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The Effects of Peritoneal Dialysis on the Physiological Disposition of Oxacillin, Ampicillin and Tetracycline in Patients with Renal Disease

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ABSTRACT

Seven patients with acute or chronic renal failure who were receiving intermittent peritoneal dialysis and who required parenteral oxacillin, ampicillin or tetracycline were studied to determine the disposition of these antibiotics in severe renal disease and the effects of peritoneal dialysis. While severe renal impairment markedly prolongs persistence in the serum of ampicillin and tetracycline, there is little effect on oxacillin. Whereas required doses of ampicillin and tetracycline are lower in the presence of severe renal disease, oxacillin should be given in doses equivalent to those used for patients with normal renal function. Peritoneal dialysis does not alter these dosage requirements.

Four patients receiving ampicillin or tetracycline in the infusing solution during peritoneal dialysis were studied to determine the amount of systemic absorption. Local prophylaxis alone is not achieved with this method of administration, since small amounts of both antibiotics are absorbed systemically from the infusing solution. The serum concentration of tetracycline attained is inadequate for treatment of systemic infections but is probably significant, with repeated use in intermittent dialysis, in causing adverse effects. Tetracycline should be abandoned in the local prophylaxis of peritonitis during peritoneal dialysis.

SOMMAIRE

On a étudié sept malades en état d'insuffisance aiguë ou chronique du rein, qui étaient soumis à des dialyses péritonéales intermittentes et qui devaient recevoir de l'oxacilline par voie parentérale, ou de l'ampicilline ou de la tétracycline. Le but de cette étude était de déterminer le sort de ces antibiotiques chez des malades souffrant de rénopathie grave et de suivre les effets de la dialyse péritonéale. Une insuffisance rénale grave prolonge notablement les concentrations sériques d'ampicilline et de tétracycline, alors que cette pathologie n'a guère d'effet sur l'oxacilline. Il en ressort que les doses thérapeutiques d'ampicilline et de tétracycline doivent être diminuées chez des rénaux et que, par contre, il faut leur donner des doses d'oxacilline équivalentes à celles qu'on donnerait à des malades dont la fonction rénale est normale. La dialyse péritonéale ne modifie pas ces posologies.

On a aussi observé quatre malades qui recevaient de l'ampicilline ou de la tétracycline dans le liquide de perfusion, au cours de la dialyse, en vue d'établir l'importance de l'absorption. Ce mode d'administration ne permet pas de réaliser un traitement prophylactique local efficace, étant donné que de faibles doses des deux antibiotiques s'absorbent dans l'économie à partir de la solution de perfusion. La concentration sérique de tétracycline ainsi réalisée est insuffisante pour traiter des infections générales, mais est, par contre, suffisante, si on renouvelle fréquemment les dialyses intermittentes, pour provoquer des réactions défavorables. On devra abandonner le tétracycline comme traitement prophylactique local de la péritonite pendant la dialyse péritonéale.

THE course of patients with acute or chronic renal failure is often complicated by concurrent bacterial infection requiring treatment with antibiotics. Since most antibiotics are dependent on the

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kidney for excretion, the choice of correct dosage becomes difficult in these patients. The effect of uremia upon the excretion of a number of antibiotics has been reported.[1-4] A surprising difference in the persistence of benzyl penicillin and oxacillin in patients with renal failure has been shown.[4] This paper reports the physiological disposition of another useful penicillin derivative, ampicillin, as well as oxacillin and tetracycline, in patients with severe renal disease.

Peritoneal dialysis is useful in the management of acute and chronic renal failure.[5] Although the effects of hemodialysis upon the excretion of antibiotics have been reported, there is little information concerning the consequences of peritoneal dialysis.[6] This paper reports the removal of oxacillin, ampicillin and tetracyline by peritoneal dialysis.

Peritonitis is a major complication of peritoneal dialysis. Prevention of this infection has been attempted by adding small amounts of various antibiotics to the peritoneal infusing solution. The amount of systemic absorption of tetracycline during this local prophylaxis has been reported recently.[7] This paper reports the absorption of ampicillin and tetracycline during administration in the peritoneal infusing solution.

