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Trimethoprim-sulfamethoxazole in cyst fluid from autosomal dominant polycystic kidneys

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Trimethoprim-sulfamethoxazole in cyst fluid from autosomal dominant polycystic kidneys. Cyst infection in patients with autosomal-dominant polycystic kidney disease (ADPKD) is often refractory to therapy, in part because of the limited entry of commonly used antibiotics into cyst fluid. To study the efficacy of trimethoprim-sulfamethoxazole in cyst infection, cyst fluid was obtained by percutaneous aspiration or at surgery from eight patients with ADPKD receiving trimethoprim-sulfamethoxazole. Cysts were categorized as nongradient or gradient by cyst-fluid sodium concentration. Trimethoprim-sulfamethoxazole concentrations within cysts were determined and cyst fluid inhibitory and bactericidal titers were assessed in vitro against *Escherichia coli*, *Proteus mirabilis* and *Streptococcus fecalis*. The mean cyst fluid trimethoprim and sulfamethoxazole concentrations were 15.2 μg/ml and 42.5 μg/ml, respectively. Preferential accumulation of trimethoprim was observed in gradient cysts, exceeding serum levels more than eightfold. Sulfamethoxazole penetrated cysts to a lesser extent, with concentrations ranging from 10 to 70 percent of the serum level. Cyst fluid sampled prior to trimethoprim-sulfamethoxazole administration (control) demonstrated no antibacterial activity, while cyst fluid inhibitory and bactericidal titers following antibiotic administration were 1:32 or greater in most instances. These studies indicate that trimethoprim-sulfamethoxazole is likely to be efficacious in the treatment of cyst infection in polycystic kidneys.

Autosomal-dominant polycystic kidney disease (ADPKD) is a common hereditary condition characterized by bilaterally enlarged kidneys due to the presence of multiple fluid-filled cysts of varying size. Urinary tract infection is a frequent occurrence in patients with ADPKD [1–6]. While the precise incidence of infectious involvement of the cysts themselves is unknown, this complication is often refractory to standard antimicrobial therapy, resulting in considerable morbidity [6–8]. One possible reason for the difficulty in eradicating cyst infection is the failure of many antibiotics to achieve therapeutic concentrations within cyst fluid [9]. Whether local factors within the cyst environment (such as pH) modify the acitivty of antibiotics is unknown.

A previous study from our institution has shown that "therapeutic" levels of trimethoprim-sulfamethoxazole can be achieved in the cyst fluid of patients with ADPKD despite the presence of renal dysfunction [10]. In the present study we measured trimethoprim-sulfamethoxazole concentrations in cyst fluid from patients (7 noninfected, 1 infected) receiving the drug and also evaluated the antibacterial activity of such fluid in vitro against common urinary tract pathogens, representative of those most frequently involved in cyst infection. This is the first study to report cyst fluid bactericidal titers as a means of evaluating potential antibiotic efficacy of drugs used for the treatment of cyst infection.

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Methods

Patients

Six men and two women with a mean age (±SE) of 44±4 years who had ADPKD were studied. All patients had typical features of the disease including bilaterally enlarged cystic kidneys and a positive family history. After giving informed consent, glomerular filtration rate was estimated by endogenous creatinine clearance, inulin clearance, or technetium-99m diethylenetriamine pentaacetic acid (DTPA) clearance. One patient had normal renal function, four had variable degrees of renal insufficiency, and two were on chronic dialysis for end-stage renal failure. In addition, one patient who had received a successful kidney transplant required removal of her solitary polycystic kidney nine weeks postoperatively because of persistent renal infection. Her other polycystic kidney had been removed one year prior to transplant for similar reasons. Characteristics of the patient population are shown in Table 1.

Antibiotic administration

All patients were given trimethoprim-sulfamethoxazole. In the seven noninfected patients, 160 mg trimethoprim and 800 mg sulfamethoxazole was administered orally twice daily as a combined preparation for periods of 3 to 40 days (mean ± SE = 12 ± 4 days). The only infected patient (patient 1) received 180 mg trimethoprim and 900 mg sulfamethoxazole, as well as 1000 mg ampicillin, intravenously every 6 hours for 17 days as treatment for a presumed cystic kidney infection characterized by fever, flank pain, and positive blood and urine cultures growing *Escherichia coli*.

