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Benefit from high intrarenal levels of gentamicin in the treatment of *E. coli* pyelonephritis

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Benefit from high intrarenal levels of gentamicin in the treatment of *E. coli* pyelonephritis. The importance of high intrarenal levels of gentamicin on the outcome of experimental pyelonephritis was studied in rats receiving either a short course (three days) of gentamicin (G) alone or combined with a longer course (14 days) of ampicillin (A), cephalothin (C), or trimethoprim (T), or two weeks of therapy with ampicillin, cephalothin, trimethoprim and gentamicin given alone. While ampicillin, cephalothin and trimethoprim were undetectable in the medulla within six hours of cessation of therapy, gentamicin was still detectable in levels six folds above the MIC up to six months after treatment had ceased. Six months after the end of treatment, the percentage of sterile left kidneys in animals treated with ampicillin (50%), cephalothin (15%), trimethoprim (20%) was lower than the percentage of animals receiving 14 days of gentamicin (100%), or the combinations AG:89%, CG:67% and TG:60%, $P < 0.01$. Following three days of gentamicin, 50% of the left kidneys were sterilized. When compared to ampicillin, cephalothin or trimethoprim alone, combined therapies significantly reduced the number of CFU in the kidneys $P < 0.01$. These combinations were almost as effective as two weeks of therapy with gentamicin. Short–term therapy (three days) with an aminoglycoside which concentrates in the renal parenchyma, combined with an antibiotic which will accumulate in other parts of the nephron, may result in "pharmacological synergy". This new approach to therapy of pyelonephritis may be promising.

In the last ten years, new approaches to the management of lower urinary tract infections have been evaluated, but no major innovation has been suggested for the treatment of pyelonephritis. The unique capacity of gentamicin and other aminoglycosides to accumulate within the kidneys of humans and animals has been known for many years [1, 2], but only in rare instances have investigators tried to study the pharmacokinetic behavior of these antibiotics in infected renal parenchyma [3], or to correlate intrarenal distribution of these antibiotics with their therapeutic efficacy in pyelonephritis [4–6]. Previous investigations have revealed that gentamicin appeared to be superior to ampicillin and trimethoprim–sulfamethoxazole in the treatment of experimental pyelonephritis [7]. More so, several studies have recently described the remarkable efficacy of gentamicin used in combination with ampicillin [7, 8] in renal infections.

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The purpose of the present study was to evaluate, over a period of six months, the intrarenal distribution and the comparative efficacy of short and long–term therapy with ampicillin, cephalothin, trimethoprim, and gentamicin administered alone or in combination for the treatment of acute pyelonephritis in rats.

Methods

Animal experiments

Female Sprague–Dawley rats weighing 175 to 200 g were used for all experiments. Pyelonephritis was induced by direct injection of the left kidney with 0.1 ml of an inoculum containing 10^7 to 10^8 CFU of *Escherichia coli* Yale strain [5]. The bacteria were injected directly into the medulla through the upper and lower poles of the kidney, as described by Kaye [9]. This inoculation produced two kinds of infection: a severe pyelonephritis of the left kidney, with extensive inflammation and abscess formation induced by the inoculation, and a less severe pyelonephritis of the right kidney, with few foci of inflammation and slight swelling of the organ due to reflux of infected urine into the right ureter and kidney, rats being naturally prone to vesico-ureteral reflux. Treatment was started 24 hours after inoculation and the rats were divided into eight groups. The amount of drug given was based on previous observations in rats which demonstrated that the doses given resulted in serum concentrations which were considered as "equivalent" to those observed in humans. Eight groups of 50 to 55 rats were given the therapeutic regimens summarized in Table 1. In each group, 2/3 of the animals were evaluated for bacterial outcome while 1/3 were used to determine the concentration of drugs in the kidney parenchyma. Rats were sacrificed at 1, 2, 4, 6, 24 hours and on day 25, and six months after therapy.