METHODS

Patients

Seven patients with acute or chronic renal failure who were receiving intermittent peritoneal dialysis and who required parenteral antibiotics for complicating infections were studied. Three patients received oxacillin, four ampicillin, and three tetracycline. All patients were studied during peritoneal dialysis and in the intervals between dialyses.

Ampicillin or tetracycline was added to the peritoneal infusate of four patients as a prophylactic measure; 28 dialysis periods were studied in these four patients.

The severity of renal disease was assessed by the 24-hour endogenous creatinine clearance test.[8] Efficiency of peritoneal dialysis was measured by the peritoneal clearance of urea.[9]

Dialysis

Peritoneal dialyses were performed using standard techniques.[5, 10] Commercial dialysis solution with a pH of 5.1, containing 140.5 mEq./l. sodium, 3.5 mEq./l. calcium, 1.5 mEq./l. magnesium, 101.0 mEq./l. chloride, 44.5 mEq./l. lactate and 15 g./l. of dextrose, was used. Two one-litre bottles of peritoneal infusing solution were attached to an indwelling intraperitoneal catheter by a standard administration set. Five hundred ml. of fluid from each of these bottles was allowed to flow by gravity into the peritoneal cavity over five minutes, was left within the cavity for 30 minutes and was then drained over 10 minutes. This procedure was repeated until either 14 or 20 litres of fluid had been infused and drained over a period of approximately 11 and 16 hours, respectively.

Administration of Antibiotics

Oxacillin, ampicillin or tetracycline was given intravenously to seven patients on 60 occasions. One gram of oxacillin was given over 15 minutes as the buffered sodium salt dissolved in 20 ml. of normal saline. One gram of ampicillin was given over 15 minutes as its sodium salt dissolved in 100 ml. of normal saline. One gram of tetracycline was given over one hour as crystalline tetracycline hydrochloride buffered with ascorbic acid and dissolved in 250 ml. of normal saline.

Ampicillin or tetracycline was given intraperitoneally to four patients on 28 occasions. Five hundred milligrams of the sodium salt of ampicillin or of crystalline tetracycline hydrochloride was dissolved in 250 ml. of normal saline and 12.5 ml. of this solution was added to every litre or every second litre of peritoneal infusing solution.

Antibiotic Assays

Samples of venous blood were taken before the start and at intervals after the end of intravenous dosing, as well as during intraperitoneal administration of antibiotics. The serum was stored at —20° C. until antibiotic assays were done. Samples of each litre of peritoneal outflow fluid were similarly stored. In the studies in which antibiotics were added to the infusing solutions, aliquots of this fluid were taken after thorough mixing and stored at —20° C. Twenty-four-hour urine collections were made during periods of study and aliquots were also stored. Assays were performed using the disc plate method with *Sarcina lutea* as the indicator organism for oxacillin and ampicillin and *Bacillus cereus* for tetracycline.[11] Standards for serum, peritoneal outflow and urine were prepared in phosphate buffer at pH 7.4 and for peritoneal infusate samples in the same buffer at pH 5.1. These assays allowed determinations of concentrations as small as 0.06 μg./ml. of oxacillin, 0.02 μg./ml. of ampicillin, and 0.20 μg./ml. of tetracycline.

Determination of Serum Half-Life

The serum half-life of the three antibiotics given intravenously was determined using the method of least squares.[12] The first sample was taken after allowing from 45 to 60 minutes for complete mixing of each antibiotic in its distribution space. The antibiotic concentration at that time was considered to be the initial level. Half-life determinations were based on the initial level and at least three subsequent serum levels determined at different times. Half-lives were not corrected for urine losses of antibiotics, since these in no case exceeded 1% of the given dose during dialysis periods on 3% of the dose during dialysis-free intervals.