Table 1. Patient profile and types of cysts sampled

Patient no.	Age/sex	GFR *ml/min*	Circumstances of aspiration	Number of cysts aspirated following TMP-SMX treatment			Duration of treatment *days*
				Nongradient	Gradient	Indeterminate	
1	51/F	33 (allograft)	Unilateral nephrectomy for persistent infection following successful renal transplant	17	1	0	17
2	42/M	Dialysis	Pretransplant bilateral nephrectomy	13	19	7	3
3	44/M	70	Symptomatic; percutaneous aspiration	1	1	0	40
4	32/F	83	Symptomatic; cyst marsupialization	4	0	5	8
5	39/M	39	Symptomatic; percutaneous aspiration	2	1	1	7
6	54/M	20	Symptomatic; percutaneous aspiration	5	0	0	7
7	32/M	Dialysis	Symptomatic; percutaneous aspiration	3	1	1	7
8	61/M	34	Symptomatic; percutaneous aspiration	1	1	1	7
Subtotal				46	24	15	
percent of total				54	28	18	

Collection of samples

Cyst fluid was obtained by ultrasound-guided aspiration of 3 to 8 large cysts with a 22 gauge needle (5 patients) or at surgery (3 patients). Fluid obtained at surgery was principally from superficial (subcapsular) cysts, although deeper cysts were also aspirated through the cavities of unroofed superficial cysts. Patients underwent either procedure for indications unrelated to this study (Table 1). Cyst fluid was obtained from two patients at the time of nephrectomy for presumed cystic kidney infection (patient 1) or pretransplant preparation due to a history of recurrent, urinary tract infection (patient 2). Cysts from the remaining patients were sampled at the time of cyst decompression for the management of pain [11]. There were no complications of cyst aspiration or surgical removal of the kidneys. Serum samples were obtained as close to the time of aspiration or surgery as possible, usually within 15 to 30 minutes. An aliquot of cyst fluid was incubated on a blood agar plate to screen for contamination by aerobic bacteria. In addition, cyst fluid from patient 1 was cultured for anaerobic bacteria, aerobic bacteria and fungi on appropriate media. The remaining fluid was stored at −70°C in tightly capped glass vials for later analysis.

Six months following surgery for cyst aspiration, patient 4 underwent repeat aspiration following 320 mg trimethoprim and 1600 mg sulfamethoxazole given intravenously 12 hours and 3 hours prior to cyst sampling. Analysis of six cysts derived from this patient are considered separately.

Analysis of cyst fluid

Cyst fluid sodium concentrations were measured by flame photometry (KLiNa Flame, Beckman Instruments, Inc., Fullerton, California, USA). Cyst fluid sodium concentrations greater than 100 mEq/liter were designated as "non-gradient" cysts and cysts with values less than 20 mEq/liter were categorized as "gradient" cysts. Cysts with sodium concentrations between 20 and 100 mEq/liter or with insufficient volume for sodium determination were designated as "indeterminate." Trimethoprim in cyst fluid and serum was assayed in duplicate by an agar bioassay [12], with a lower limit of sensitivity of 1 μg/ml. For the trimethoprim assay paraaminobenzoic acid and thymidine phosphorylase were added to the medium to give a final concentration of 100 μg/ml and 0.1 IU/ml, respectively. Paraaminobenzoic acid was added to inhibit the effect of sulfamethoxazole while thymidine phosphorylase was added to inactivate any residual thymidine present in the medium. Samples containing ampicillin from patient 1 were pre-treated with penicillinase (Difco) to give a final concentration of 1600 U/ml. Sulfamethoxazole concentrations were determined by the chemical method of Bratton and Marshal [13]. Only the free (therapeutically active) sulfonamide, and not the conjugated compound, was measured, with detectable levels above 0.2 μg/ml. The presence of other antimicrobials in the specimen did not interfere with the chemical assay for sulfonamides. Cyst fluid trimethoprim-sulfamethoxazole concentrations are reported as the mean ± SE, and concentrations in gradient versus nongradient cysts were compared utilizing the Mann-Whitney u-test for nonparametric data. Significance was defined as $P < 0.05$.

