Today's Treatment

Diseases of the urinary system

Prescribing for patients with renal failure

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Many drugs are eliminated from the body, wholly or in part, by renal excretion. If given in standard dosage to patients with poor renal function they will accumulate in body fluids and may reach toxic concentrations. Nevertheless, most such drugs may be prescribed safely provided the dose is suitably modified. To determine the correct dose we need to know more about their pharmacological properties than is necessary when prescribing for patients with normal kidneys.

Pharmacological considerations

Firstly, given that the drug is stable in plasma, what proportion is the renal clearance of the total clearance? If it approaches 100%—that is, elimination is almost entirely by the kidneys (for instance, streptomycin)—its plasma half life will vary inversely with the patient's glomerular filtration rate. Thus if a patient's glomerular filtration rate (or creatinine clearance) is 30% of normal that patient will need 30% of the usual dose. But, drugs eliminated largely by extrarenal routes (such as sodium fucidate) will need no modification of dosage however severely impaired the patient's renal function. Most drugs are excreted by both renal and extrarenal mechanisms, and in practice the relation between half life and glomerular filtration rate is usually established empirically, and a table relating dosage to renal function is prepared.

Next, we need to know whether a high blood level of the drug is toxic. If it is, as in the case of the aminoglycosides, great care must be taken to get the dose right, and, when prolonged courses are given, or in patients with unstable renal function, the plasma concentration should be checked at intervals. With non-toxic agents adjustment of dosage is not critical.

When a chemotherapeutic agent is used to treat infection of the urinary tract we need to be certain that it achieves an adequate concentration in the urine. In renal failure nitrofurantoin, for example, is poorly excreted and is of no value.

Excretion of many drugs is influenced by factors other than glomerular filtration rate, such as urine pH and urine flow rate. These properties are used in the techniques of forced diuresis to treat overdosage, but in the ordinary clinical case the range of variation in pH and flow rate is rarely extreme enough to make an important difference to the plasma concentration.

We must take account of the effect of impaired renal function on drug metabolites. Most drugs are lipid soluble and are metabolised to water-soluble compounds before excretion in the urine or bile. Renal impairment may result in their retention. If these metabolites are pharmacologically active—for instance, acetohexamide and procainamide—drug action is prolonged and the dose should be reduced. Metabolites may be inactive therapeutically but toxic, such as chloramphenicol, in which case they should not be used in uraemia. The altered ratio of metabolite to active drug in renal failure may lead to confusion when plasma concentrations are measured by non-specific methods. For example, the usual assay of tolbutamide detects inactive metabolites as well, so that a falsely high plasma concentration is obtained.

Kidney failure can itself alter drug metabolism. The vitamin D metabolite, 25-hydroxycholecalciferol is hydroxylated to the much more active 1,25-dihydroxycholecalciferol in the kidney, so that patients with uraemia need massive doses of calciferol. Alternatively, the metabolic block may be bypassed by using a synthetic analogue of 1,25-dihydroxycholecalciferol, 1-alpha-hydroxycholecalciferol. The metabolism of diphenylhydantoin is actually enhanced by the uraemic state, so that higher than usual levels should be needed. Decrease in binding to plasma protein, however, causes more active drug to be available so that overall no dose adjustment is needed in this case.

Potentially nephrotoxic drugs must be used with caution. While the risk may be small and acceptable in patients with normal kidneys, it may be an unwarranted hazard to those whose renal function is already compromised. Tetracyclines are especially dangerous. While not damaging the kidney itself they can aggravate pre-existing uraemia and should never be used when renal function is impaired.

Finally, for patients being treated with haemodialysis or peritoneal dialysis we need to know about the dialysability of the agent. If substantial amounts are removed across the membrane an increased dosage will be needed, usually by giving an additional dose at the end of dialysis.

Despite all these complexities patients with renal failure need not be denied necessary treatment. Table I lists the dosage modification of some more commonly used drugs for different degrees of renal functional impairment.

Use of dosage table

Glomerular filtration rate is usually estimated clinically as the clearance of creatinine. A simpler guide to renal function is the blood urea concentration, but this depends on other factors, such as dietary protein intake and the rate of tissue catabolism, and is unreliable when renal function is changing rapidly. The plasma creatinine concentration, however, depends only on renal function and is recommended as the best simple approximation, provided that renal function is fairly stable.

TABLE I—Dosage modification of more commonly used drugs for different degrees of renal function impairment