Rats were anaesthetized with pentobarbital (dose, 50 mg/kg) 75 minutes before sacrifice. Fifteen minutes after the anaesthesia, the bladder was emptied by suprapubic puncture. When the animals were killed, the urine from each animal was collected for determination of drug concentration and bacterial content. Then, a midline abdominal incision was made and both kidneys were extracted. The kidneys used to determine drug concentrations were removed from their capsule and slit by a longitudinal incision. Under a dissecting microscope, the kidneys were separated into cortical, medullary, and papillary components. Each entire cortex, medulla and papilla was weighed individually, diluted in a volume of phosphate buffer solution three

Table 1. Treatment regimen given 24 hours after the induction of pyelonephritis due to E. coli in rats

Treatment	Dose	Time
Ampicillin	100 mg/kg Q6H	14 days
Cephalothin	50 mg/kg Q6H	14 days
Trimethoprim	10 mg/kg Q12H	14 days
Gentamicin	10 mg/kg Q12H	14 days
Gentamicin	10 mg/kg Q8H	3 days
Ampicillin–Gentamicin	100 mg/kg Q6H–10 mg/kg Q8H	14 days—3 days
Cephalothin–Gentamicin	50 mg/kg Q6H–10 mg/kg Q8H	14 days—3 days
Trimethoprim–Gentamicin	10 mg/kg Q12H–10 mg/kg Q8H	14 days—3 days
Controls	0.9% NaCl	14 days

times the weight of the cortex and medulla and 12 times that of the papilla (pH 7.4), and homogenized at 4°C with a Dyna-Mix homogenizer (Fisher Scientific, Pittsburgh, Pennsylvania, USA). Once homogenized, the samples were analyzed for concentrations of ampicillin, cephalothin, trimethoprim, and gentamicin. The kidneys used for bacterial counts were also removed from their capsule but not dissected into cortex, medulla and papilla. The kidneys were homogenized in 3 ml of 0.9% NaCl with the use of the Dyna-Mix homogenizer (Fisher); the number of *E. coli* present in each sample was then determined.

Drug levels

The concentrations of ampicillin [5], cephalothin, trimethoprim [10], and gentamicin [6] were estimated as described before in the serum, urine, cortex, medulla, and papilla. Concentrations were determined with the use of a standard filter-paper disk agar diffusion assay [2]. Standard solutions were prepared in serum for assays of drug in serum, in 0.9% NaCl for urine, and in homogenates of cortex, medulla, and papilla for renal tissue. The determination of ampicillin, cephalothin, and gentamicin was made on Tryptic Soy Agar inoculated with *Bacillus subtilis* as the test organism, and trimethoprim was determined on Iso-Sensitest Agar inoculated with *Bacillus pumilus*.

Recovery of the antimicrobial agents, after the addition of drug-free homogenates of cortex, medulla, and papilla to known concentrations of antibiotics was 94 ± 6% for ampicillin, 91 ± 4.3% for cephalothin, 93 ± 6% for trimethoprim, and 98 ± 1.6% for gentamicin (mean ± SEM).

Efficacy in vitro

For the strain of *E. coli* used, the MICs in μg/ml were 3.9 for ampicillin, 6.2 for cephalothin, 0.35 for trimethoprim, and 1.6 for gentamicin. Time–killing curve technique [11] was used to determine whether or not ampicillin, cephalothin, and trimethoprim were synergistic when combined with gentamicin. An overnight inoculum of *E. coli* Yale strain was diluted to 10^5 to 10^6 organisms per ml with Mueller Hinton Broth. Antibiotics were added to make a final concentration of one half the MIC for each drug. Undiluted or diluted samples were removed initially and at 1, 2, 4, 6, and 24 hours plated on MacConkey agar, and incubated at 37°C. Colony counts were performed 24 hours after incubation. Synergy was defined as > 100-fold increased killing at 24 hours by both drugs, as compared to the single most effective drug alone.

Efficacy in vivo

Appropriate dilutions of urine and homogenized kidneys were made, and 0.1 ml of the sample was placed in each of three pour plates containing MacConkey's agar. The number of CFU of *E. coli* in the urine and kidneys was determined after an incubation of 18 hr at 37°C. To prevent the inhibition of growth that could occur if gentamicin was still present in the tissue, sodium polyanetholsulfonate (2.0%), was added to the pour plates. This compound could inhibit more than 1,200 μg of gentamicin/g of tissue in the renal homogenate. This technique allowed us to detect a minimum of 10 CFU/ml of urine and 30 CFU/g of renal tissue. Urine specimens or kidneys were considered sterile if no CFU was detected by this technique.

Statistical methods

Statistical comparison of the incidence of sterilization between single and combination therapy was done by means of the χ^2 test with Yates' correction. The differences in the log number of CFU/g of tissue in the kidneys between single therapies and their respective combinations were compared for significance by Mann–Whitney test using normal two-tail approximation.

