Aids to Clinical Pharmacology and Therapeutics

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Preface

We all differ in our approach to learning in the medical course. In general, 'Aids' and 'Notes' have greater popularity with students than with their teachers. One possible explanation of this phenomenon is that such short-cut texts are academically poor and do not represent the real world because a practised doctor does not sieve through lists when confronted with a clinical problem. Students, on the other hand, gain confidence in seeing the imposition of some sort of order on the chaos of facts which confront them. Of course, in a subject such as clinical pharmacology, which is imperfectly understood in terms of mechanism and whose subject matter is in a constant state of flux, order may be spurious and illusory. Despite this, we have made an attempt to tame the facts and the material presented contains the nucleus of our courses at the United Medical Schools. Around this core is other material which may be of use for students taught elsewhere. Practice is geographically variable and a drug used widely in our hospital may be substituted by another in another institution. Therefore this book is in some respects over-comprehensive. Our advice is to use it in conjunction with a pen to emphasise the drugs and practices which are of importance in your hospital and medical course.

We believe this subject cannot be learnt in abstraction from a book but that the student should learn therapeutics at the bedside. The drug chart and the patient's response to each item on it should be sought with that eager attention with which you strain to hear an opening snap or pleural rub on your patients. In addition you should consult larger textbooks for discussion in depth of those aspects of particular relevance to the treatment of a difficult clinical problem. Of all the subjects in the medical curriculum, clinical pharmacology is the one which will be most widely applicable in your future career: the surgeon, psychiatrist or general practitioner requires just as sound a background in therapeutics as the cardiologist or gastroenterologist. All are users of drugs but all may also be abusers of drugs to the detriment of their patients. We hope that this little book may also assist qualified doctors reading for higher examinations or perhaps just reading. Students in other

faculties such as pharmacy may also find some of the lists and tables a useful summary of the information required in their examinations.

Our secretaries, Carmel Kennedy and Christine Wier, performed, as usual, a minor miracle in sorting out our handwritten manuscript to produce immaculate typescript with never a cross word. Nicola Schmidt-Renfree drew the diagrams with care. Professor John Trounce and Dr Helen Gillies have helped us by their encouragement and comments on various parts of the text. We are indebted to them all for their assistance.

London
1989

H.J.R.
R.G.S.

Howard Rogers

During the preparation of this new edition Howard Rogers died. His contribution amply justified that his name remains as author.

We have attempted to reduce the bulk of the text, whilst incorporating some recent changes in therapeutic practice.

R.G.S.

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Contents

Drug absorption, distribution, metabolism and excretion

DRUG ABSORPTION

Transmembrane movement of drugs

Drugs must pass several membranes to reach site of action.

1. *Passive diffusion* — commonest and most important
   - — no energy required
   - — not saturable or inhibited by metabolic inhibitions
   - — non-selective
   - — obeys Fick's law (so concentration gradient important)
   - — non-ionised drug is lipid soluble and diffuses easily (so oil/water partition coefficient, pH and pK_a important).
2. *Active* — relatively unusual
   - — specific, e.g. iodide, amino acids
   - — competition for transport can occur
   - — drugs resembling natural substrate can be transported, e.g. methyldopa, levodopa, 5-fluorouracil, methotrexate uptake in gut; renal tubular secretion of weak acids and bases
   - — requires energy
   - — can occur against concentration gradient.
3. *Facilitated* — carrier-mediated but no energy required e.g. B_{12}-intrinsic factor complex but not important for drugs.
4. *Pinocytosis* — physical engulfment by cell
   - — little importance for drugs; vitamins A, D, E, K absorbed this way.

BIOAVAILABILITY

Relative amount of administered drug dose reaching systemic circulation and rate at which this occurs.

Formulation can contain same amount of drug but availability to body may be vastly different.

Bioequivalence — two or more pharmaceutical formulations produce comparable bioavailability characteristics in an individual when administered in equivalent dosage regimes.
Bioinequivalence — statistically significant difference in bioavailability between preparations.
Therapeutic inequivalence — clinically important difference in bioavailability.
Absolute bioavailability — availability of a drug product relative to i.v. administration.
Relative bioavailability — availability as compared to recognised standard preparation.

