Pharmacokinetics of antibiotics in peritoneal dialysis

In renal disease, the handling of drugs by the body is profoundly altered. This is due not only to decreased renal elimination of drug, but also to many other factors including the amount of non-renal elimination of drug, changes in the biotransformation of drugs and alterations to plasma protein binding, volume of distribution and hepatic clearance. In addition to these, in peritoneal dialysis, both intermittent (IPD) and continuous ambulatory (CAPD), a certain amount of drug will be eliminated by peritoneal dialysis. This amount can be expressed as the peritoneal clearance
(Cl\text{pet}) of the drug:

\[ Cl_{\text{pet}} = \frac{A_{\text{pet}}}{AUC} \]

where \( A_{\text{pet}} \) is the amount recovered in dialysate per unit time, and AUC is the area under drug-plasma concentration time curve. Generally speaking, the peritoneal clearance of antibiotics is small in relation to total body clearance. Peritoneal clearance is influenced by a number of factors including those pertaining to the dialysis fluid—its volume, osmolality and retention time; the physicochemical properties of the drug; and the peritoneal membrane characteristics—the degree of perfusion, and whether it is inflamed, as in peritonitis.

When antibiotics are administered systemically to patients on peritoneal dialysis, the major factor affecting the pharmacokinetics is the impaired, or absent, renal function. Thus over a period of time the antibiotic, if it is one which is normally excreted largely by the kidneys, accumulates to produce high blood concentrations and the time to reach steady-state is increased. The situation in fact is little different from that in non-dialysed patients in end-stage renal failure. A useful and practical method of obtaining the maintenance dose and dose interval of a drug is that of Dettli (1974). The maintenance dose is half the loading dose, and the dosage interval is equal to the estimated half-life of the drug. Full reviews of drug pharmacokinetics in peritoneal dialysis are those of Manuel, Paton & Cornish (1983) and Lamiere, Bogaert & Belpaire (1986).

An interesting phenomenon found with many antibiotics such as aminoglycosides, cephalosporins and vancomycin is the so-called 'unidirectional' absorption from the peritoneal cavity (Somani et al., 1982). The movement of antibiotic from the circulation to dialysate, across the peritoneal membrane, is poor, whereas absorption of drug from dialysate into the blood stream is high. This phenomenon would seem to be explained simply by the small volume of the peritoneal cavity relative to the large volume of distribution in the body. After systemic administration of gentamicin and vancomycin very low concentrations are achieved in dialysate in CAPD patients (Glew et al., 1982; Somani et al., 1982; Blevins et al., 1984). The levels are often insufficient to treat peritonitis and therefore intraperitoneal (ip) administration of these drugs is recommended for this purpose.

When administering antibiotics intra-peritoneally it is important to know that they are chemically stable in the dialysis fluid. Most penicillins, cephalosporins, aminoglycosides and vancomycin are stable at room temperature for at least 24 h, even in the presence of heparin (500 units/l) (Sewell & Golper, 1982; Sewell et al., 1983). The ip route of administration will often produce blood levels of antibiotic sufficient to treat a systemic infection, but the usual reason for using the ip route is to treat peritonitis in patients on peritoneal dialysis. Between 49 and 65% of ip gentamicin is absorbed systemically within a 6 h dwell period (Pancorbo & Comty, 1981; Somani et al., 1982). If gentamicin is put into every bag of dialysis fluid at 8 mg/l, after a few days the serum concentration rises towards this concentration. In an attempt to lessen the risks of toxicity, either the ip concentration should be lowered to 4 mg/l after 48 h, or the drug should be put into alternate bags (Working Party, 1987). With cephalosporins, and to some extent vancomycin, although absorption of these drugs from ip administration is about 50% (Nielson, Sorensen & Hansen, 1979; Local et al., 1981), the margin of safety is higher so that the same concentration of drug can be put in every bag.

For the treatment of peritonitis in CAPD patients it has long been desirable to use an effective oral agent as initial, empirical therapy. This would greatly simplify the treatment, and enable it to be on an outpatient basis. The oral cephalosporin cephalexin has been shown to produce dialysate levels approximately two thirds of simultaneous blood levels, and well above the minimum therapeutic levels (Drew et al., 1984). Similarly, cephadrine dialysate concentrations were high and not significantly different following oral or ip administration (Boeschoten et al., 1985). The reason why these oral agents are unsuitable as first line therapy for peritonitis in CAPD is not poor dialysate levels, but an inadequate spectrum of activity to cover the usual pathogens, particularly coagulase-negative staphylococci. The search for suitable oral agents continues, and interesting contenders may be the quinolones. Ciprofloxacin produces dialysate levels similar to serum levels, and high enough to treat many pathogens (Fleming et al., 1987).

A. J. BINT
Department of Microbiology,
Royal Victoria Infirmary,
Newcastle upon Tyne.
NE1 4LP, UK
Leading articles

Interactions of antibiotics with other drugs

There are numerous drug interactions involving antimicrobial agents—more than 120 are listed in a recent textbook (Norris & Mandell, 1985)—and it is impossible to describe each of these in detail. For ease of consideration, however, they can be broadly divided into three types; pharmaceutical, pharmacodynamic, and pharmacokinetic interactions (Kristensen, 1976).

Pharmaceutical interactions occur outside the body when physically incompatible drugs are mixed before administration. One of the best known is the formation of complexes and subsequent mutual inactivation that occur when carbenicillin and gentamicin are mixed. Such interactions are generally preventable merely by avoiding any combination of drugs in the same intravenous infusion fluid unless compatibility is proven. Pharmacodynamic interactions depend upon opposite or additive effects at the site of drug action. They are often predictable but sometimes the interaction is an indirect one and less obvious: the effect of amphotericin B in producing hypokalaemia, for example, may alter the therapeutic effect of digoxin.

Most interactions involving antibiotics are pharmacokinetic ones and occur when one drug (the precipitant) alters the absorption, distribution or elimination (either metabolism or excretion) of another (the target drug). Antibiotics may be the targets of such interactions, especially when their absorption or excretion depend upon opposite or additive effects at the site of drug action. They are often predictable but sometimes the interaction is an indirect one and less obvious: the effect of amphotericin B in producing hypokalaemia, for example, may alter the therapeutic effect of digoxin.

Drugs which have a high affinity for serum protein-bound drugs. As a consequence the plasma concentration of the unbound drug

References