RESULTS

Parenteral Antibiotics

Fig. 1 shows the mean serum concentrations of oxacillin in three non-dialysis periods in one oliguric patient after intravenous dosing with 1 g. of oxacillin. The initial serum oxacillin concentration was 38.2 ± 3.5 μg./ml. The serum half-life of oxacillin during non-dialysis periods was 1.5 hours. This figure shows that the serum concentrations of oxacillin were unaffected by peritoneal dialysis. The mean initial serum oxacillin level in three periods of peritoneal dialysis was 39.0 ± 3.1 μg./ml. The serum half-life of oxacillin during periods of dialysis was 1.4 hours. Mean peritoneal outflow fluid oxacillin concentrations decreased after a peak of 11.9 ± 1.8 μg./ml. in the first outflow fluid. Less than 5% of the administered dose of oxacillin was removed in the dialysate.

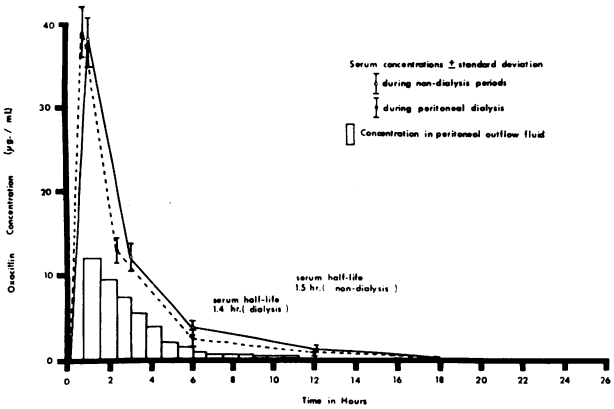

Fig. 1.—Mean concentrations of oxacillin (Patient 1) in the serum and peritoneal outflow fluid in three periods of dialysis and mean concentrations of oxacillin in the serum in three periods without dialysis in a patient with severe renal disease. One gram of oxacillin given intravenously at time O, peritoneal dialysis from ¾ to 11¼ hours.

Fig. 2 shows the mean serum concentrations of ampicillin in three non-dialysis periods in one oliguric patient after intravenous dosing with 1 g.

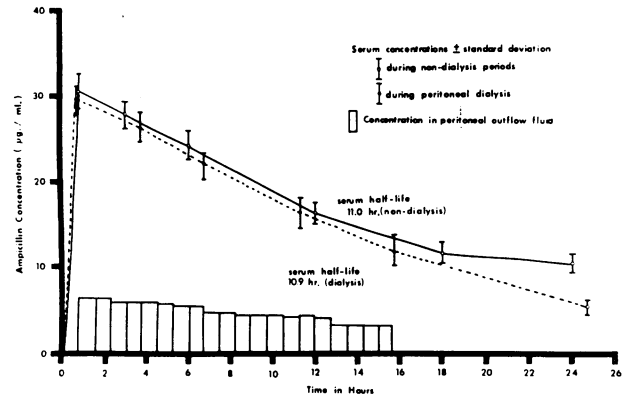

Fig. 2.—Mean concentrations of ampicillin (Patient 4) in the serum and peritoneal outflow fluid in three periods of dialysis and mean concentrations of ampicillin in the serum in three periods without dialysis in a patient with severe renal disease. One gram of ampicillin given intravenously at time O, peritoneal dialysis from ¾ to 15 hours.

of ampicillin. The initial serum ampicillin concentration was 30.6 ± 2.0 μg./ml. The serum half-life of ampicillin during non-dialysis periods was 11.0 hours. This figure shows that the serum concentrations of ampicillin were unaffected by peritoneal dialysis. The mean initial serum ampicillin level in three periods of peritoneal dialysis was 29.6 ± 1.9 μg./ml. The serum half-life of ampicillin during periods of dialysis was 10.9 hours. Mean peritoneal outflow ampicillin concentrations decreased slowly after a peak of 6.3 ± 0.8 μg./ml. in the first outflow fluid. Less than 7% of the administered dose of ampicillin was removed in the dialysate.