In vitro assessment of cyst fluid activity

In six of the eight patients (patients 3 to 8) fluid was also obtained by percutaneous aspiration from 1 to 3 cysts prior to the administration of trimethoprim-sulfamethoxazole. Cyst fluid inhibitory and bactericidal titers were determined by serial macrobroth dilution, both before (control) and after trimethoprim-sulfamethoxazole treatment, against standard test organisms *Escherichia coli*, *Proteus mirabilis* and *Streptococcus fecalis*, common pathogens in urinary tract infection. The method used is similar to the serum inhibitory and bactericidal titer [14], except that cyst fluid was tested instead of serum. The inhibitory titer was taken as the maximal dilution of the cyst fluid that inhibited growth of the organism. The bactericidal titer represented the maximal dilution of the cyst fluid which provided 99.9% killing of the organism. The minimum inhibitory concentrations (MICs) of trimethoprim and sulfamethoxazole alone against these organisms were as follows: *Escherichia coli*, 0.31 and 4.7 μg/ml; *Proteus mirabilis*, 0.74 and 3.8 μg/ml, respectively, and *Streptococcus fecalis*, 0.35 μg/ml (trimethoprim only). The MICs of the combination of trimethoprim/sulfamethoxazole were as follows: *Escherichia coli*, 0.051/0.94 μg/ml; *Proteus mirabilis*, 0.028/0.56 μg/ml; *Streptococcus fecalis*, 0.10/1.84 μg/ml.

Table 2. Mean cyst fluid trimethoprim-sulfamethoxazole concentrations ($\mu g/ml$)

	Trimethoprim	Sulfamethoxazole
Total	15.2 ± 3.2[a] (40)	42.5 ± 2.4 (85)
cyst/serum	3.9 ± 1.3	0.43 ± 0.03
Nongradient	11.9 ± 2.7 (31)	52.6 ± 3.6 (46)
cyst/serum	2.6 ± 0.6	0.46 ± 0.03
Gradient	42.8 ± 17.0[a] (4)	24.6 ± 2.0 (24)
cyst/serum	8.5 ± 3.0	0.36 ± 0.09
Indeterminate	13.8 ± 9.6 (5)	39.9 ± 2.8 (15)

Numbers in parentheses indicate the number of cysts sampled
[a] Excludes single gradient cyst with trimethoprim concentration = 216 $\mu g/ml$

Results

Among the eight patients, fluid was sampled from a total of 96 cysts, 11 cysts prior to trimethoprim-sulfamethoxazole administration and 85 cysts following treatment. All cysts were sterile, including those from patient 1 who was receiving trimethoprim-sulfamethoxazole for clinical cyst infection. Of the 11 cysts aspirated prior to trimethoprim-sulfamethoxazole therapy, 7 were nongradient, 3 were gradient and 1 was indeterminate. Those cysts sampled during or after antibiotic administration included 46 nongradient, 24 gradient and 15 indeterminate (Table 1). In 44 cysts the trimethoprim concentrations were not performed, including the 39 cysts from patient 2. In addition, the volume of fluid from some cysts was insufficient to perform comprehensive analysis, accounting for the fact that complete data are unavailable for all cysts.

