PART XIV

WORKSHOP ON DRUG METABOLISM IN CHRONIC URAEMIA

Chairman: D N S Kerr
A CHILD’S GUIDE TO CLINICAL PHARMACOLOGY IN RENAL FAILURE

CHAIRMAN: KERR (Newcastle upon Tyne) Renal failure can affect the handling of drugs in many ways. Gastrointestinal absorption may be decreased (e.g. calcium from calcium salts), increased (e.g. aluminium from aluminium hydroxide) or unpredictable because of delayed gastric emptying and vomiting. Drug metabolism may be affected by the loss of a pathway of degradation (e.g. insulin) or activation (e.g. vitamin D) in the kidney. It may be retarded by uraemic depression of enzyme activity in the liver and other tissues or accelerated by hepatic enzyme induction through uraemia itself or the retention of drugs and their metabolites. Protein binding may be altered by uraemia or acidosis (e.g. phenytoin, diazoxide) or by hypoproteinaemia if the patient has proteinuria (e.g. clofibrate). There may be changes in the apparent volume of distribution or the pattern of distribution of the drug which in turn affect its metabolism. The sensitivity of end organs such as the heart, brain, bone and bone marrow may be diminished or enhanced or may be unpredictable, as when the response of the heart to cardiac glycoside changes with the plasma potassium during and after haemodialysis. However the most important changes, by far, are those in the renal elimination of the drug and its metabolites.

To use drugs intelligently in renal failure, the nephrologist should turn to one bookshelf and look up the clinical pharmacology of the drug in normal subjects, if he does not know it already, then turn to a second bookshelf and consult a series of books on the effect of renal failure on all these aspects of drug handling. The first bookshelf is comfortably full; a small selection of the many excellent books on clinical pharmacology are listed in section 1 of the Bibliography below. The second bookshelf is very bare. It contains two small but excellent books and a number of book chapters. Reidenberg’s little monograph gives an excellent summary of the principles of pharmacology in renal failure. The more recent book
by Anderson, Gambertoglio and Schrier gives a concise drug-by-drug account. These and the book chapters are a sufficient guide to the literature up to 1973. In sections 3 and 4 of the bibliography I have listed a few of the review and original articles published since 1974.

Even the well-organised nephrologist, who has armed himself with these and other treatises on drugs in renal failure, will still find that there are many gaps in our knowledge. This round table is designed to help the doctor faced with a decision about a drug which is not well documented to make an intelligent guess at the correct dosage, or to avoid the drug if guessing is clearly unsafe. Each of the contributors will deal with one aspect of drug handling in renal failure — Professor Dettli with renal excretion, Professor Rawlins with drug binding and distribution, Professor Leber with drug metabolism and Dr Maddocks with enzyme induction. They will concentrate on principles rather than details. I will start with the most fundamental principle of all — to understand clinical pharmacology in renal failure you must first know the clinical pharmacology in the normal. The first characteristic of the drug to note is its relative solubility in water and lipid.

**Water Soluble Drugs**

To the surprise of many clinicians learning their clinical pharmacology in middle age, water soluble drugs are poorly absorbed from the gut and are given by injection. They have a low affinity for metabolic pathways in the liver and circulate

![Diagram](image-url)

**Figure 1. A water soluble drug — gentamicin**
as the original drug. They may be partly protein-bound but the free (unbound) fraction is readily excreted by glomerular filtration and the protein-bound fraction may be removed by tubular secretion, as happens with penicillin. Active drug appears in the urine. We would expect renal failure to reduce urinary concentration and to cause considerable accumulation of the active drug in the blood stream. Figure 1 shows a well-known example of a water-soluble drug, gentamicin, which is notoriously liable to cumulate in renal failure.

**Lipid Soluble Drugs**

Lipid soluble drugs are well absorbed from the gut and have a strong affinity for metabolic pathways in the liver. This is presumably an evolutionary trick; lipid soluble residues in the diet cannot be excreted through the kidney so we have

![Diagram of lipid soluble drug - propranolol](image)

*Figure 2. A lipid soluble drug – propranolol*

had to evolve enzymes which turn them into water soluble compounds. Drugs slot into these ancient metabolic pathways. Figure 2 shows a typical lipid soluble drug, propranolol. Propranolol can be cleared from the blood during one passage through the liver when it is given in low dosage. In adequate therapeutic dosage it emerges from the liver partly as the parent drug and partly as metabolites. Propranolol circulates more than 90% bound to protein and very little is excreted by the kidney. An important metabolite is 4-OH-propranolol which has about the same beta-blocking action as the parent drug. It, too, circulates tightly bound to protein and escapes renal excretion. Both of these compounds recirculate to the
liver and are metabolised further to conjugates and other water-soluble compounds which are then excreted through the kidney. We would expect renal failure to cause an accumulation of these inactive metabolites but not of the parent drug or its active 4-hydroxy metabolite. So we would expect little change in the beta-blocking activity of propranolol in renal failure and this accords with clinical experience.