Results

Renal levels of antibiotics

The concentrations of ampicillin, cephalothin, trimethoprim, and gentamicin in the cortex, medulla, and papilla of infected kidneys are shown in Figure 1. Gentamicin was still detectable in the medulla up to six months after two weeks of therapy, and up to 25 days following 3 days of treatment. Ampicillin, cephalothin, and trimethoprim could not be detected in the infected cortex and medulla for more than six hours. With the exception of trimethoprim which was still detectable in the cortex at six hours, both cephalothin and ampicillin were below MIC within four hours of the injection. Furthermore, with the exception of gentamicin given for 14 days, none of the drugs was detectable in the papilla 24 hours after the last injection. The concentrations of gentamicin in the papilla were always lower than those found in the cortex and medulla.

As shown in Table 2, serum levels were equivalent to those observed in humans. At six hours, none of the serum had any demonstrable antibiotic activity. Urinary levels of ampicillin, cephalothin, and trimethoprim were undetectable at 24 hours after cessation of therapy while high levels of gentamicin were still detectable at that time. The ratios of the concentrations of drug in the cortex and the medulla to the respective MICs of the antimicrobial agents against the *E. coli* are presented in Figure 2. Gentamicin and trimethoprim exhibited higher peak ratios in the kidney than ampicillin and cephalothin. The time during which the *E. coli* in the kidney was exposed to significant concentrations of drugs can be observed in Figure 2. Following 14 days of gentamicin, the bacteria were continuously exposed to the drug for more than six months after the end of treatment. More so, both in the cortex and the medulla, *E. coli* was exposed to concentrations above MIC for at least 25 days

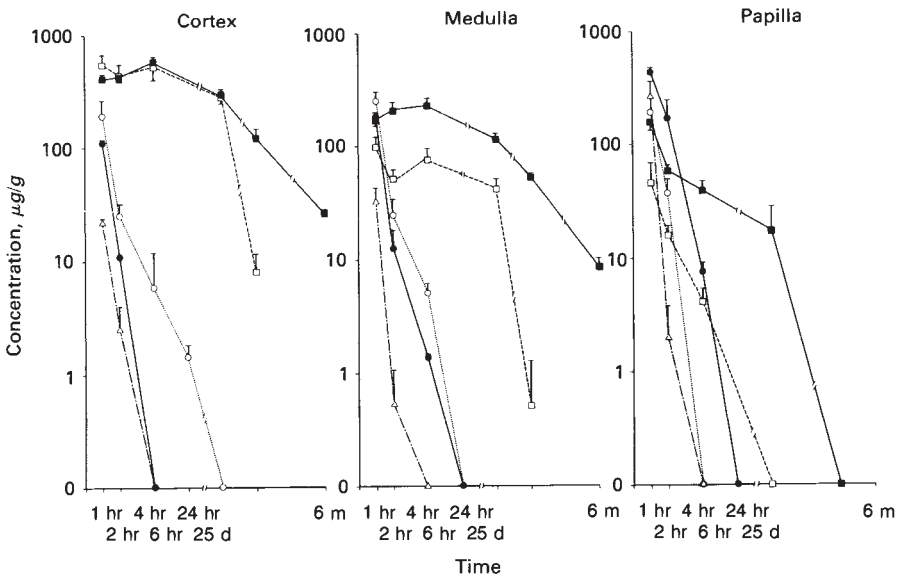

Fig. 1. *Concentrations of gentamicin, ampicillin, cephalothin, and trimethoprim in the cortex, medulla and papilla of pyelonephritic kidneys due to Escherichia coli.* Concentrations were determined from 1 hr to six months after cessation of therapy. The mean ± SEM values of five animals are indicated for each interval. Symbols are: (■—■) G14: gentamicin 14 days; (□--□) G3:gentamicin 3 days; (●—●) A: ampicillin; (△-•-△) C: cephalothin; (○---○) T: trimethoprim.