Drug				Dose interval (hours) in categories of impaired renal function				Dialysable		Comment (BC = measure blood concentration in severe renal failure)
				None	Mild	Moderate	Severe	Haemodialysis	Peritoneal dialysis	
Antibacterial agents										
Benzylpenicillin	..	..	..	8	8	8	12	+	?	BC in "massive" therapy
Ampicillin	..	..	..	6	6	8	12	+	—	
Cloxacillin	..	..	..	6	6	6	6	—	?	
Carbenicillin	..	..	..	4	4	8	12	+	—	Exacerbates uraemia No use for urine infection Potentially nephrotoxic
Tetracycline	..	..	..	6	Avoid	Avoid	Avoid	—	—	
Doxycycline	..	..	..	24	24	24	24	—	—	
Cephaloridine	..	..	..	6	12	Avoid	Avoid	+	+	
Cephalexin	..	..	..	6	6	8–12	24–48	+	+	
Cephalothin	..	..	..	6	6	8	12–24	+	+	Metabolites may be toxic
Cephazolin	..	..	..	8	12	16	24	—	—	
Cephradine	..	..	..	6	12	24	48	?	?	
Chloramphenicol	..	..	..	6	6	Avoid	Avoid	—	—	
Co-trimoxazole	..	..	..	12	12	24	24–48	+	?	
Colistin	..	..	..	12	24	48	72	+	+	
Gentamicin	..	..	..	8	12	24	48–72	+	—	
Streptomycin	..	..	..	12	24	48	72	+	+	
Kanamycin	..	..	..	8	24	48	72	+	+	
Lincomycin	..	..	..	6	6	6	8	—	—	
Sodium fusidate	..	..	..	8	8	8	8	—	?	
Sulphadimidine	..	..	..	6	6	6	12	?	?	
Nalidixic acid	..	..	..	6	6	6	6	?	?	
Nitrofurantoin	..	..	..	6	Avoid	Avoid	Avoid	+	?	
Insufficient urine concentration										
Para-aminosalicylic acid	..	..	..	12	12	Avoid	Avoid	+	?	
Isoniazid	..	..	..	12	12	12	12	+	+	
Rifampicin	..	..	..	24	24	24	24	?	?	
Ethambutol	..	..	..	24	24	36	48	+	+	
Antifungal agents										
Amphotericin	..	..	..	24	24	24	36	—	?	
Flucytosine	..	..	..	6	8	12–24	24–72	+	+	
Hypnotics and tranquillisers										
Phenobarbitone	..	..	..	12	12	12	24	+	+	
Short and medium acting barbiturates	..	..	..	8	8	8	8	—	—	
Diazepam	..	..	..	8	8	8	8	—	?	
Chlordiazepoxide	..	..	..	8	8	12	24	—	?	
Phenothiazines	..	..	..	8	8	12	18	—	—	
Antidepressants										
Tricyclics	..	..	..	8	8	8	8	—	+	
Lithium carbonate	..	..	..	8	8	Avoid	Avoid	+	+	
Antihistamines										
Chlorpheniramine	..	..	..	6	6	6	6	?	?	
Diphenhydramine	..	..	..	6	6	8	12	—	—	
Anticonvulsants										
Diphenylhydantoin	..	..	..	8	8	8	8	+	?	
Primidone	..	..	..	8	8	12	24	+	?	
Trimethadione	..	..	..	8	8	12	24	?	?	
Cardiovascular drugs and antihypertensives										
Digoxin	..	..	..	24	36	48	72	—	—	
Propranolol	..	..	..	8	8	8	8	—	?	
Methyldopa	..	..	..	8	8	12	16	+	+	
Guanethidine	..	..	..	24	24	36	48	?	?	
Hydralazine	..	..	..	8	8	8	8	—	—	
Lignocaine	..	..	..	Bolus or infusion	Unchanged	Unchanged	Unchanged	?	?	
Procainamide	..	..	..	4	4	6	8	+	?	
Immunosuppressive agents										
Corticosteroids	..	..	..	Various	Unchanged	Unchanged	Unchanged	?	?	
Azathioprine	..	..	..	24	24	24	36	+	?	
Cyclophosphamide	..	..	..	24	24	36	48	+	?	
Antidiabetic agents										
Chlorpropamide	..	..	..	24	36	Avoid	Avoid	?	?	
Tolbutamide	..	..	..	8	8	8	12	?	?	
Phenformin	..	..	..	8	8	8	Avoid	?	?	
Acetohexamide	..	..	..	12	24	Avoid	Avoid	?	?	

+ = Yes. — = No.

TABLE II—Categories of impaired renal function

	None	Mild	Moderate	Severe
Creatinine clearance (ml/min)	>70	30-69	10-29	<10
Plasma creatinine (μmol/l)	<114.9	114.9-265	265-884	>884
Plasma creatinine (mg/100 ml)	<1.3	1.3-3	3-10	>10
Plasma urea (mmol/l)	<5.8	5.8-13.3	13.3-41.5	>41.5
Plasma urea (mg/100 ml)	<35	35-80	80-250	>250

In table I renal function is categorised as mild, moderate, or severe (table II).

It is usually more convenient to lengthen the time interval between doses than reduce the size of individual doses, and table I specifies dose intervals appropriate to each category of renal impairment. It indicates also whether the drug is dialysable to any important extent, in which case an additional dose should be given at the end of each dialysis.

The data on which table I is based are often incomplete and their quality is varied. Furthermore, the metabolic disturbance of uraemia is complex and no two patients are alike. For these reasons the information given must be interpreted with caution and used only as a rough guide. Careful clinical judgement is necessary as well. The more toxic drugs should be used only when there is no safer alternative and when given in more than short courses their blood concentration should be monitored.

What are the cause and treatment of spontaneous subconjunctival haemorrhage in the elderly?

Subconjunctival haemorrhage probably occurs more often in the elderly because the small blood vessels become more fragile with age, particularly in patients with systemic vascular disease such as arteriosclerosis, hypertension, diabetes, or anaemia. Apart from treatment of any systemic condition, no local treatment is needed.