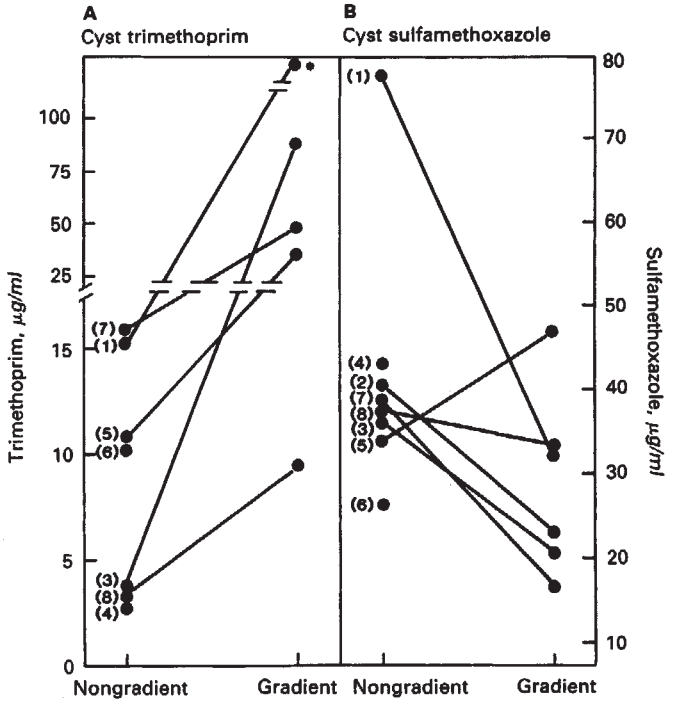

Fig. 1. *Cyst fluid trimethoprim-sulfamethoxazole concentrations.* **A.** Mean trimethoprim concentrations. **B.** Mean sulfamethoxazole concentrations. In both panels lines connect mean "nongradient" and "gradient" cyst antibiotic levels for each patient. Two patients had no "gradient" cysts samples. ( ) denotes the patient number from Table 1. Patient 2 did not have trimethoprim determinations. * represents a single cyst with trimethoprim = 216 μg/ml.

Cyst fluid trimethoprim-sulfamethoxazole concentration

Antibiotic concentrations in nongradient, gradient and indeterminate cysts are shown in Table 2. The average trimethoprim concentration in cyst fluid was 15.2 ± 3.2 μg/ml (N = 40). This excludes a single gradient cyst with a concentration of 216 μg/ml since this value was greater than two standard deviations from the mean. When compared to simultaneous serum trimethoprim concentrations, the mean cyst/serum ratio for all subjects was 3.9 ± 1.3. Cyst/serum trimethoprim ratios for all cysts showed a wide range, however, extending from 0.5 to 15.3. The mean cyst/serum ratio of trimethoprim in nongradient cysts was 2.6 ± 0.6, while that in gradient cysts was 8.5 ± 3.0.

Compared with trimethoprim, cyst/serum sulfamethoxazole ratios were consistently lower with an average value of 0.43 ± 0.03 ($P < 0.005$). The range for individual cyst concentrations was 10 percent to 70 percent of the serum sulfamethoxazole concentration. In nongradient cysts there was a mean cyst/serum ratio for sulfamethoxazole of 0.46 ± 0.03. In gradient cysts the average sulfamethoxazole cyst/serum ratio was 0.36 ± 0.09. Figure 1 shows each patient's mean trimethoprim and sulfamethoxazole concentrations in nongradient and gradient cysts. Preferential accumulation of trimethoprim in gradient cysts compared to nongradient cysts is evident, the difference being significant ($P < 0.005$). In contrast, sulfamethoxazole accumulation is significantly less in gradient cysts than in nongradient ones ($P < 0.001$).

Concentrations of trimethoprim and sulfamethoxazole were well above the MIC for the test organisms *E. coli*, *P. mirabilis* and *S. fecalis* in all cysts sampled. Cyst fluid levels of both drugs could not be correlated with the measured glomerular filtration rate. In fact, excellent concentrations were achieved in all patients, including those on dialysis. Likewise, the antibiotic concentrations in cyst fluid were unrelated to the duration of treatment over the 3 to 40 day range. Instead, adequate levels were achieved within a short time. In this regard patient 4, who underwent repeat cyst marsupialization 6 months following the initial procedure, had trimethoprim-sulfamethoxazole levels exceeding the MIC for *E. coli*, *P. mirabilis* and *S. fecalis* in all 6 cysts within 12 hours of instituting treatment. In this patient, cyst/serum trimethoprim and sulfamethoxazole ratios were 0.49 ± .03 and 0.40 ± .03, respectively.

