TREATMENT OF URINARY TRACT INFECTIONS WITH SULFATHALIDINE (PHTHALYLSULFATHIAZOLE)*†

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THE treatment of urinary tract infections has always been a matter of some concern. This is evidenced by the multiplicity of methods: acidification, alkalinization, urinary antiseptics, sulfonamides, and antibiotics. With the development of specific drugs, it was hoped that the treatment would no longer be a problem. This is quite true in the great majority of uncomplicated acute infections. Cook has stated that 90 per cent of such cases can be cured with one of the sulfonamides.[1] Penicillin has been of considerable help in complicated cases where most sulfonamides cannot be used safely because of toxicity or sensitivity. However, this antibiotic has failed to be of value in infections caused by the colon-typhoid group of organisms. Streptomycin has a supposed specific action on these organisms. However, it is contraindicated in pregnancy because of the possible injury to auditory and vestibular nerves.[2] There are some urinary infections that do not respond, and others that have a tendency to recur.

It is the urinary tract infections caused by *Esch. coli* that aroused our special interest. Many acute infections with this organism respond to sulfadiazine or sulfathiazole, but the chronic cases often are not affected. In complicated cases occurring during pregnancy or postoperatively, one must use these drugs with considerable caution. Thus it is necessary to find a compound which will cure urinary infections of *Esch. coli* in both acute and chronic cases and which will be sufficiently nontoxic to allow its use in cases with complications such as impaired renal function, severe anemias, pregnancy, etc.

With this in mind, Everett and his co-workers[3] studied the use of sulfasuxidine in such cases and found it to be of considerable value. This drug had been used in gastrointestinal surgery to reduce the *Esch. coli* content of the bowel. It was found by Poth and his collaborators[4, 5] at Johns Hopkins University that only 5 per cent of the drug was excreted in the urine. Blood levels were never more than 1.5 mg. per cent of sulfathiazole and 2 mg. per cent of succinylsulfathiazole (sulfasuxidine). Because of its scanty absorption and low toxicity, sulfasuxidine is well tolerated even in complicated cases. However, Poth,[5] Clay and Pickrell,[6] and Johnson[7] reported several unfavorable reactions, one of which was a case of fatal agranulocytosis. Most of the reactions were said to be due to a sensitivity or idiosyncrasy to sulfathiazole. Everett[3] stated that his chief objection to the drug was its expense due to the large dosage required.

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Everett advances two theories as explanation for the cure of urinary infections by this scantily absorbed drug. Succinylsulfathiazole itself has little "in vitro" value. However, some of the drug hydrolyzes in the body to succinyl acid and sulfathiazole or other similar compounds. Either this small amount of free or "split" drug excreted in the urine is enough to render it sterile or else the tissues of the urinary tract are allowed to rid themselves of infection when the source of contamination in the bowel is temporarily eliminated.

Sulfathalidine (phthalylsulfathiazole), like sulfasuxidine, is a member of the N^4-carboxyacyl-sulfathiazole family. It has also been found to act in vivo in a manner similar to sulfasuxidine. About 90 to 95 per cent of the drug remains in the gastrointestinal tract. Poth and Ross[8] found that in a dog receiving 0.5 Gm. per kilogram per day, the bacterial count fell from 10,000,000 to less than 10 per Gm. of wet stool in six days. As indicated by the alteration of the coliform flora in the bowel of man, phthalylsulfathiazole, in half the dosage, is as effective as succinylsulfathiazole.[9] Poth also found that the maximum concentration of the conjugated drug (phthalylsulfathiazole) in the blood, with a dose of 1.0 Gm. per kilogram of body weight per day, has not exceeded 3.3 mg. per cent. Streicher[10] has found that, irrespective of the dose, the concentration of sulfathalidine in the blood stream of human beings ranges from 0.5 to 1.5 mg. per cent. Poth and Ross[9] report that approximately 5 per cent of the orally administered therapeutic dose is excreted in the urine. Crystals have not been observed following oral administration of the drug. This is due to the fact that the free form is not excreted in large quantities and because the conjugated drug forms soluble salts even at a pH of 5.6. Thus it may be seen that high bacteriostatic concentrations are readily produced and maintained within the bowel, that blood levels are clinically insignificant, and that drug crystalluria or renal obstruction has not been observed.

