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Cyst fluid antibiotic concentrations in polycystic kidney disease: Differences between proximal and distal cysts

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Cyst fluid antibiotic concentrations in polycystic kidney disease: Differences between proximal and distal cysts. The concentrations of several antibiotics were measured in the cyst fluid of six adult patients with polycystic kidney disease. Seventy-nine cysts were aspirated at surgery or autopsy. Sixty-one cysts could be categorized as arising from the proximal nephron and 16 from the distal nephron by cyst fluid to serum sodium ratios. Serum, urine, and cyst fluid were simultaneously analyzed for sodium, creatinine, and various antibiotics. Gentamicin, tobramycin, cephapirin, and ticarcillin were either undetectable or present in low concentrations in renal cysts. Cyst fluid antibiotic concentrations did not correlate with cyst volume or creatinine clearance. Cysts of proximal nephron origin had higher antibiotic concentrations than distal cysts. In one patient with normal renal function, inulin was undetectable in renal cysts after a continuous 36-hour i.v. infusion. Para-aminohippurate, however, was detected in the renal cysts of this patient. These data help explain the poor clinical response of infected renal cysts to antibiotic therapy. They also suggest that antibiotics and other solutes may enter cyst fluid across tubular cells in addition to entry by glomerular filtration.

Concentration intra kystique d'antibiotiques dans la maladie polykystique rénale: Différences entre les kystes proximaux et distaux. Les concentrations de plusieurs antibiotiques dans le liquide des kystes ont été mesurées chez six sujets adultes atteints de maladie polykystique. Soixante dix neuf kystes ont été ponctionnés pendant des interventions chirurgicales ou des autopsies. Soixante et un kystes ont pu être classés comme proximaux et seize comme distaux en fonction du rapport de concentration de sodium kyste/plasma. Des déterminations de concentration de sodium, de créatinine et de divers antibiotiques ont été réalisées simultanément pour le plasma, l'urine et le liquide des kystes. La gentamicine, la tobramycine, la cephapirine et la ticarcilline étaient soit non détectables soit à des concentrations très faibles dans les kystes. Les concentrations d'antibiotiques dans les kystes n'étaient pas corrélées avec le volume du kyste ou la clearance de la créatinine. Les kystes proximaux avaient des concentrations d'antibiotiques plus élevées que les kystes distaux. Chez un malade dont la fonction rénale était normale l'inuline n'était pas détectable dans les kystes après une perfusion continue de 36 heures. Le para-aminohippurate, cependant, a été détecté dans les mêmes kystes. Ces résultats permettent de comprendre la réponse clinique faible des kystes infectés au traitement antibiotique. Ils suggèrent aussi que les antibiotiques ainsi que d'autres substances dissoutes peuvent pénétrer dans les kystes à travers les cellules tubulaires en sus de la pénétration par filtration glomérulaire.

Polycystic kidney disease (PCKD) is responsible for 5 to 10% of patients with end-stage renal disease in the United States [1]. When these patients develop upper urinary tract infections with involvement of their cysts, a high incidence of perinephric abscess may occur despite prolonged antibiotic therapy [2]. To explore mechanisms for the refractory nature of these infections, we evaluated cyst fluid concentrations of several antibiotics in six patients with PCKD. In one of these patients, cyst fluid concentrations of inulin and para-aminohippurate (PAH) were also evaluated following a 36-hour continuous i.v. infusion of inulin and PAH. The results help explain the poor response of infected cysts to antibiotic therapy and provide support for the concept that the renal cysts of PCKD are focal dilatations of functioning nephrons.

Methods

Cyst fluid was obtained from six patients with PCKD (Table 1). The patients ranged in age from 45 to 63 years (mean, 53.6 years). All patients had typical features of PCKD, with bilaterally enlarged cystic kidneys and positive family histories. Four patients (patients 1, 3, 4, and 6) had end-stage renal disease and were on chronic maintenance hemodialysis. Two other patients had creatinine clearances of 15 ml/min (patient 2) and 106 ml/min (patient 5).

In the four patients whose cyst fluid was aspirated during surgery, simultaneous serum and urine samples were also obtained. Patients 4 and 6 died of cerebral vascular events following cardiac surgery. Cyst fluid was obtained at autopsy performed within 6 hours of the patients' demise. As conditions allowed, an attempt was made to sample cysts throughout the kidney in an approximately equal distribution. All cysts punctured were emptied as completely as possible, and the fluid was cultured. The contents were frozen for later chemical and antibiotic determinations. Previous experiments showed that freezing did not influence the accuracy of these determinations.

