

ANTIBIOTIC THERAPY IN PATIENTS ON REGULAR DIALYSIS TREATMENT

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Patients with severe chronic renal failure who are being maintained on regular dialysis treatment are constantly at risk from infections, particularly staphylococcal shunt infections and infections with various gram-negative organisms. It has long been known that renal impairment will affect the rate of removal from the body of many antibiotics, and that antibiotic therapy may be hazardous because the blood levels obtained are unpredictable. On the other hand, if the drug dosage is restricted because of known renal failure, then inadequate serum levels may lead to failure of therapy. The inception of regular dialysis treatment introduces another variable factor into the use of antibiotics in these patients, since it is likely that each dialysis will temporarily increase the clearance of the drugs. This study is an attempt to lay down rational guide lines to antibiotic therapy in patients on regular dialysis.

METHODS

Many of the existing studies on blood levels of antibiotics in renal failure utilised tube dilution methods for assaying serum antibiotic levels; these methods are too inaccurate to be valuable, particularly at higher blood levels. Accordingly we have used the fish-spine bead diffusion technique described by Humphrey and Lightbown (1952) for measuring blood levels; this and other cup plate diffusion techniques are accurate to at least 1 $\mu\text{g/ml}$ at all levels. The antibiotics chosen for study were kanamycin, streptomycin, colistin and carbenicillin, all potentially effective against a wide range of gram-negative organisms, and cloxacillin, most likely to eradicate penicillinase producing staphylococci. The drugs were given in single doses to patients on regular dialysis treatment; in each case either there was a therapeutic indication or the free consent of the patient was obtained. All patients had creatinine clearances of less than 3 ml/min., and all were maintained on twice-weekly haemodialysis using Kolff twin-coil kidneys and Chron-a-coil (Baxter). Blood samples were taken before administration of the antibiotic, and at intervals thereafter. The serum was separated at once and stored at -20°C , until duplicate assays were performed.

RESULTS

1. Kanamycin

Figure 1 shows the mean curves obtained in 4 patients after the administration of 0.5 g of kanamycin intramuscularly before and after dialysis. If the dose is given before dialysis, the clearing effect of the dialysis prevents the blood level rising too high, and the retention of the drug thereafter means that therapeutic levels persist for over 72 hours. A single dose of 0.5 g of kanamycin given before each dialysis will give blood levels which are bactericidal for 90% of *E. coli* and 80% of *Proteus spp.*, continuously (Fekety *et al.*, 1962). Giving the same dose of kanamycin after dialysis produces even higher blood levels, and the risk of toxicity would be justified only by a very severe infection with a resistant organism.

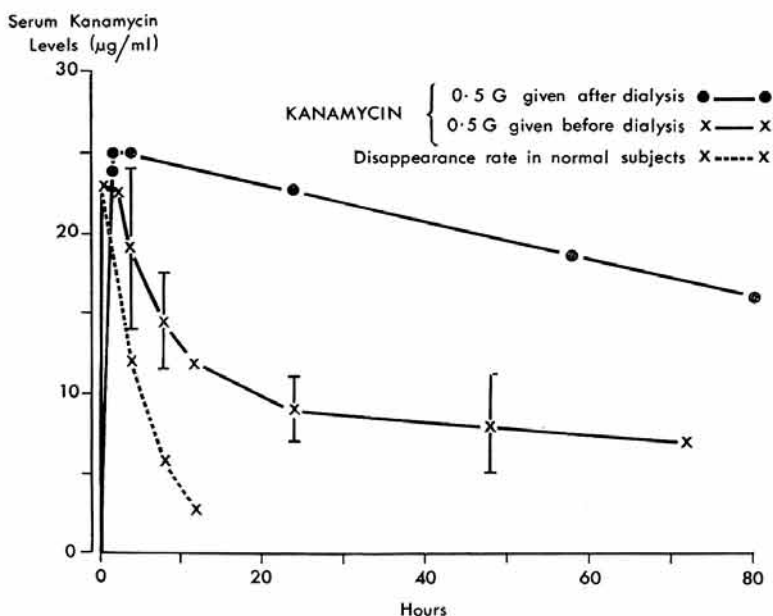


Fig. 1

2. Streptomycin

The curves obtained after a single dose of 0.5 g of streptomycin were identical with those for kanamycin (Fig. 1). Levels bactericidal for 90% of *E. coli* can be produced and maintained with 0.5 g of streptomycin given before each dialysis, and toxic levels are avoided by the dialysis effect. If the drug is used against *M. tuberculosis*, the problem is more complex since blood levels greater than 8 $\mu\text{g/ml}$ are to be aimed at. Such levels can be obtained by giving the dose of streptomycin post-dialysis, but since such therapy would be long term, monitoring of the levels would certainly be necessary after the first three days.