Factors influencing bioavailability

1. Drug characteristics
   (i) instability
   (ii) incomplete absorption
   (iii) first pass elimination.
2. Formulation characteristics
   (i) Excipients and other ingredients
   (ii) Compression and physical factors affecting formulation dissolution and solubility
   (iii) State of drug, e.g. surface area, particle size.
3. Interactions with other substances in gut — food, drugs.
4. Patient characteristics
   — disease (e.g. malabsorption, hepatic dysfunction)
   — gastro-intestinal factors (motility, pH, blood flow)
   — genetic factors, e.g. acetylator status.

Bioavailability assessment

1. *Plasma data — single dose*
   (i) time of peak plasma concentration
   (ii) peak plasma concentration
   (iii) area under plasma concentration, time curve (AUC).
   Usually oral and i.v. doses (D) given in random order to panel of subjects.

$$\text{Since } (AUC)_{p.o.} = \frac{FD}{kV} \quad \& \; (AUC)_{i.v.} = \frac{D}{kV}$$

where F is bioavailability fraction if k and V remain constant between doses (k = elimination rate constant V = distribution volume)

$$F = \frac{(AUC)_{p.o.}}{(AUC)_{i.v.}}$$

   — *multiple dose*: as (i), (ii), (iii) above during a single dosage interval.

2. *Urine data*
   (i) total fraction of dose excreted
   (ii) rate of drug excretion
   (iii) time of maximum excretion.
3. *Clinical observation and pharmacological effects*, e.g. salivary secretion, heart rate.

Potential for bioinequivalence of dosage forms

Low	*Intermediate*	*High*
Elixirs	Capsules	Compressed tablets
Syrups	Suspensions	Enteric-coated tablets
Solutions	Chewable tablets	Sustained release formulations
		Suppositories

Examples of drugs for which bioinequivalence demonstrated among marketed oral formulations:

Aspirin	Digoxin	Phenytoin
Chloramphenicol	Nitrofurantoin	Prednisolone
Chlordiazepoxide	Oxytetracycline	Warfarin

Therapeutic inequivalence shown in most of the above. Bioinequivalence often results in therapeutic inequivalence if therapeutic index low.

Sustained release preparations
Aim to prolong action of drugs with short $T_{\frac{1}{2}}$ by pharmaceutical means, e.g. resin coated pellets in capsules, drug enclosed in wax or plastic matrix.

Potential advantages
1. Prolonged effects
2. Improved compliance
3. Comparable or improved efficacy
4. Improved tolerability

May be valuable if
(i) Short $T_{\frac{1}{2}}$ (1–?8 h)
(ii) Prolonged treatment necessary (improves compliance)
(iii) Constant plasma levels needed for efficacy.

Potential disadvantages
1. Cost — more expensive than conventional tablets
2. Delayed absorption — delayed onset of action or failure of dissolution
   — increased first-pass effects
   — ? increased effect on gut flora
3. Prolonged toxicity
4. Risk of overdose — dosage form failure
   — intentional
5. Increased risk of gut toxicity

Enteric coated tablets or granules
Film coat (polymer like cellulose acetate phthalate) which resists dissolution by stomach acid but disrupts or dissolves in alkaline intestinal juice. Occasionally used to reduce gastric irritation, e.g. aspirin, prednisolone.

FACTORS AFFECTING GASTRO-INTESTINAL DRUG ABSORPTION

1. Drug
a. Lipophilicity (e.g. oil/water partition coefficient)
b. pKa
c. Metabolism in gut

2. Formulation
Dissolution rate

3. Patient
a. pH of gut
b. Rate of gastric emptying
c. Intestinal motility (transit time)
d. Surface area available for absorption
e. Presence of food in gut
f. Interactions with drugs in gut.

EFFECT OF FOOD ON DRUG ABSORPTION

Decreased absorption	*Increased absorption*
Tetracycline (milk, cottage cheese)	Propranolol
Methotrexate (milk)	Hydrochlorothiazide

ROUTES OF DRUG ADMINISTRATION

Sublingual/buccal absorption
1. Rapid absorption
2. Avoids first-pass gastro-intestinal/hepatic elimination.

Examples: glyceryl trinitrate, oxytocin, methyltestosterone, buprenorphine

Rectal administration
1. Only partially avoids first-pass metabolism.
2. Small surface area (passive absorption only) and drug may be expelled so absorption rate and bioavailability erratic.
3. Unsuitable for irritant drugs.
4. Drugs given as solution (retention enema) more rapid and efficient than given as solid formulation with wax base (suppository).
5. Useful if patient vomiting.