Table I summarizes the findings of studies made in seven oliguric patients during periods of dialysis and during dialysis-free intervals after intravenous dosing with oxacillin, ampicillin and tetracycline. The serum half-life of tetracycline could not be determined accurately for periods of dialysis, since the half-life far exceeded the 11-16 hours of each period of dialysis. The serum half-life values represent the persistence of tetracycline over several periods of dialysis and non-dialysis. The concentra-

TABLE I.—EFFECTS OF PERITONEAL DIALYSIS UPON THE PERSISTENCE OF OXACILLIN, AMPICILLIN AND TETRACYCLINE IN PATIENTS WITH RENAL FAILURE

		Without peritoneal dialysis				*During peritoneal dialysis*				
Antibiotic	*Patient*	*Creatinine clearance (ml./min./ 1.73 sq. m.)*	*Number of studies*	*Peak serum concentration (μg./ml. ± S.D.)*	*Serum half-life (hours)*	*Urea clearance (ml./min.)*	*Number of studies*	*Peak serum concentration (μg./ml. ± S.D.)*	*Serum half-life (hours)*	*Peak peritoneal outflow concentration (μg./ml. ± S.D.)*
Oxacillin	1	7.2	3	38.2 ± 3.5	1.5	28.0	3	39.0 ± 3.1	1.4	11.9 ± 1.8
(1 g. intraven-	2	8.0	3	41.0 ± 4.0	1.1	31.3	3	40.0 ± 3.5	1.2	10.8 ± 1.5
ously)	3	2.1	3	37.5 ± 3.2	1.5	28.5	3	40.2 ± 4.0	1.5	9.7 ± 2.0
Ampicillin	4	6.2	3	29.6 ± 1.9	11.0	27.1	3	30.6 ± 2.0	10.9	6.3 ± 0.8
(1 g. intraven-	1	7.2	4	32.1 ± 4.0	15.2	29.0	3	29.1 ± 3.8	14.6	7.2 ± 1.3
ously)	2	8.0	4	35.0 ± 3.5	14.5	30.3	3	31.4 ± 4.1	13.8	7.3 ± 2.0
	5	4.8	4	28.2 ± 3.2	14.8	28.5	3	30.8 ± 3.6	14.2	6.5 ± 1.2
Tetracycline	5	4.8				27.1	3	18.2 ± 5.0	45*	5.0 ± 1.3
(1 g. intraven-	6	8.5				30.5	3	20.1 ± 3.5	72*	6.1 ± 0.8
ously)	7	6.1				29.1	3	16.2 ± 2.5	61*	4.9 ± 1.2

*The serum half-life of tetracycline represents its persistence in the serum over several periods of dialysis and non-dialysis.

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tion of tetracycline in the peritoneal outflow fluid remained at or near the peak concentration of the first outflow fluid. Less than 7% of the administered dose of tetracycline was removed in the dialysate.

Intraperitoneal Administration

Fig. 3 shows the serum antibiotic concentrations during the administration of ampicillin or tetracycline in the peritoneal infusing solution. Significant serum levels of these antibiotics were attained after an exchange of 14 litres. Table II shows the mean antibiotic concentration in the inflow solution and outflow fluid in these patients. Although 25 mg. of tetracycline was added to a litre of infusing solution, assay of this fluid showed only

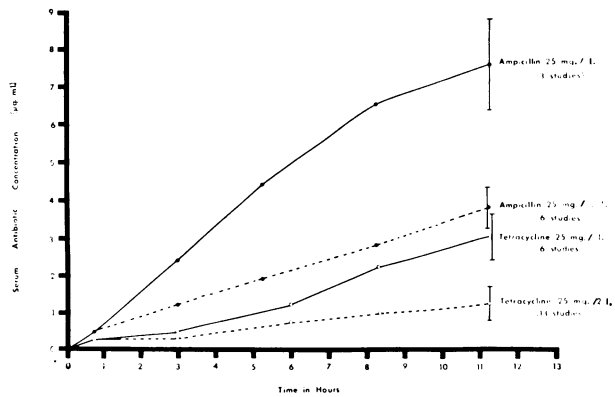

Fig. 3.—Mean serum antibiotic concentrations during intraperitoneal administration of small doses of ampicillin and tetracycline during peritoneal dialysis. Each point represents the mean serum concentration of ampicillin on tetracycline. The concentrations at the end of a 14-litre dialysis are shown ± standard deviation.