Cyst fluid, serum, and urine were analyzed for sodium and creatinine (autoanalyzer, Technicon™) and several antibiotics. For clinical reasons, all patients had been receiving antibiotics in full therapeutic doses for 36 to 48 hours prior to cyst aspiration. Only patient 2 had clinical cyst infection, with cultures of aspirated fluid growing *E. coli* and *Staphylococcus aureus*, both $> 10^5$ colonies per ml. Prior urine culture had grown $> 10^5$ *E. coli* per ml. Five patients received an aminoglycoside (tobramycin or gentamicin). Patients 2, 4, and 5 also received cephapirin, and patient 6 received ticarcillin. Gentamicin and tobramycin were assayed in triplicate by a radioenzy-

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Table 1. Renal function and type of cysts aspirated in six patients with polycystic kidney disease

Patient no.	C_{Cr} *ml/min*	Aspiration (when performed)	No. of cysts aspirated	No. of prox. cysts	No. of distal cysts	No. of indeterminate cysts
1	<5	Surgery (at bilateral nephrectomy)	4	3	1	0
2	15	Surgery (at perinephric abscess)	3	2	1	0
3	<5	Surgery (at bilateral nephrectomy)	3	0	1	2
4	<5	Autopsy	36	36	0	0
5	105	Surgery (at marsupialization of cysts)	13	13	0	0
6	<5	Autopsy	20	7	13	0
Total			*79*	*61*	*16*	*2*

Table 2. Mean concentration of antibiotics in serum, urine, and cyst fluid in patients with polycystic kidney disease

Drug	No. of patients	In serum	In urine	In cyst[a]	Ratio of cyst:serum	Ratio of cyst:urine
		μg/ml				
Gentamicin	3	2.3	11	0.59 (33)	0.26	0.05
Tobramycin	2	3.7	28	0 (5)	0	0
Cephapirin	3	46.0	448	8.8 (43)	0.19	0.02
Ticarcillin	1	400.0	—	47.0 (20)	0.12	—

[a] Parentheses contain number of cysts punctured.

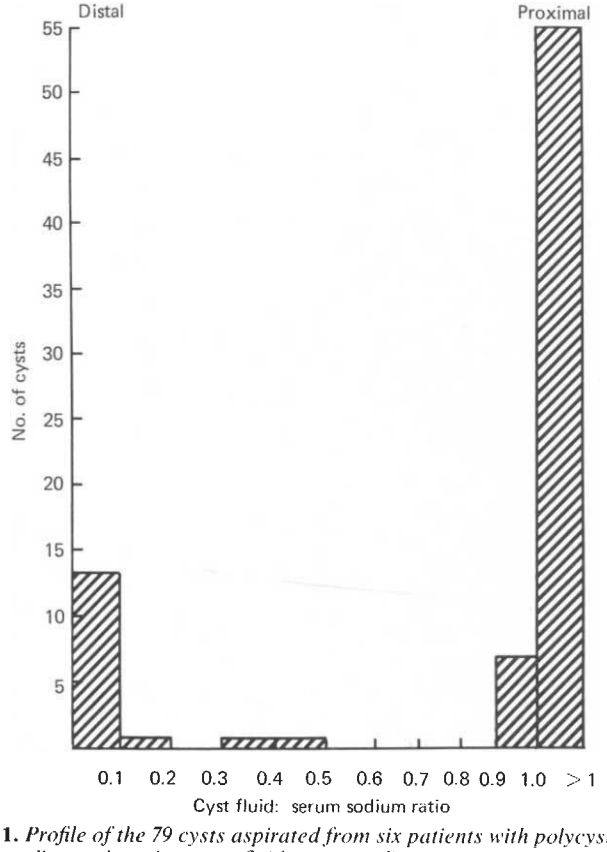

Fig. 1. *Profile of the 79 cysts aspirated from six patients with polycystic kidney disease based on cyst fluid:serum sodium ratio.*

matic-acetylation method [3]. The lower limit of assay sensitivity was 0.25 μg/ml. Cephapirin and ticarcillin were measured in duplicate by an agar microbioassay [4]. The lower limit of sensitivity of this assay was 1 μg/ml.

Table 3. Mean cyst level of gentamicin and cephapirin in the three patients receiving the drug

Drug	C_{Cr}[a] *ml/min*	In serum	In cyst[b]	Ratio of cyst:serum
		μg/ml		
Gentamicin				
patient 1	<5	3.1	1.3 (4)	0.42
patient 5	106	1.8	0.46 (9)	0.26
patient 6	<5	2.0	0.62 (20)	0.31
Cephapirin				
patient 2	15	105.0	15.5 (3)	0.15
patient 1	<5	27.0	10.6 (31)	0.39
patient 5	106	6.3	1.7 (9)	0.27

[a] No relationship between the creatinine clearance (C_{Cr}) and the cyst drug levels is apparent.
[b] Numbers in parentheses indicate number of cysts sampled.