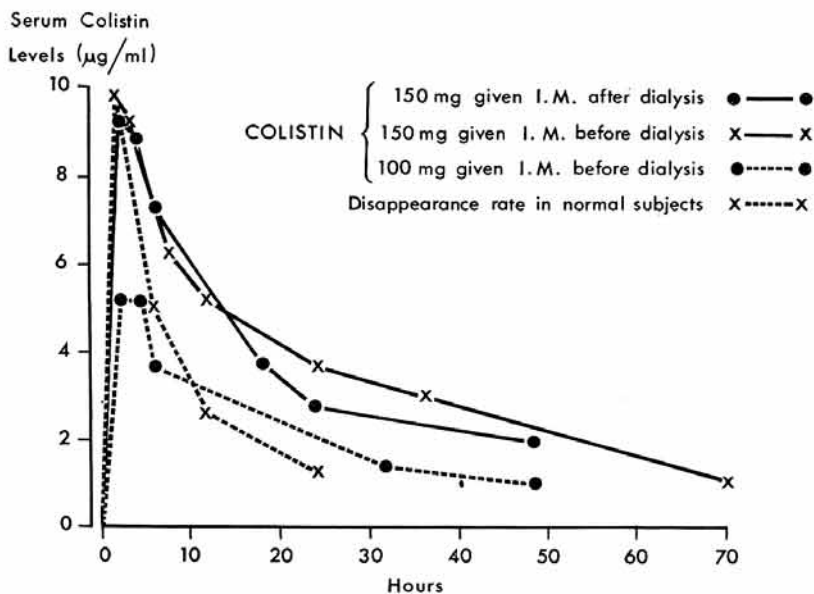


Fig. 2

3. Colistin

The mean curves obtained in 5 patients given various doses of colistin sulphomethate are shown in Figure 2. The importance of this drug is that it may well be the drug of choice for *Pseudomonas* infections. The levels obtained with a dose of 100 mg were inadequate. With a dose of 150 mg given intramuscularly, the curves obtained were very similar whether given before or after dialysis; furthermore the degree of retention of colistin in the anephric patient is less than might be expected since it is thought to be excreted largely via the kidneys (Colley and Frankel, 1963). Blood colistin levels over 5 $\mu\text{g/ml}$ are bactericidal for 90% of *Pseudomonas* strains, and levels between 5 and 10 $\mu\text{g/ml}$ will be achieved by giving 150 mg of the drug intramuscularly each 24 hours. Much higher blood levels of colistin can be obtained by giving larger doses intravenously, but there have been reports of convulsions, coma and respiratory arrest when colistin has been given in high dosage to uraemic patients (Greenberg and Sanford, 1967).

4. Carbenicillin

The mean curves obtained from 5 patients given 1 g of carbenicillin are shown in Figure 3. This drug is one of the newer penicillins, and is bactericidal for 90% of *Proteus* spp. at blood levels above 12 $\mu\text{g/ml}$. The intramuscular injection of 1 g of carbenicillin pre-dialysis gave blood levels similar to those in the normal, at least during the 10 hours of dialysis, although some retention occurred thereafter. The same dose given at the end of dialysis produced therapeutic levels for 24 hours, and in view of the relative safety of the drug it would seem advisable to give carbenicillin in a dose of 1 g daily, giving the dose on dialysis days after the procedure.