Table 2. Concentrations of antimicrobial agents in serum and urine of infected rats after the last injection[a]

Drug, length of treatment[b]	Serum levels (μg/ml)					Urinary levels (μg/ml)					
	1 hr	2 hr	4 hr	6 hr	24 hr	1 hr	2 hr	4 hr	6 hr	24 hr	25 day
Ampicillin	39.0 (1.7)	7.4 (2.7)	<0.5	<0.5	<0.5	18220 (555)	6760 (518)	33.6 (9.6)	25.0 (20.9)	<0.5	<0.5
Cephalothin	22.8 (2.5)	0.4 (0.4)	<0.5	<0.5	<0.5	4125 (354.4)	770.0 (18.9)	2.7 (2.3)	0.5 (0.4)	<0.5	<0.5
Trimethoprim	1.5 (0.1)	0.4 (0.2)	<0.5	<0.5	<0.5	742 (55.7)	773.3 (34.0)	94.0 (13.1)	24.0 (1.0)	<0.5	<0.5
Gentamicin (3 days)	10.2 (3.6)	2.8 (0.9)	0.5 (0.5)	N.D.[c]	<0.5	2556 (877)	2002 (625)	130.8 (40.0)	N.D.	6.4 (1.3)	<0.5
Gentamicin (14 days)	11.5 (0.34)	1.0 (0.1)	<0.5	N.D.	<0.5	2983 (157.9)	723.3 (57.3)	230.0 (44.7)	N.D.	N.D.	<0.5

[a] Numbers indicate mean μg/ml (± SEM).
[b] See Table 1 for description of dosages given.
[c] N.D. No data.

following cessation of therapy with the short course (three days) of gentamicin. Following treatments with ampicillin and cephalothin, the respective daily exposures of the bacteria to the drugs were 8 and 7.2 hours, while trimethoprim was found above MIC for over 12 hours each day of treatment.

In vivo efficacy

Table 3 represents the percentage of left kidneys and urine sterilized on day one, 25 and at 6 months following cessation of therapy. An animal was considered cured if, after appropriate dilutions, no bacteria could be detected in the left kidney and urine. Ampicillin, cephalothin, trimethoprim, and gentamicin (three days) administered alone exhibited little activity in the left kidneys for the first 25 days. At six months, gentamicin used alone for three days was more effective than single therapy with TMP and cephalothin. Fourteen days of gentamicin was the most effective regimen ($P < 0.01$) with 100% of animals cured 25 days and six months after cessation of therapy. Six months after the end of treatment, the percentage of sterile left kidneys in animals treated with ampicillin (50%), cephalothin (15%), and trimethoprim (20%) was lower ($P < 0.01$) than the percentage of animals receiving the combinations AG:89%, CG:67%, and TG:60%. Twenty–five days after the treatment had ceased, the combination gentamicin plus trimethoprim was the most effective combination $P < 0.03$. Gentamicin plus ampicillin was the best combination at six months. In the urine, therapy with ampicillin or trimethoprim, and three days of gentamicin alone, respectively eradicated the bacteria in 50%, 50%, and 44% of rats at six months, while cephalothin did sterilize the urine in 23% of the animals. Gentamicin administered for 14 days sterilized all urine. The combinations were also very effective at days one, 25, and six months, except for the combination gentamicin plus cephalothin where at 25 days and six months, 44% and 56% of urine were found to be sterile. Whereas 100% of animals that were used as controls at each time interval still had infected left kidneys, 17% of rats evaluated at six months had sterile urine.

The mean log numbers of CFU of *E. coli*/g of tissue in the left kidneys of rats evaluated at one and 25 days and at six months after cessation of therapy are expressed in Figure 3. When compared with ampicillin, cephalothin, or trimethoprim given alone, combined therapies significantly reduced the number of

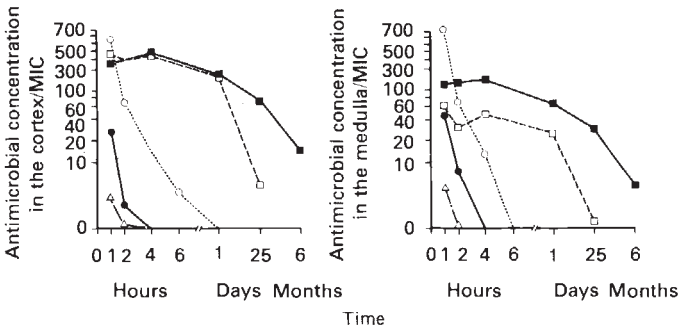

Fig. 2. *Ratio of the concentration of antimicrobial agents in the cortex and the medulla of kidneys/the MIC for the infecting strain of* ***Escherichia coli*** *after cessation of therapy with either ampicillin, cephalothin, trimethoprim, gentamicin for 3 days, or gentamicin for 14 days.* The mean values for five animals are indicated for each time interval. Symbols are the same as Figure 1.