Poth and Ross[8] reported that no toxic reactions had been demonstrated in dogs receiving oral doses of the drug. Intravenous injections caused vomiting at first but did not occur on further injections. There have been few toxic reactions seen in human beings. The same authors[9] reported headache, nausea without vomiting, and fever in one woman who had developed the same reaction to sulfasuxidine. She was obviously sensitive to sulfonamides. These workers warn that as more persons receive the drug, it can be expected that more toxic manifestations will be seen; however, such reactions will be relatively infrequent.

Methods and Results of Study

The patients reported herein were those having a urinary infection as a complication of some gynecologic surgical procedure or of pregnancy. The diagnosis, initially made from signs and symptoms and by microscopic examination of a catheterized specimen of urine, was confirmed by culture.

The first culture was made before therapy was begun. In most cases, cultures were repeated at the end of the first week's treatment and subsequently every week until negative. Additional cultures were made every second week for several months.

Cultures were managed as follows: After centrifugation of the specimen, the sediment was streaked on a heart infusion agar with 1 per cent filtered lactose and an indicator of bromthymol blue. For the growth of anaerobes, particularly streptococci, two loopfuls of sediment were inoculated into recently heated thioglycollate broth with methylene blue indicator. All organisms which grew during incubation of these media at 37 degrees for two days were identified.

There were a total of 47 cases treated with sulfathalidine. *Esch. coli* was the organism involved in 27 cases. Four of these had mixed infections. The

other twenty cases had various other bacterial invaders. The types of cases with *Esch. coli* infections, along with the immediate results of treatment, are noted in Table I.

TABLE I. TWENTY-SEVEN CASES WITH URINARY INFECTIONS OF ESCH. COLI TREATED WITH SULFATHALIDINE

CASES ASSOCIATED WITH	PYELITIS		CYSTITIS		TOTAL	IMMEDIATE RESULTS AFTER TREATMENT	
	ACUTE	CHRONIC	ACUTE	CHRONIC		SYMP. CURE	BACT. CURE
Pregnancy	2	4	9	0	15	13	12
Gynecological Conditions	0	0	8	4	12	14	14
Total	2	4	17	4	27	27	26

The majority of the cases were treated with sulfathalidine for one to two weeks. However, since five persons did not return as directed, more drug was given because of the interruption of treatment. Four of the latter had three weeks' treatment and the fifth, four weeks. The routine of treatment was 6 Gm. per day, divided into 6 equal doses every four hours, for the time of hospitalization (approximately one week), and 4 Gm. daily for the ensuing time. Eight cases, two of which had chronic infections, were treated with 2 or 3 Gm. daily. There was no difference in the response of this latter group and that of the group treated with a larger amount of drug.

No patient received more than 6 Gm. daily, or approximately 0.1 Gm. per kilogram of body weight. The total amount of drug given to each patient varied from 27 to 86 Gm.; however, most of the patients received 42 to 72 Gm., or an average of 53 Gm. This compares very favorably with the amount of succinylsulfathiazole necessary to obtain comparable results. Everett used 0.25 Gm. of succinylsulfathiazole per kilogram per day for one week and another 0.125 Gm. per kilogram for one to two additional weeks. For a person of 60 kg., this is probably a total dosage of 157 to 210 Gm. of sulfasuxidine, or approximately three and one-half times the total dose of sulfathalidine.

The first culture taken after treatment of each case of *Esch. coli* was negative. After treatment was begun, negative cultures were obtained in fourteen or 50 per cent within the first week, and seven or 27 per cent within the second week, an over-all total of 21 or 77 per cent within two weeks or less. Unfortunately, some of the patients were discharged from the hospital in a very short time, so that in thirteen cases or approximately 50 per cent, including the above-mentioned seven or 27 per cent, the first control culture was taken later than one week after treatment. Also, since most of the patients were treated in the clinic, it was not practical to obtain cultures other than at weekly intervals. In one case, the specimen contained *Esch. coli* after the second week of treatment. This occurred just before delivery in a patient having ureteral block; however, with no additional treatment, there was a negative culture after delivery two months later. After two weeks' rest from the drug, another patient had a recurrence which was cured permanently with ten days of treatment.

There were four mixed infections of *Esch. coli* and *Staphylococcus albus* or an enterococcus, all of which were cured of the bacilli with sulfathalidine. One of the cases of staphylococcus infections cleared without additional treatment and the other was cured with penicillin. The enterococci were eradicated with mandelic acid but reinfections occurred.