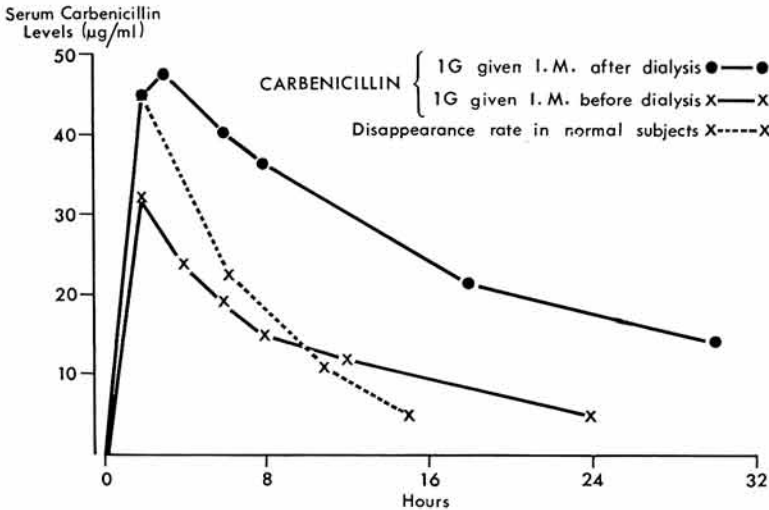


Fig. 3

5. Cloxacillin

Mean curves from 4 patients given 1 g of cloxacillin are shown in Figure 4. Retention of this drug is not marked in anephric patients, the half life being less than double the normal even when the dose is given at the end of dialysis. However, 100% of penicillinase-producing staphylococci are destroyed at blood cloxacillin levels over 3 $\mu\text{g/ml}$, so that a single dose of 1 g given at the end of a dialysis and repeated daily will be continuously effective.

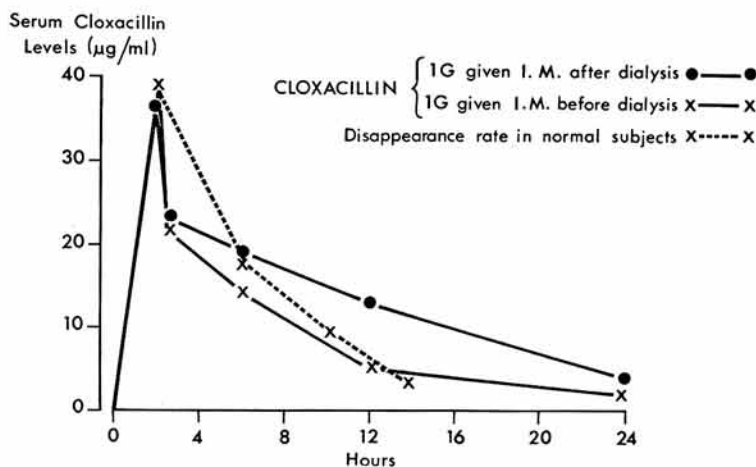


Fig. 4

DISCUSSION

The results are summarised in Table I, and in general the findings are in agreement with others in the literature. The exception to this is the work of Curtis and Eastwood (1968) with colistin. They found prolonged elevation of plasma levels of colistin in renal failure, and demonstrated an increased rate of removal during dialysis. This discrepancy is probably due to the fact that they were giving larger doses of the drug intravenously, and consequently dealing with much higher blood levels. In addition, they were using two-layer Kiil dialysers, with cuprophane membranes, and this may well be more permeable than the cellophane in the twin-coil kidney.

We do not suggest that this study and the dosage recommendations will remove all the problems of antibiotic therapy in patients on regular dialysis treatment, but they will allow a more rational dosage regime to be prescribed in the first instance, and avoid the perils of toxic effects or inadequate blood levels.

TABLE I

Antibiotic	Suggested dosage	Blood levels ($\mu\text{g/ml}$)	Duration (hours)	Organisms sensitive
Kanamycin	1 mg/kg i.m. pre-dialysis	> 8	72	$\left\langle \begin{array}{l} 90\% \text{ E. coli at } 5 \mu\text{g/ml} \\ 80\% \text{ Proteus at } 8 \mu\text{g/ml} \end{array} \right.$
	1 mg/kg i.m. post-dialysis	> 18	72	
Streptomycin	1 mg/kg i.m. pre-dialysis	> 10	40	90% <i>M. tuberculosis</i> at 8 $\mu\text{g/ml}$
	1 mg/kg i.m. post-dialysis	> 15	72	
Colistin	2.5 mg/kg i.m. pre-dialysis	> 3	24	$\left\langle \begin{array}{l} 90\% \text{ E. coli at } 5 \mu\text{g/ml} \\ 90\% \text{ Pseudomonas at } 5 \mu\text{g/ml} \end{array} \right.$
	2.5 mg/kg i.m. post-dialysis	> 3	24	
Carbenicillin	25 mg/kg i.m. pre-dialysis	> 5	24	$\left\langle \begin{array}{l} 89\% \text{ Proteus at } 12 \mu\text{g/ml} \\ 44\% \text{ E. coli at } 12 \mu\text{g/ml} \end{array} \right.$
	25 mg/kg i.m. post-dialysis	> 20	24	
Cloxacillin	25 mg/kg i.m. pre-dialysis	> 5	12	100% <i>Staphylococci</i> at 3 $\mu\text{g/ml}$
	25 mg/kg i.m. post-dialysis	> 5	24	

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