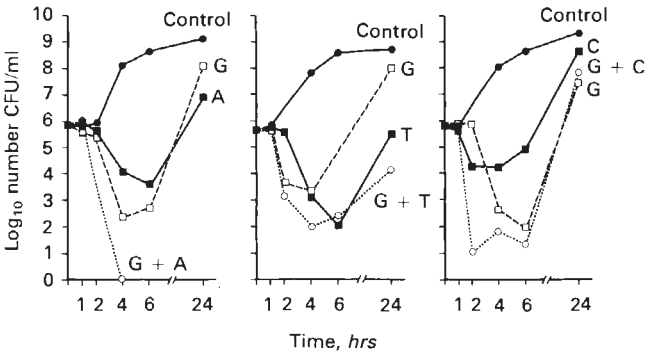

Fig. 4. *Bacterial killing of* ***Eschierichia coli*** *Yale strain by ampicillin (A), cephalothin (C), trimethoprim (T), and gentamicin (G) alone or in combination.* Data are given as log 10 number of CFU of *E. coli* found after incubation.

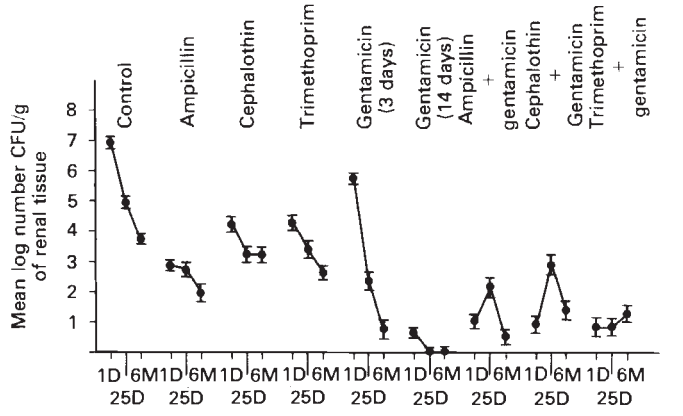

Fig. 3. *Mean log numbers of CFU of* ***E. coli****/g of tissue in the left kidneys of rats evaluated on days 1 and 25, and 6 months after the end of each therapeutic regimen.*

CFU in the kidneys ($P < 0.01$). These combinations were as effective as two weeks of therapy with gentamicin. Gentamicin administered alone for three days reduced significantly the mean number of bacteria from $10^{5.8}$ CFU at one day to less than 10^1 at six months. A reduction in the number of CFU over the six month period was also observed in the controls.

In vitro synergism

The rate of killing of *E. coli* Yale strain by ampicillin, cephalothin and trimethoprim alone, or in combination with gentamicin is represented in Figure 4. Synergism against *E. coli* was demonstrated between ampicillin and gentamicin. Cephalothin and trimethoprim in combination with gentamicin did not show any synergism.

Discussion

The results of the present investigation demonstrate that gentamicin, which accumulates within the renal parenchyma, was more effective than ampicillin, cephalothin, and trimethoprim in the treatment of severe pyelonephritis. When gentamicin was combined with ampicillin, cephalothin, or trimethoprim, we could reduce the duration of therapy with gentamicin to three days, thereby diminishing its nephrotoxic potential and still benefit from the unique intrarenal pharmacological properties and therapeutic advantage of this aminoglycoside.

Several models of experimental pyelonephritis have been used to evaluate the efficacy of antimicrobial agents in this type of infection [12–14], but in most studies [4, 8, 15, 16], the animals were followed for a short period (three weeks) and in many instances, a significant number of animals did recover spontaneously from their infection. In the present experiment, the model of direct inoculation was used because it has the advantage of inducing bilateral pyelonephritis, which can be maintained in almost 100% of the animals for a period of up to one year after inoculation [3]. The present study also stresses the fact that urine may be sterile in the face of severe pyelonephritis. In fact, 17% of the control animals had sterile urine while 100% of the kidneys were infected.

