | | Wichman *et al.*, 1968 |
| Meperidine | 22 | 3–4 | Caldwell *et al.*, 1977<br>Tomson *et al.*, 1982 |
| Nortriptyline | 56 | 18–22 | Sjöqvist *et al.*, 1972 |
| Morphine | 2·7 | 0·9–4·3 | Dahlström *et al.*, 1979 |
| Lidocaine | 2·9–3·3 | 1·0–2·2 | Mihaly *et al.*, 1978 |
| Propoxyphene | 1·7–7·7 | 1·9–4·3 | Wilson *et al.*, 1976 |

hepatic blood flow is of importance for the $T_{\frac{1}{2}}$ whereas the enzyme activity plays little role for the disposition of an i.v. dose. However, enzyme activity determines the AUC and $C_{ss}$ after single or multiple oral administration, respectively.

Most drugs are oxidized by the cytochrome P-450 containing microsomal mono-oxygenase system. The multitude of subtypes of this cytochrome (Lu and West, 1980) has raised questions about their relation with the *in vivo* oxidation of different xenobiotics. Very little is known about this, and for obvious reasons this field is difficult to explore in man. However, interesting data on the neonatal kinetics of xanthines have been linked to data on the human fetal metabolic activity of cytochrome P-448 *in vitro*. This form of the cytochrome is inducible by methylcholanthrene, and other polycyclic hydrocarbons, and is believed to catalyse the oxidation of theophylline and caffeine (Lohman and Miech, 1976; Aldridge *et al.*, 1979). Both of these drugs have extremely long plasma half-lives in newborns, with the half-life of theophylline varying between 14 and 58 hours while that of caffeine is about 96 hours (Aranda *et al.*, 1976). In adults the corresponding values are 3.5–8 h (Ellis *et al.*, 1974, 1976) and 4 h (Aranda *et al.*, 1979) for theophylline and caffeine, respectively. These large age-dependent differences are, as far as one knows, without counterparts for other drugs. The data are also interesting in relation to the extremely low benzo(*a*)pyrene metabolism in human fetal as compared to human adult liver microsomes (Pelkonen and Kärki, 1973) since the oxidation of benzo(*a*)pyrene is also catalysed by cytochrome P-448.

Table 3 includes data on some other drugs which have been investigated both in infants and adults on a comparative basis. The plasma elimination half-lives of these drugs are consistently longer in the newborns than in the adults.

From the literature at least two main *conclusions* about the drug metabolizing activity in neonates and infants can be drawn. First, certainly for a few drugs, and probably for several others, the metabolic clearance (as estimated from their plasma half-lives) is lower than in adult life. The age at which the adult rate of metabolic elimination is achieved is usually unknown. Second, there is no way at present to predict generally the development of drug metabolizing activity in infancy and childhood. Each drug has its own characteristics.

## Plasma protein binding

Routine analyses of drug concentrations in plasma usually measure the total drug (i.e. the unbound plus the bound moieties). This is satisfactory where interindividual variation in drug binding is negligible. For some drugs, however, the binding may be age-dependent or

**Table 3 Half-lives (hours) of some unclassified drugs in newborns and adults**

| *Drug* | $T_{\frac{1}{2}}$ *in newborns* | $T_{\frac{1}{2}}$ *in adults* | *Reference* |
|---|---|---|---|
| Amikacin | 2·8 | 2·9 | Lanao *et al.*, 1982 |
| Aminopyrine | 30–40 | 2–4 | Reinicke *et al.*, 1970 |
| Bupivacaine | 25 | 1·3 | Caldwell *et al.*, 1976 |
| Chloramphenicol | 5·1 | ND | Kauffman *et al.*, 1981 |
| Diazepam | 25–100 | 15–25 | Morselli *et al.*, 1973 |
| Furosemide | 7·7–19·9 | 0·5 | Aranda *et al.*, 1978; Peterson *et al.*, 1980; Cutler *et al.*, 1974 |
| Gentamicin | 1·25 | ND | Bravo *et al.*, 1982 |
| Indomethacin | 14–20 | 2–11 | Traeger *et al.*, 1973 |
| Oxazepam | 21·9 | 6·5 | Tomson *et al.*, 1979 |
| Primidone | 7–28·6 | 3·3–12·5 | Kaneko *et al.*, 1982; Morselli, 1977 |
| Phenylbutazone | 21–34 | 12–30 | Gladtke, 1968 |
| Valproic acid | 23–35 | 10–16 | Ishizaki *et al.*, 1981; Gugler and von Unruh, 1980 |

ND = *no data*

abnormal (in certain disease states) and it may then be important to know the unbound concentration.

The issue of 'therapeutic' plasma concentration ranges in adults and children has interested clinicians and therapists for a long time. In this context it is mandatory to consider how large the fraction of the total drug is unbound, since only this fraction is in equilibrium with the drug concentration at the receptor site. Several drugs are known to be bound less to fetal or cord/infant plasma than to adult plasma, and a few drugs have been shown to be bound more extensively (Table 4). Therefore, it seems necessary for differences in binding to be taken into consideration in attempts to establish a drug concentration–effect relationship. This is also evident from equation (8) which describes the dependency of $C_{ss}$ on binding.

In addition, binding in plasma may have an influence on the kinetics of drugs. For 'low clearance' drugs the systemic clearance is dependent on the degree of binding, and the $T_{\frac{1}{2}}$ is prolonged with increased binding. In addition, decreased binding (increased $f_B$) leads to a marked decrease in the total blood concentration but has little effect on the concentration of unbound drug, which is the fraction that is important for its effects. This is in contrast to drugs with $Cl_i'$ values higher than Q. For them, a decreased binding leads to a higher unbound concentration