Cyst fluid inhibitory and bactericidal titers

Cyst fluid inhibitory and bactericidal titers both before and during trimethoprim-sulfamethoxazole administration are summarized in Figure 2. With the exception of the single cyst from patient 7, fluid sampled from 11 cysts prior to trimethoprim-sulfamethoxazole administration showed no in vitro antibacterial activity against the common urinary tract pathogens *E. coli*, *P. mirabilis* and *S. fecalis* as both the cyst fluid inhibitory and bactericidal titers were consistently less than a 1:2 ratio for these organisms. Patient 7 had recently received an unknown antibiotic for an upper respiratory infection prior to cyst sam-

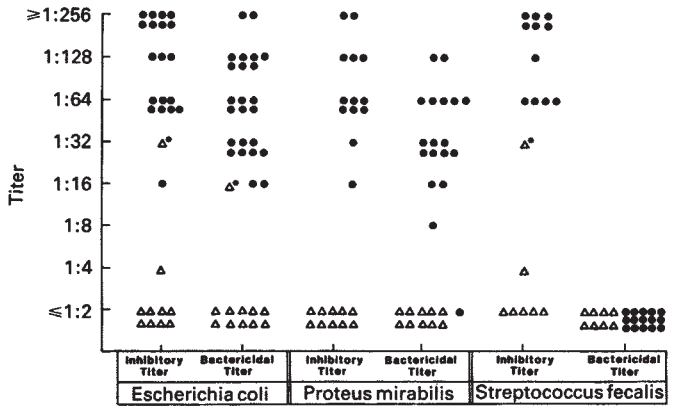

Fig. 2. *Cyst fluid inhibitory and bactericidal titers versus Excherichis coli, Proteus mirabilis and Streptococcus fecalis.* Each data point represents fluid from a singl cyst. Symbols are: (△) fluid sampled prior to trimethoprim-sulfamethoxazole administration; (●) fluid sampled following trimethoprim-sulfamethoxazole adminstration; (*) a single cyst from patient 7 who had recently received another antibiotic prior to sampling.

pling, which may explain the observed antibacterial activity of that single cyst fluid sample.

Following trimethoprim-sulfamethoxazole administration fluid from all cysts evaluated demonstrated excellent inhibitory activity against the three organisms, with a titer usually in excess of 1:32. In a few instances the turbidity of the cyst fluid precluded determination of the inhibitory titer. With one exception, adequate cyst fluid bactericidal titers also were achieved against *E. coli* and *P. mirabilis*, being greater than or equal to 1:32 in most instances. In one cyst the fluid bactericidal titer against *P. mirabilis* was less than 1:2. Since the concentrations of both trimethoprim and sulfamethoxazole in that cyst were comparable to those in other cysts, the reason for the lack of bactericidal activity is unclear and may represent a technical artifact. While demonstrating inhibitory activity, cyst fluid obtained following trimethoprim-sulfamethoxazole was not bactericidal against *S. fecalis*. Fluid from the six cysts sampled from patient 4 following 12 hours of treatment already demonstrated adequate inhibitory and bactericidal titers against *E. coli* and *P. mirabilis*, equaling or exceeding 1:16 in most cysts (data not included in Fig. 2).

Discussion

It is conservatively estimated that between 50 and 70 percent of all patients with ADPKD will experience at least one clinical urinary tract infection during the course of their disease [1, 3, 4]. When upper urinary tract infection with cyst involvement occurs, eradication of the infection is often unsuccessful despite prolonged antibiotic therapy. This may lead to the development of perinephric abscess necessitating surgical drainage or nephrectomy in a high percentage of cases. Over a 42 month period, Sweet and Keane observed 8 of 24 patients with ADPKD undergoing chronic hemodialysis who developed symptomatic urinary tract infection [6]. Despite prompt and prolonged treatment with appropriate antibiotics, five patients subsequently developed perinephric abscess. Three of these patients died. Similarly, antibiotic therapy failed in four of five patients with infected polycystic kidneys reported by Waters, Hershman and Klein [8]. These reports underscore the therapeutic difficulties and adverse consequences of infection in polycystic kidneys. Whether infection also enhances cyst formation and accelerates the deterioration of renal function is unclear [15].

While difficult to document in the literature, it is thought that cyst infection is ususally caused by common urinary tract pathogens, by the ascending route, following lower urinary tract colonization. Thus, *Escherichia coli* and other enteric organisms can be anticipated. Data by Schwab confirms this clinical impresssion [16].