14.8 ± 2.3 and 16.1 ± 2.1 μg./ml. of bacteriologically active tetracycline. The peritoneal infusing solution contained 3.5 mEq./l. of calcium and 1.5 mEq./l. of magnesium. The same reduction in antibacterial activity was found when tetracycline was added to a solution of distilled water, at pH 5.1, containing the same amounts of calcium and magnesium as the peritoneal infusate, but full activity was found if the same amount of tetracycline was added to distilled water only, at pH 5.1.

TABLE II.—ANTIBIOTIC CONCENTRATIONS IN PERITONEAL INFUSATE, PERITONEAL OUTFLOW FLUID AND SERUM

Amount of antibiotic added to peritoneal infusate	*Number of studies*	*Mean antibiotic concentration in infusate containing drug (μg./ml.± S.D.)*	*Mean antibiotic concentration in outflow fluid (μg./ml.± S.D.)*	*Mean serum antibiotic concentration at the end of 14-litre dialysis (μg./ml.± S.D.)*
25 mg. tetracycline to every second litre	13	14.8± 2.3	4.2± 2.9	1.1± 0.4
25 mg. tetracycline to every litre	6	16.1± 2.1	8.7± 3.1	2.8± 0.6
25 mg. ampicillin to every second litre	6	24.8± 2.4	9.2± 2.0	3.7± 0.5
25 mg. ampicillin to every litre	6	24.6± 2.3	18.8± 2.1	7.5± 1.2

DISCUSSION

The major excretory route for the penicillins is the kidney. Sixty per cent of an injected dose of benzyl penicillin is excreted in the urine, while some is excreted in the bile and some is unaccounted for and assumed to be broken down in the liver.[13] In the presence of severe renal failure the serum half-life is prolonged from the 0.8 hour seen in normal patients to 7.2 to 10.5 hours.[14]

Forty-five per cent of an injected dose of oxacillin is excreted in the urine.[13] The findings in this study of a half-life of oxacillin, in the presence of uremia, of 1.1 to 1.5 hours confirm the report of Bulger[4] that the persistence of this penicillin in the serum is prolonged only slightly by the presence of severe renal failure.

Twenty-two to 41% of an injected dose of ampicillin is excreted in the urine and some of the remainder is accounted for by biliary excretion.[13] In contrast to oxacillin, ampicillin shows a greater persistence in the serum of patients with severe renal failure, reaching a half-life of from 11.0 to 15.2 hours.

The explanation for this discrepancy between the penicillins is not clear. It is most likely that the ability of the liver to detoxify and excrete the various penicillins varies. Further studies of the hepatic metabolism of the penicillins and the excretion of the penicillins in the presence of liver failure, and coincident liver and kidney failure, are needed.

The half-life of oxacillin and ampicillin in the presence of uremia is not altered by peritoneal dialysis. Approximately 5% of the administered dose of oxacillin and 7% of ampicillin is lost in the outflow fluid. This small amount provides, however, a concentration of antibiotic in the peritoneal fluid for a period of four to six hours after 1 g. of oxacillin and for at least 12 hours after 1 g. of ampicillin, which should be effective against susceptible bacteria causing peritonitis.

On the basis of these results recommendations can be made regarding the dose requirements of patients with severe renal failure suffering concurrent infections. The dose of oxacillin should not be altered from that used in patients with normal renal function. One gram of ampicillin intravenously every 24 hours provides adequate antibacterial therapy in oliguric patients. Peritoneal dialysis does not alter these dose requirements.

The prolonged persistence of tetracycline in the presence of renal failure is confirmed by this study.[1] Small quantities of tetracycline diffuse across the peritoneal membrane but these do not appreciably alter the serum half-life of this antibiotic. It is doubtful whether tetracycline concentrations which are adequate to treat peritonitis effectively are achieved in the peritoneal fluid with the more standard parenteral doses of tetracycline of 250 to 500 mg. given during peritoneal dialysis. If this antibiotic is used, supplementary doses should be given in the peritoneal infusing solutions.