6. Used for systemic (e.g. theophylline, prochlorperazine, aspirin, oxycodone, indomethacin) or local (e.g. corticosteroids for inflammatory bowel disease) effects.

Intramuscular injection

1. Gastro-intestinal and hepatic first-pass elimination avoided.
2. Absorption influenced by
   (i) local blood flow, massage and movement (e.g. exercise increases absorption; morphine absorption decreased after myocardial infarct; insulin absorption increased by sauna).
   (ii) site, e.g. lignocaine absorption absorbed faster from deltoid than vastus lateralis or gluteus maximus.
   (iii) physical properties of drug — poorly water soluble drugs, e.g. diazepam, phenytoin precipitate in muscle and are poorly and erratically absorbed.
   (iv) sex of patient — females may absorb less from gluteal injection.

   Thus absorption less reliable than i.v. but solubility of drug not necessary.
3. Compliance ensured.
4. Onset of action more rapid than oral route.
5. Prolonged absorption can be produced by modification of injection
   — high viscosity vehicles like glycerin
   — fatty acid esters which slowly hydrolyse, e.g. fluphenazine decanoate for maintenance therapy in schizophrenia
   — water insoluble suspensions, e.g. procaine penicillin.
6. Complications
   (i) Pain, e.g. benzypenicillin (maximum volume by i.m. is 4–5 ml)
   (ii) Muscle and skin necrosis, e.g. digoxin, sterile or septic abscesses, pigmentation, e.g. iron
   (iii) Sciatic nerve damage following gluteal injection
   (iv) Elevated CPK may confuse diagnosis of myocardial infarction
   (v) Inadvertant intravascular injection.

Intravenous injection

1. Only route (apart from intra-arterial) when bioavailability considerations immaterial. Useful if:
   (i) drug not absorbed p.o., e.g. gentamicin
   (ii) high first-pass elimination, e.g. lignocaine
   (iii) too irritant for i.m. or p.o. route, e.g. nitrogen mustard.
2. Almost instantaneous response but bolus of highly concentrated drug may cause cardiac, respiratory etc complications so i.v. injections should usually be slow over 1–2 minutes (circulation time).

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3. Rate of administration flexible, e.g. nitroprusside, lignocaine, and plasma levels can be accurately maintained.
4. Drug administered may not be recalled c.f. p.o. when absorption can be reduced.
5. Only water-soluble or aqueous miscible systems can be given.
6. Tonicity of solution and lack of irritant properties important, some preparations cause thrombophlebitis, e.g. diazepam.
7. Risks
   (i) anaphylaxis — greater with this route than others
   (ii) infection especially in immunosuppressed and seriously ill
   (iii) tissue damage if irritant drug extravasates, e.g. doxorubicin, actinomycin D, thiopentone.

Subcutaneous injection

1. Absorption influenced by same factors as i.m. injection but absorption slower and more erratic. Can sometimes increase bioavailability with hyaluronidase, local heat, massage, exercise.
2. Sustained release effect obtained from pellets of solid drug, e.g. testosterone replacement. Duration of insulin action controlled by crystalline size, e.g. semilente, lente, ultralente insulins
3. Some injections painful, may cause necrosis or abscesses.

Percutaneous absorption

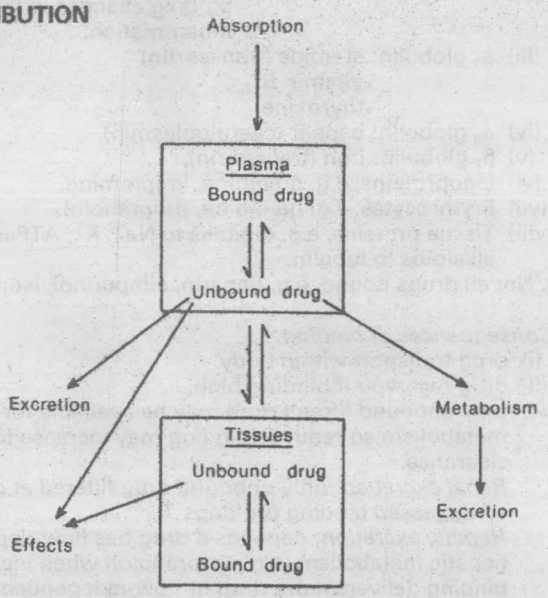
1. Drug absorption increased
   (i) polythene occlusion increases skin hydration (N.B. danger of systemic steroid overdosage)
   (ii) lipid solubility, e.g. poisoning by absorption of nicotine, organic phosphates through skin
   (iii) loss of stratum corneum
   (iv) site — plantar < scalp < posterior auricular (depends on thickness of stratum corneum and number of hairs and sweat glands)
   (v) age — steroids absorbed more readily in children than adults
   (vi) vehicle.
2. Topical application minimises systemic absorption — but can occur, e.g. steroids.
3. Route can be utilised to avoid first-pass elimination and prolong systemic action, e.g. glyceryl trinitrate.