As we have previously shown [3], the results of our pyelonephritis experiments clearly demonstrate that effective levels of gentamicin could be maintained continuously within the infected renal parenchyma of rats up to six months after two weeks of therapy and more than 25 days when the aminoglycoside was administered for only three days. Aminoglycosides, especially gentamicin, have been known to accumulate in the kidneys of humans [17], and animals [18], but only in rare instances have investigators tried to correlate intrarenal distribution of antimicrobial agents with the efficacy in pyelonephritis [4, 7]. Glauser, Lyons and Braude [19] have shown that the development of pyelonephritis in rats can be prevented as long as aminoglycosides are administered before the induction of pyelonephritis. Miller, Phillips and North [4], using a slightly different animal model, have also described a reciprocal relationship between the concentrations of gentamicin in the cortex and medulla and the persistance of bacteria, but they have not eliminated, as we did by the use of sodium polyanethol sulfonate, the presence of aminoglycosides in the tissue which might have interfered with colony counts. The superiority of our therapeutic regimens might be explained by the fact that Miller et al administered gentamicin as a single dose for 11 days while multiple injections were used in the present study. It is known that the cumulation kinetics of gentamicin can be affected by mode of administration, and that single daily dose results in lower levels of aminoglycoside in the kidney than multiple daily

Table 3. Percentage (%) of left kidneys and urine sterilized one, 25 days, and six months after cessation of therapy.

Treatment regimen, days	Left kidneys			Urine		
	1 day	25 days	6 months	1 day	25 days	6 months
Controls, *14*	0/12 (0%)	0/12 (0%)	0/12 (0%)	0/12 (0%)	0/12 (0%)	2/12 (17%)
Ampicillin, *14*	0/9 (0%)	2/10 (20%)	5/10 (50%)	4/10 (40%)	6/10 (60%)	5/10 (50%)
Cephalothin, *14*	1/12 (8%)	3/13 (23%)	2/13 (15%)	1/12 (8%)	1/13 (8%)	3/13 (23%)
Trimethoprim, *14*	1/10 (10%)	3/11 (27%)	2/10 (20%)	0/10 (0%)	2/11 (18%)	5/10 (50%)
Gentamicin, *3*	0/9 (0%)	3/8 (37%)	4/8 (50%)	8/10 (80%)	4/9 (44%)	4/9 (44%)
Gentamicin, *14*	4/6 (67%)	6/6 (100%)	6/6 (100%)	6/6 (100%)	6/6 (100%)	6/6 (100%)
A + G_3	4/8 (50%)	4/8 (50%)	8/9 (89%)	8/9 (89%)	8/9 (89%)	8/9 (89%)
C + G_3	7/9 (78%)	3/9 (33%)	6/9 (67%)	8/9 (89%)	4/9 (44%)	5/9 (56%)
T + G_3	8/10 (80%)	9/11 (82%)	6/10 (60%)	9/10 (90%)	8/11 (73%)	7/10 (70%)

Abbreviations are: A, 14 days ampicillin; C, 14 days cephalothin; T, 14 days trimethoprim; and G_3, 3 days gentamicin

injections [20]. In fact, the renal levels observed in our study were much higher than those of Miller et al [4].

The intrarenal pharmacokinetics of ampicillin, cephalothin, and trimethoprim was quite different from that of gentamicin and they could not be maintained in tissues at levels above MIC for more than six hours after the injection. As demonstrated in normal animals [10, 21], trimethoprim could concentrate in all parts of the infected kidney at levels 170 times higher than those of serum and 500 times above the MIC of the *E. coli*, while the medullary levels of ampicillin and cephalothin were found to be less than three times higher than the serum levels but still 30 times above the MIC.

The reasons for such high failure rate in the kidneys of animals treated with ampicillin, cephalothin, and trimethoprim in the presence of high levels of drugs within the urine and renal parenchyma are not entirely clear. The above data suggest that the mere detection of high concentrations of antibiotics in the infected renal tissue does not necessarily imply that these levels are effective in vivo [22, 23]. These results can most likely be explained by the incapacity of the agents to reach bacteria sequestered within the infected renal parenchyma and the rapid regrowth of bacteria due to the short tissue half lives of the antibiotics.