Small quantities of tetracycline and ampicillin are absorbed after administration in the peritoneal infusing solution. One accepted procedure, the addition of 25 mg. of tetracycline to every second litre of dialysis fluid, results in a serum concentration of 1.1 ± 0.4 μg./ml. at the end of a 14-litre dialysis. This level is similar to that reported recently in another study of the absorption of tetracycline from the peritoneal cavity.[7] This serum concentration is inadequate in the treatment of systemic infections but is probably significant during repeated use in intermittent dialysis in causing adverse effects. This antibiotic should be abandoned in the local prophylaxis of peritonitis during peritoneal dialysis.

Ampicillin reaches a higher serum level than does tetracycline during intraperitoneal administration, partly owing to the chelation of 40% of the administered dose of tetracycline by the infusing solution and partly because of the larger distribution space for tetracycline.[13] Local prophylaxis alone is not served by the addition of ampicillin to the infusing solution, and if systemic effects are desired the antibiotic should be given in adequate doses parenterally.

SUMMARY

Seven patients with renal failure who were receiving intermittent peritoneal dialysis were studied after the administration of oxacillin, ampicillin or tetracycline. While severe renal impairment markedly prolongs the persistence in the serum of ampicillin and tetracycline, it has little effect on oxacillin. Peritoneal dialysis does not alter the special dosage requirements of these antibiotics in patients with renal disease.

Four patients who received ampicillin or tetracycline in the infusing solution during peritoneal dialysis were studied. Local prophylaxis alone is not achieved with this method of administration since small amounts of both antibiotics are absorbed systemically from the peritoneal infusing solution.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

EDUCATION AND DISCIPLINE ARE BETTER WORDS

Many neurotic patients have suffered from some form of physical trauma which constituted the occasion of their illness. Frequently this was slight, but the patient being readily open to suggestion, the tenderness and weakness which are legitimately consequent upon bodily injury, readily became permanent, and liable to great exaggeration. While the subject of heredity is doubtless a matter of great importance in the consideration of these cases, yet the fact that it is outside of our control renders the consideration and the study of their *environment* a matter of vital importance, and the development and education of the *individual personality*, a matter of supreme importance. In the study of the condition and outlook of such patients, the domestic relations, the love affairs, the advice and attitude of the medical attendant, are all potent factors; and a careful consideration may enable us to place the responsibility where it chiefly belongs. A careful analysis of the patient's state should be made in which all the avenues of the soul may have to be explored. Modern neurologists are pretty well in agreement that suggestibility especially characterizes the hysteric—a suggestibility so extreme that once an idea has taken possession of the mind there is an irresistible and automatic tendency to translate it into action. In most of the cases related it will be observed that unwholesome, foolish suggestions were largely responsible for their disabled condition and invalidism. Just as wrongful suggestions may be responsible for the course of error into which patients fall, so helpful, wise, hopeful suggestions may be, and are, available as valuable therapeutic agencies. These may be employed in the normal waking state or when the patient is hypnotized, in which latter state, the patient is acted upon rather than taught to become the actor—a state which implies that though the patient move toward betterment, yet the bracing and inspiring effects of conviction and *self*-control are absent—the control is exercised by another and consequently there is a failure to gain the *self*-control which results from self-effort. I am disposed to say that suggestion is a weak word as expressing the basis of treatment, and that we should rise to something stronger, more tonic and bracing. Suggestion seems to imply a passive state in which the patient follows indifferently and without resolve, one where the emotions hold sway. The intellect has not been grasped and convinced, and the patient moves toward the right, not because she knows it is right, but because a superior outside control, not herself, is dictating her course. Education and discipline are better words. The physician should hold himself responsible for devising means by which the invalid may be instructed and convinced of the error and therefore the folly of her ways, in order that her enlightened judgement may, under guidance, see, choose and resolutely pursue a wise course.

The approach to these patients in order to be successful should be indirect rather than direct; that is their will and judgement may not wisely be approached at first; better make it indirect by employing simple and usually physical agencies to train the will, to call it into activity gradually and in such a manner as may not arouse opposition in the patient. In my own practice I have found the physical training of the orthopedic gymnasium a potent agency in attaining this end. The particular work done in the gymnasium is not so important as that the director shall possess tact, and shall be well instructed by the physician concerning the peculiarities of each patient and the course to be followed.—B. E. McKenzie, *Canad. Med. Ass. J.*, 6: 128, 1916.