Table II shows the number of cases which were observed for varied periods. It may be seen that eight cases, followed for two months, and fourteen cases, followed for three months to one year after the time of treatment, were cured symptomatically and bacteriologically.

TABLE II. TIME CASES WERE FOLLOWED AFTER TREATMENT

TIME	BACTERIOLOGIC AND SYMPTOMATIC CURES	INCOMPLETE TREATMENT	REINFECTIONS
2 months	8		
3 months	3		1
4 months	2	1	
5 months	2		
6 months	4		
7 months	1		
8 months	1		
1 year	1		
Immediate cure but no follow-up after treatment	3		
Total	25	1	1

There was only one case of reinfection with *Esch. coli.* This appeared three months after the original treatment. However, there were four cases of reinfections with other organisms after the *Esch. coli* was eliminated. Three of these were *Aerobacter aerogenes* and one was *Alkaligenes fecalis.*

Case Reports

Mrs. F. L., aged 24 years. This patient developed acute cystitis after an abdominal hysterectomy in December, 1944. She was known to have a right ureteral stricture and was under the care of a urologist prior to surgery. Cultures taken in the hospital were positive for *Esch. coli.* The patient was known to be quite sensitive to sulfathiazole and was given sulfacetamide with poor results. Mandelic acid was also tried but not successfully. On Jan. 3, 1945, she was given 2 Gm. sulfathalidine for the first dose, and 2 Gm. daily thereafter for fourteen days. On January 9th, six days later, the urine was free from pus cells, and the patient was symptomatically cured. No further trouble took place. Subsequent urine cultures were negative for *Esch. coli.*

Miss B. F., aged 40 years. This patient had a chronic pyelo-cystitis, which began in October, 1945. Cultures were positive for *Esch. coli* at this time. The patient was treated by a urologist in October and November, 1945, with sulfacetamide, but with poor results. In January and February, 1946, she had severe right kidney pain and was treated with penicillin, but the urine continued to contain pus and *Esch. coli* organisms. In March, 1946, the urine showed many pus cells and the pain in the right kidney region returned. In April, 1946, when there was a recurrence of pain and positive cultures, the patient was put on mandelic acid by the urologist, but again the results of treatment were poor. On Dec. 16, 1946, the patient had another recurrence of kidney infection with a positive culture for *Esch. coli.* At this time she was put on sulfathalidine, 2 Gm. immediately and 2 Gm. daily for fourteen days. On December 19th, three days later, symptoms were much improved and there was a marked decrease in the number of pus cells in the urine. On December 23rd, there were very few pus cells, and on February 13th, the urine culture was sterile. It was sterile also on March 6, 1947. Since the recrudescence in December, 1946, there has been no return of symptoms. The last urine culture on August 6th, eight months after treatment, was negative.

It has been mentioned that 20 other cases of various types of infections were treated. The same routine of treatment was used for these as for the patients having *Esch. coli* infections. Table III shows the results of treatment of these cases.

TABLE III. URINARY INFECTIONS WITH ORGANISMS OTHER THAN ESCH. COLI

ORGANISM	TYPE OF INFECTIONS					
	ACUTE			CHRONIC		
	NO. CASES	SYMP. CURES	BACT. CURES	NO. CASES	SYMP. CURES	BACT. CURES
Staphylococcus	5	5	5			
Streptococcus	3	3	2			
Aerobacter aerogenes	1	1	1	4	0	0
Alkaligenes				2	2	0
Mixed	4	4	3	1	1	1
Total	13	13	11	7	3	1

The acute cases due to staphylococci or streptococci were cured of their infection but the chronic ones were not. There was a striking failure of the drug to influence the condition in cases infected with *Aerobacter aerogenes* and *Alkaligenes fecalis*. This was also noted by Everett in his work on sulfasuxidine. Nevertheless, all cases except four which were infected with *A. aerogenes* improved symptomatically.

As a control of the drug, seven cases of *Esch. coli* and seven other infections were treated with sulfadiazine. The sulfadiazine was given only while the patients were at the hospital; so treatment varied from three to fourteen days. All cases of colon infections were acute and were cured. Of the other infections, two acute cases of staphylococcus and streptococcus were cured, one paracolon pyelitis was cured temporarily, but four cases of *A. aerogenes* or *Alk. fecalis* were not cleared of their infections. Three of these failures were improved symptomatically, however.