Although ampicillin, cephalothin, and trimethoprim did not sterilize more than 50% of the severely infected left kidney after six months of follow-up, the number of CFU within the parenchyma was reduced when compared with the controls. Our results are in accordance with those of other investigators who have observed a 100-fold reduction in the number of CFU after therapy with either ampicillin or cephalothin for the treatment of enterococcal or *E. coli* pyelonephritis [8, 24, 25]. The marked reduction in the CFU of *E. coli* in the animals treated with three days of gentamicin and the complete sterilization of the kidneys after 14 days of gentamicin further stress the fact that the long δ phase of aminoglycoside retention in the kidney might be beneficial and that sufficient free gentamicin might be available in the infected parenchyma to sterilize the kidney. Local inactivation of gentamicin by its binding to either pus cells from the infected kidney [26], or renal tissues [27] could also explain the limited efficacy of gentamicin when given for only three days. The 45% binding of trimethoprim to medullary cells [10] might also have affected its local activity. This binding was not as striking with ampicillin (10%) [5], and cephalothin (10%) (unpublished data). More so, the electrolyte content and osmolality of medullary tissue fluid, which are similar to those observed in concentrated urine could have reduced the activity of gentamicin [28]. We cannot exclude factors such as the inflammatory process which may have modified vascular permeability and limited the accessibility of the antibiotics to the infected site. Finally, one may speculate that the overall poor efficacy of cephalothin might be partially explained by its conversion into desacetylcephalothin [29]. In fact, we have shown in rabbits that the metabolite of cephalothin (desacetylcephalothin) contributes to 75% of plasma concentrations. Cabana et al [30] have also shown that the metabolite of cephapirin (desacetylcephapirin) contributes to 75% of plasma concentration in rats. If cephalothin is metabolized to such an extent in rats, it could certainly have affected the activity of cephalothin in the treatment of pyelonephritis.

The remarkable efficacy of ampicillin, cephalothin, and trimethoprim in combination with gentamicin observed in our study is in accordance with past observations which have shown that combination therapy is more effective than single drug regimen. McCabe and Jackson [31] have also found that combinations of drugs that were synergistic in vitro were more effective in humans than combinations that were not synergistic in vitro; but in several of their patients treated with synergistic combinations, the infection recurred. Glauser et al have described the great efficacy of the combination of gentamicin with ampicillin [8] or ceftriaxone [16] in the treatment of experimental pyelonephritis. We have also observed the same efficacy of the combination gentamicin–ampicillin in a different type of experiment [7].

Although several factors may have contributed to the superiority of the combinations over single therapy, we can evoke, at least for the combination ampicillin plus gentamicin, the possibility that this combination, which was shown to be synergistic in vitro, might have resulted in in vivo synergism. This does not seem to be the case with the combinations cephalothin plus gentamicin and trimethoprim plus gentamicin where no in vitro synergism could be demonstrated. To explain this in vivo synergism, we believe that the combined drugs are working at different sites in the infected renal parenchyma, resulting in what we term *pharmacological synergy*. By reducing substantially the number of CFU in the kidney, combined therapy could have diminished the inflammatory process rapidly and thus allowed a better diffusion of the antimicrobials at the site of infection, resulting in a better therapeutic response. Our data also suggest that though the MIC of the antibiotics

studied against the *E. coli* varied enormously from one drug to the other, it did not seem to influence the outcome of therapy.

Continuously maintained bactericidal levels are usually required to achieve cure in cases of severe infections, such as bacterial endocarditis [32], or of infections in neutropenic patients [33], for whom host defenses may not necessarily operate in conjunction with the antimicrobial agents. From our results, it appears that, in the presence of severe pyelonephritis, it may be necessary to maintain effective levels of antibiotics for a considerable period of time in order to achieve a therapeutic effect. More so, the addition of another antimicrobial agent further enhanced the effectiveness of gentamicin. The mere finding that the above combinations could sterilize the left kidney, where the severity of the infection is extreme, suggests that three days of i.v. gentamicin, or other aminoglycosides, in combination with either ampicillin, a cephalosporin, or trimethoprim, followed by two weeks of oral therapy with non-aminoglycoside drugs should be further evaluated in the treatment of severe pyelonephritis in humans.

The pharmacologic and therapeutic advantage of aminoglycosides, especially gentamicin, has to be weighed against its potential nephrotoxicity. Recent studies from our laboratory suggest that pyelonephritic kidneys are more susceptible to aminoglycosides than the normal kidneys [34]. By reducing the number of days of treatment with aminoglycosides, we can shorten hospitalization and reduce the oto and nephrotoxic potential of these drugs while benefiting from their unique intrarenal pharmacological properties.

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