From simple knowledge of their relative solubility in water and lipid we could have guessed that penicillin and the aminoglycosides would accumulate in renal failure, that the tetracyclines would have a spectrum of behaviour with the more water-soluble members like oxytetracycline accumulating in renal failure while a more lipid soluble relative like doxycycline was little affected by renal function. We could have surmised that most sedatives and psychotropic drugs would not accumulate in renal failure for it is a useful simple rule that any drug sufficiently lipid soluble to enter the brain is unlikely to be excreted by the kidney.

However it is not enough to know about the parent drug as we have already seen with propranolol. I shall close with another example, chosen because closer familiarity with clinical pharmacology in the normal could have prevented some embarrassing mistakes that were published in the Lancet last year (Pierides et al, 1975). There is considerable concern at the moment about the hypertriglyceridaemia of chronic renal failure which is believed to be one of the main causes of the high death rate from vascular disease in patients on regular dialysis. The most effective drug for the treatment of hypertriglyceridaemia is clofibrate. It is lipid soluble and would not be expected to accumulate in renal failure. For this reason, or from ignorance, doctors have often prescribed it in normal dosage to patients in renal failure. However a closer look at its pharmacology shows that this is unwise. The active compound is p-chlorophenoxy-isobutyric acid (CPIB). It is water-soluble and therefore poorly absorbed from the gut. The manufacturers therefore produced an ethyl ester, called clofibrate, which was lipid soluble and therefore well absorbed from the gut but rapidly metabolised to the active compound, CPIB. We would therefore expect renal failure to cause accumulation, not of clofibrate, but of CPIB.

This was borne out by our experience (Pierides et al, 1975). Within a few days of starting the drug in normal dosage, a man with a GFR of 7 ml/min began to complain of aching in the muscles and soon developed the full syndrome of CPIB toxicity, with massive release of muscle enzymes into the blood. Although he stopped taking the drug after 10 days the muscle enzyme concentration continued to rise for several days and it took over a week at this GFR to excrete the surplus CPIB, which was a several times the therapeutic level four days after stopping the drug. Clofibrate can be given safely to patients in renal failure in a greatly reduced dosage but it is unwise to do this in severe renal failure unless the concentration of CPIB can be monitored.

**Conclusion** If you cannot find the answer in Reidenberg or Anderson, Gamberto-
glio and Schrier, it is still worthwhile looking up Goodman and Gilman and using your powers of deduction. If you are still in doubt, call the:

CLINICAL DRUG INFORMATION SERVICE (University of Newcastle upon Tyne) – Newcastle upon Tyne (0632) 25131 – and ask for CDIS (Telephone manned 24 hours a day by Professor Rawlins, Professor Thompson and colleagues) or your national equivalent, if any.

Bibliography

Section 1: Books on Clinical Pharmacology in General

General principles


Drug-by-drug accounts

Avery, GS (1976) *Drug Treatment*. Churchill Livingstone, Edinburgh
Data Sheet Compendium (1976) Revised annually. Association of the British Pharmaceutical Industry

Section 2: Books and Chapters on Clinical Pharmacology in Renal Failure

Books


Book chapters

Renal excretion and nephrotoxicity of drugs. AF Lant. In DAK Black (1972) *Renal Disease, Chapter 21*. Blackwell, Oxford

Section 3: Review articles 1974–76

Drug dosage in renal failure. L Dettli (1976) *Clinical Pharmacokinetics, 1*, 126
Drug metabolism in uremia. MM Reidenberg (1975) *Clinical Nephrology, 4*, 83
Prediction of drug dosage in patients with renal failure using data derived from normal subjects. PG Welling, WA Craig and CM Kunin (1975) *Clinical Pharmacology and Therapeutics, 18*, 45

Section 4: Articles on Individual Drugs 1974–76

Antibiotics and antibacterials

Clindamycin. BA Peddie et al (1975) *Australian and New Zealand Journal of Medicine, 5*, 198
C Simon et al (1975) *Schweizerische medizinische Wochenschrift, 105*, 1615