Pulmonary absorption

1. Almost instantaneous absorption (large surface area).
2. Difficult to deliver drug into lung and to dose accurately — particles > 10 μm impact in pharynx and nose and are swallowed. Optimum size is 1–2 μm which may reach alveoli and terminal bronchiole. Tidal volume and bronchial anatomy also important.

3. For local therapy, e.g. disodium cromoglycate, dexamethasone, isoprenaline but can use for systemic effects, e.g. ergotamine.
4. Anaesthetics

DRUG DISTRIBUTION



Protein binding of drugs
Drugs can bind to tissue proteins but plasma protein binding best understood.

1. *Characteristics of binding*
   Usually but not always reversible.
   Competition for binding may occur between drugs or drugs and endogenous compounds.

2. *Proteins responsible for binding.*
   (i) Albumin — affinity for acidic drugs.
   — 2 sites: I (warfarin site) also binds frusemide, phenytoin, valproate, indomethacin, glibenclamide, bilirubin.
   II (diazepam site) also binds probenecid, salicylate, glibenclamide,
   — fatty acids bind at separate site but can cause conformational change so altering drug binding.

(ii) α_1 acid glycoprotein — affinity for basic drugs, e.g. propranolol, imipramine, chlorpromazine, lignocaine.
— protein increases with ESR so binding changes with inflammation.
(iii) α_1 globulin: steroids (transcortin)
vitamin B_{12}
thyroxine
(iv) α_2 globulin: copper (caeruloplasmin).
(v) β_1 globulin: iron (transferrin).
(vi) Lipoproteins, e.g. quinidine, imipramine.
(vii) Erythrocytes, e.g. quinidine, propranolol.
(viii) Tissue proteins, e.g. digitalis to Na^+, K^+, ATPase, vinca alkaloids to tubulin.

N.B. Not all drugs bound, e.g. heparin, allopurinol, isoniazid.

3. Consequences of binding

(i) drug transport within body.
(ii) drug reservoir if binding high.
(iii) only unbound ('free') drug may be available for action or metabolism so reduced binding may increase toxicity and clearance.
Renal excretion: only unbound drug filtered at glomerulus so increased binding prolongs $T_{\frac{1}{2}}$.
Hepatic excretion: depends if drug has flow-dependent hepatic metabolism (e.g. propranolol) when increased binding delivers more drug or flow-independent (e.g. warfarin) where only unbound drug is eliminated.
(iv) bound drug cannot diffuse into tissues so binding determines volume of distribution and penetration into tissues, e.g. CSF, and secretions, e.g. saliva.
(v) displacement from binding clinically important if:
a. drug highly bound (e.g. change from 99% to 98% binding increases free drug by 100%)
b. small volume of distribution (follows from a).
c. low therapeutic index with steep dose-response curve.

BUT new steady-state reached and free drug concentration reaches previous level so drug effects only increase transiently.

(vi) saturation of binding produces non-linear pharmacokinetics, e.g. phenylbutazone, prednisolone.

N.B. for highly bound drugs with large V_d displacement interactions have no significant pharmacological effects.

Examples of displacement interactions:

Displaced drug or substance	*Displacing agent*
Bilirubin	Sulphonamides, Salicylates
Methotrexate	Sulphonamides, Salicylates
Tolbutamide	Phenylbutazone, Salicylates
Warfarin	Salicylates, Phenytoin

N.B. some interactions may result from more than one action e.g. phenylbutazone inhibits metabolism of most active (S–) isomer of warfarin.

DRUG METABOLISM

Drug metabolism chemically modifies drugs and may:

a. Abolish the activity (e.g. oxidation of barbiturates, phenytoin, alcohol; hydrolysis of suxamethonium, acetylcholine; conjugation of isoprenaline, salicylate).

or

b. Promote or increase activity (e.g. conversion of chloral to trichlorethanol; conversion of phenacetin to paracetamol; activation of cyclophosphamide to alkylating metabolites).

or

c. Produce no change in activity (e.g. dealkylation of tricylic antidepressants, benzodiazepines).