An attempt was made to measure the cyst fluid as close to the preceding antibiotic dose as possible. Because of the logistics involved, however, samples were obtained 4 to 6 hours after the last dose, and represent trough levels of drug. For the two patients whose cysts were aspirated at autopsy, serum was drawn 3 and 6 hours, respectively, preceding cyst puncture.

In addition to antibiotics, patient 5 received an infusion of inulin and PAH starting 36 hours prior to surgery. Priming doses of inulin (0.5 ml/kg of 10% solution) and PAH (0.03 ml/kg of a 20% solution) were given i.v. followed by a continuous infusion (6.6 mg/ml for inulin and 3.3 mg/ml for PAH, at 180 ml/hr). Blood and urine were sampled every 12 hours during this infusion for inulin and PAH. At surgery, simultaneous samples of blood, urine and cyst fluid were obtained and analyzed for inulin, PAH, sodium, creatinine and antibiotics. Inulin was measured by a photometric technique [5], and PAH was measured with an autoanalyzer (Technicon™, Technicon Instruments Corp. Tarrytown, New York).

Table 4. Comparison of antibiotic levels between proximal and distal cysts

Drug	No. of patients	In serum μg/ml	In cyst fluid[a] μg/ml	
			Proximal	Distal
Gentamicin	3	2.3	1.04 (19)	0 (14)
Tobramycin	2	3.7	0 (2)	0 (3)
Cephapirin	3	46.0	8.1 (42)	38 (1)
Ticarcillin	1	400.0	135.0 (7)	0 (13)

[a] Numbers in parentheses indicate number of cysts punctured.

Table 5. Mean cyst fluid, serum, and urine concentrations of inulin and PAH following their continuous i.v. infusion over 36 hours in patient 5

	Inulin	PAH
	mg/dl	
In serum	0.78	6.30
In cyst fluid	<0.1[a]	1.44
In urine	14.00	515.00
Cyst:serum	<0.13	0.23

[a] Lower limit of assay sensitivity.

Results

A total of 79 cysts were sampled. The cyst volumes ranged from 1.5 to 967 ml. The usual cyst volume was 4 to 6 ml.

Based on cyst fluid electrolyte analysis as described by Grantham [1], the punctured cysts were separated into two groups. Those with cyst fluid:serum sodium ratios greater than 0.9 were designated as proximal nephron cysts, and those with cyst fluid:serum sodium ratios less than 0.2 were designated as distal cysts. Of the 79 cysts sampled, 61 were proximal, 16 were distal, and 2 were indeterminant (Fig. 1). Patients 4 and 5 had only proximal cysts sampled (Table 1).

The antibiotic concentrations of the renal cysts are shown in Table 2. Gentamicin, cephapirin, and ticarcillin were detected in low concentrations in the renal cysts. Tobramycin was not detected in any cyst sampled. When compared with simultaneous serum concentrations, gentamicin, cephapirin, and ticarcillin reached only 26%, 19%, and 12% of the serum levels, respectively. Patient 2 had a positive cyst fluid culture despite 48 hours of antibiotics prior to surgery. Urine culture taken at surgery grew 10^3 colonies of *E. coli* sensitive to the antibiotics the patient was receiving (tobramycin and cephapirin).

The cyst-fluid antibiotic concentration was unrelated to the measured creatinine clearance in any patient. For example, the cyst fluid:serum ratio of cephapirin and gentamicin is relatively constant despite the wide variation in creatinine clearance among patients (Table 3). The cyst fluid antibiotic concentrations likewise could not be correlated with cyst volume when multiple measurements were made from single patients.

Comparison of antibiotic levels showed differences between "proximal" versus "distal" cysts (Table 4). Gentamicin and ticarcillin were undetectable in distal cysts but could be measured in proximal cysts. Proximal cyst fluid:serum ratio was 0.45 for gentamicin and 0.34 for ticarcillin compared with 0.26 and 0.12, respectively, for these drugs in all cysts. Although cephapirin was detected in a distal cyst from one patient, the solitary observation precludes firm conclusions about the permeability of distal cysts to this drug.

Table 5 shows the cyst fluid concentrations of inulin and PAH following a continuous 36-hour infusion to patient 5. Despite the fact that serum levels were constant and sustained over the entire duration of infusion, inulin was not detected in the renal cysts in concentrations detectable by the chemical assay. PAH, however, was present in cyst fluid in a percentage similar to that obtained with the antibiotics.