None of the patients showed evidence of toxicity or reaction from the sulfathalidine. One patient had been given four weeks' continuous treatment with sulfathalidine in a test of the value of the drug against enterococcus infection. After a month's rest, she was given another two weeks' treatment. There was no sign or symptom of toxicity with this long treatment. Another case had had the left kidney removed and now had pyelitis of the right kidney. This person received treatment for thirteen days when she began to vomit following ingestion of the medicine. She was later treated for seven days without any untoward reaction. It was very questionable that the medication was the cause of her nausea.

Discussion

Most uncomplicated, acute, urinary tract infections can be controlled by use of the sulfonamides. However, chronic cases, especially those due to *Esch. coli*, often resist all forms of therapy. With sulfathalidine, we have been able to cure both acute and chronic urinary tract infections due to colon organism. Even where there was a mixture of organisms, the colon bacilli were eradicated. The effectiveness of the drug is made evident by the short time necessary to obtain negative cultures and by the long period of negative cultures after cessation of treatment. The prompt cure of chronic cases which had previously resisted other therapy also attests to the value of sulfathalidine in *Esch. coli* urinary tract infections.

It was interesting to find that five cases of acute staphylococcal cystitis and two of three cases of acute streptococcal cystitis were cured symptomatically and bacteriologically with sulfathalidine.

It was also noted that, like sulfasuxidine, the drug had little effect on urinary tract infections due to *Aerobacter aerogenes* and *Alkaligenes fecalis.*

We agree with Everett that the most probable mode of action of both sulfasuxidine and sulfathalidine is twofold. The elimination of the foci of infection in the bowel apparently gives the urinary tract tissues time to combat the infection through their own resistance; moreover, the "beneficial effect exerted on the intestinal tract may decrease the avenues of escape of organisms into the blood stream or lymphatic channels through which they may have been reaching the urinary tract." We also feel, however, that there is some definite sensitivity of *Esch. coli* organisms to this particular type of sulfonamide or to its products in the body.

As in the case of sulfasuxidine, the lack of toxicity of sulfathalidine is a factor which allows treatment in conditions such as impaired renal function and severe anemias. These conditions are often found during pregnancy, and ordinary sulfonamides would be contraindicated.

With sulfathalidine there was not the objection of high cost of the drug due to large amounts required, as found by Everett. Whereas he found it necessary to use an average of 0.25 Gm. of sulfasuxidine per kilogram daily for one week and half this amount daily for a second week, we were able to accomplish similar results with an average dose of 0.1 Gm. thalidine per kilogram daily for one to two weeks. In eight cases, a smaller dose, 0.05 Gm. per kilogram, was used with excellent results.

As is expected with acute infections, average doses of sulfadiazine gave good results in seven cases of acute cystitis caused by *Esch. coli.* However, four cases of *A. aerogenes* and *Alk. fecalis* infections failed to respond to this drug.

Streptomycin has been reported as being efficacious for *Esch. coli,* but there have also been reports of auditory and vestibular nerve injuries from this antibiotic. Therefore, we would be hesitant to use streptomycin during pregnancy and recommend sulfathalidine as the therapeutic agent of choice.

Summary and Conclusions

1. We have used phthalylsulfathiazole successfully in the treatment of acute and chronic urinary tract infections due to *Esch. coli.*

2. Chronic cases of *Esch. coli* that were resistant to other sulfonamides, penicillin, and mandelic acid were cured bacteriologically with sulfathalidine.

3. Twenty-six out of twenty-seven cases of *Esch. coli* infections were cured symptomatically and bacteriologically.

4. Negative cultures were obtained in 50 per cent of the cases in one week or less and in 77 per cent in two weeks or less.

5. The first culture taken after treatment (which, in twelve cases, was after the first week) was negative in all cases.

6. Sulfathalidine did not seem to have any effect on cystitis caused by *Aerobacter aerogenes* or *Alkaligenes fecalis.* It did have some effect on urinary tract infections caused by staphylococci and streptococci.

7. Sulfathalidine can be used where other sulfonamides would be contraindicated because of its poor absorption and low toxicity. This is especially true in pregnancies complicated by impaired kidney function or severe anemia.

8. The dosage necessary to bring about a cure was 0.1 Gm. per kilogram of body weight daily for an average of two weeks. Eight cases were given 0.05 Gm. per kilo.

9. Due to the low dosage required, the cost of the drug does not make its use prohibitive in the low income group.

10. Its mode of action is most probably similar to that advanced by Everett and his co-workers for sulfasuxidine.

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