Metabolism usually produces a more polar molecule which increases drug elimination since it is less susceptible to tubular reabsorption or active uptake in renal tubules or biliary system. Two phases of metabolism:

Phase I — Metabolic modification (e.g. oxidation, reduction, hydrolysis)

Phase II — Synthesis — i.e. conjugation (e.g. with glucuronic acid, glycine, glutamine, sulphate, acetate)

	Phase I		*Phase II*	
Drug	oxidising etc → enzymes	metabolites	conjugating → enzymes	conjugated metabolites

PHASE I METABOLISM

Occurs in 3 areas of cell:

(i) smooth endoplasmic reticulum, e.g. barbiturates, pethidine
(ii) cytosol, e.g. ethanol, chloral
(iii) mitochondria, e.g. oxidation of tyramine by MAO.

May also occur in plasma, e.g. succinylcholine hydrolysis by plasma pseudocholinesterase.

Not all drugs broken down by enzymes, e.g. melphalan undergoes spontaneous hydroxylation to inactive metabolites.

PHASE II METABOLISM

Conjugation with
(i) glucuronic acid, e.g. salicylate, chloramphenicol, morphine.
(ii) acetate, e.g. isoniazid, hydralazine, dapsone.

ENZYME INDUCTION

Enhancement of enzyme activity due to increase in the amount of enzyme protein present in the cell. Induction of enzymes concerned with drug metabolism usually accelerates destruction of drugs and reduces their action.

Not only enzyme content of liver increased but organ size and blood flow also enhanced.

Non-microsomal metabolism is not inducible.

Three groups of inducing agents

a. Substances which stimulate metabolism in many pathways, e.g. barbiturates, carbamazepine
b. Polycyclic hydrocarbons (e.g. 3-methyl cholanthrene; 3–4 benzo (a) pyrine) produce limited metabolic stimulation.
c. Steroids: mainly microsomal enzyme stimulation.

Effects of some enzyme inducers on metabolism of endogenous and exogenous chemicals

Enzyme inducing agent	*Substances whose metabolism is enhanced*
Barbiturates	Barbiturates, coumarins, phenytoin, bilirubin, vitamin D_3, contraceptive pill
Carbamazepine	contraceptive pill, warfarin
Phenytoin	Digitoxin, dexamethasone, cortisol, thyroxine, dieldrin, DDT, tricyclic antidepressants, contraceptive pill, (the synthesis of cholesterol is also stimulated), vitamin D_3
Ethanol (weak inducer)	Ethanol, warfarin, phenytoin,
DDT, gamma benzene hexachloride (Lindane)	Cortisol, phenytoin,
Rifampicin	Steroids, including contraceptive steroids, digitoxin

Smoking accelerates the metabolism of:
amitriptyline
pentazocine
dextropropoxyphene

Inhibition of drug metabolism

Drug	*Substance whose metabolism is inhibited*
Isoniazid	Phenytoin
Chloramphenicol	Phenytoin, tolbutamide
Ethanol (single large dose)	Chloral, tolbutamide, phenytoin, warfarin
Disulfiram Sulphonylureas Metronidazole Citrated calcium carbimide Procarbazine	Acetaldehyde (from ethanol)
Cimetidine	Diazepam, chlordiazepoxide, warfarin, propranolol, phenytoin.

Environmental inhibitors of microsomal enzymes

organophosphorus insecticides
pesticide synergists (methylene dioxyphenyl derivatives)
carbon tetrachloride

Compounds metabolised by lungs — examples

1. Endogenous — 5-hydroxytryptamine
   Angiotensin I
   Prostaglandins (E & F)
2. Exogenous — chemicals (? relation to carcinogenesis)
   Benzo (a) pyrine
   — drugs (not usually the major site of metabolism but may contribute significantly; as yet mostly animal evidence)
   Isoprenaline (especially when inhaled)
   Ifosfamide

Metabolism by gut flora

Flora is a mixture of aerobic and anaerobic organisms.

Microbial breakdown of hepatic conjugates frequently essential part of enterohepatic circulation.

Metabolism by gut mucosa

Mainly conjugations rather than Phase I metabolism in mucosal cells.

Probably important for morphine, pentazocine, isoprenaline, tyramine, levodopa, oestrogens, progestogens, pivampicillin, flurazepam.

Enzymes may be inhibited, e.g. MAOIs.

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