Most antibiotics penetrate polycystic cysts poorly, which may account for the refractory nature of cyst infections. Muther and Bennett observed low or absent cyst fluid accumulation of representative members of the aminoglycoside, penicillin, and cephalosporin classes of antibiotics [9].

Several studies have indicated that the cysts in ADPKD are focal dilations of nephron segments whose epithelial lining maintains many of the functional and histologic properties of the nephron segment of origin [17–20]. This has allowed for the identification of two different populations of cysts [17, 19]. "Nongradient" cysts have fluid with sodium concentrations and pH approximating that of plasma and are felt to arise from proximal tubular segments. In contrast, "gradient" cysts are able to maintain steep transepithelial electrolyte gradients resulting in fluid with a low sodium concentration and a high hydrogen ion concentration similar to the distal tubular environment. This distinction has clinical relevance in terms of antibiotic accumulation within the cysts. Schwab et al documented cyst fluid concentrations of clindamycin, a nonpolar and lipid-soluble agent, to be inversely related to cyst fluid pH [21]. They proposed that high accumulations in the acidic environment of gradient cysts was due to non-ionic diffusion and ion trapping and predicted similar behavior with other lipid-soluble antibiotics with high pKa values.

In the present study we have documented that trimethoprim-sulfamethoxazole, a lipophilic agent with an alkaline pKa, consistently achieves therapeutic concentrations within the cyst fluid of polycystic kidneys. Excellent concentrations of trimethoprim were attained in both gradient and nongradient cysts, with enhancement over serum levels of almost fourfold. Preferential accumulation of trimethoprim was observed in gradient cysts where levels exceeded those in serum by more than eightfold. In contrast, sulfamethoxazole entered both nongradient and gradient cysts in concentrations less than those achieved in serum, being 46 percent and 36 percent, respectively, of the serum level. The efficacy of trimethoprim-sulfamethoxazole for cyst infection was further demonstrated by in vitro determination of the bacteriostatic and bactericidal properities of the cyst fluid derived from ADPKD patients receiving the drug. Fluid obtained from both nongradient and gradient cysts prior to antibiotic administration showed no intrinsic antibacterial activity. Fluid obtained following trimethoprim-sulfamethoxazole administration consistently demonstrated adequate inhibitory and bactericidal titers against the standard test organisms. Such assays provide a more comprehensive analysis which takes into account the interaction between the antibiotic and local factors within the cyst environment. While not previously employed in this setting, such assays have been

used extensively in patients with infective endocarditis [22, 23]. In that setting, serum bactericidal titers of 1:8 or greater are generally regarded as satisfactory and usually indicate an adequate drug regimen. In one respect the current study does not mimic the clinical setting in that cyst infection was not present. Thus, we have not excluded a potential role for active inflammation in altering antibiotic penetration and activity within cysts as well as the antibiotic sensitivities peculiar to a particular infecting organism. In addition, we have not determined the efficacy of trimethoprim and sulfamethoxazole alone relative to their combined presence. Therefore, the observed antibacterial properties of the cyst fluid may have been due, in large part, to the activity of trimethoprim which was present in high concentrations in all cysts. While the cyst fluid concentration of trimethoprim was consistently above the MIC for most trimethoprim-sulfamethoxazole susceptible organisms [24], with sulfamethoxazole this was less reliable. In this regard, failure to achieve cyst sterilization has been reported in a patient infected with a trimethoprim-resistant *E coli* [25]. Even when in vitro sensitivities predict cure with trimethoprim-sulfamethoxazole, occasional therapeutic failures may occur. In this situation, other lipid soluble agents such as chloramphenicol or ciprofloxacin may be useful [26, 27].

In summary, trimethoprim-sulfamethoxazole with its favorable aerobic gram-negative spectrum is likely to be efficacious in the treatment of most cyst infections due to common urinary tract pathogens. This is based on drug concentrations achieved in both proximal and distal cysts, as well as in vitro assessment of cyst fluid antibacterial activity. This appears to be true even in patients with far advanced renal-insufficiency. Cyst fluid inhibitory and bactericidal titers represent a novel approach to the evaluation of potentially useful drugs for cyst infection and may prove useful in predicting the therapeutic response of patients with infected cysts.

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