Discussion

The poor clinical response to antibiotic therapy in patients with infected polycystic kidneys is probably related to the poor concentration of antibiotics achieved in the cysts. Resistent microorganisms, anaerobic infections, and mechanical factors such as poor drainage may also play a role. It is possible that other antibiotics might demonstrate better cyst concentrations than those tested in this study. But, the drugs represent examples from commonly prescribed classes of antibiotics used for serious urinary tract infections. The role of active inflammation in altering antibiotic penetration into cysts requires further investigation. The duration of antibiotic treatment prior to cyst puncture was relatively short. More prolonged therapy might improve concentrations achieved in cyst fluid, but serious delays in control of bacteremia might be anticipated. Furthermore, the potential for drug accumulation in patients with severe renal failure might preclude use of doses required to maximize diffusion into cyst fluid. Despite greater than 2 weeks of antibiotic therapy, Sweet and Keane reported failure to sterilize cyst fluid infection, as evidenced by subsequent development of perinephric abscess. Although the concentrations of antibiotics in individual cysts might occasionally exceed the minimum inhibitory concentrations necessary for very sensitive organisms, the variability is too great to ensure clinical efficacy.

To explain the mechanism of low antibiotic levels in renal cysts, one must consider the nature of these cysts and the pathophysiology of cyst growth. Most authors regard the cysts of PCKD as massively dilated segments of nephrons [1, 6, 7]. The microdissection studies of Lambert [8] and Osathanondh and Potter [9] show that cysts of tubular origin appear to communicate proximally with glomeruli, and distally with the renal pelvis. The functional nature of cystic nephrons has been emphasized by the work of Gardner [6] and Huseman et al [10], demonstrating characteristic solute concentrations in cysts arising from different nephron segments. Studies by Jacobsson et al [11] using i.v. tritium have further characterized cyst function by measuring fluid turnovers of greater than 100ml/day in

individual cysts. Thus, cysts can be defined as focal dilatations of functioning nephrons, retaining the transport characteristics of the segment from which they arise [7].

The cysts of PCKD probably arise originally either because of distal intratubular obstruction to urine flow [12, 13] or because of an inherent defect in the basement membrane of the various nephron segments [1]. The mechanism of continued cyst growth is less clear. Bricker and Patton [14] and Lambert [8] considered glomerular filtration as the primary mechanism by which solutes enter the cysts of PCKD. These investigators demonstrated the appearance of inulin in cysts following short-term parenteral administration. These studies used single parenteral injections of large quantities of inulin resulting in peak plasma inulin concentrations from 100 to 150 mg/dl. Under these circumstances, measurable amounts of inulin were found in fluid from some cysts [8, 14]. The present study did not demonstrate measurable inulin in renal cysts, despite a constant 36-hour i.v. infusion. Plasma concentrations were, however, considerably less than those in earlier studies. Bricker and Patton also found considerable inulin-like material when assaying cyst contents prior to administration of inulin. Thus, the single high dose of inulin and the presence of material acting as an inulin blank may account partially for the apparent discrepancy [14]. If one considers, however, that the single nephron glomerular filtration rate in man is approximately 10^{-8} liters/min, 15 to 20 years are required for a cyst to reach its typical volume of 0.3 to 5.0 ml. It is therefore difficult to explain the reported concentrations of administered inulin in renal cysts by glomerular filtration alone. Although these considerations do not exclude a role for glomerular filtration in long-term cyst growth, they do suggest that the antibiotics that are usually quantitatively filtered at the glomerulus, such as aminoglycosides, and that appear in cysts within 36 to 48 hours of treatment, probably enter the cyst by some other means. This is further supported by our findings that dissociate the cyst fluid:serum ratio of cephapirin and gentamicin from the measured creatinine clearance.

Active or passive transport of solutes across cyst wall epithelium probably plays some role in cyst growth. Gardner has suggested that large molecular weight substances may be transported into cysts where they break down, becoming osmotically active. This might serve as a stimulus to fluid transport [6]. Grantham proposed that organic acids such as hippurate may be actively secreted by the epithelial cells of the cyst wall [1]. Our demonstration of PAH concentrations in renal cysts, which are 23% of simultaneous serum levels, despite dilution by relatively large cyst volume [8], is consistent with better penetration of molecules that usually undergo active net transtubular secretory transport. The penicillin and cephalosporin group of antibiotics fall into this category.

The differences in antibiotic concentrations between proximal and distal cysts lend further support for preservation of functional capacity of the epithelium lining these two populations of cysts. The poor antibiotic penetration in distal cysts suggests that the epithelium lining these cysts is less permeable, or has less secretory capacity, than does the epithelium lining the proximal cysts.

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