

INFECTIONS OF THE URINARY TRACT

Report of a Case

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Mandelic acid and sulfanilamide have proved to be valuable adjuncts in our armamentarium for the treatment of infections of the urinary tract. The classification of the causative organism followed by treatment with the proper drug is of the utmost importance. Not wholly without danger in administration, close supervision during treatment is recommended and certain precautions must be taken if satisfactory results are to be obtained. The following case illustrates the principles that should be followed in the use of these drugs.

REPORT OF CASE

A nurse, 37 years of age, entered the Clinic on May 8, 1938, complaining of "pus in the urine," frequency, urgency, and pain in the right side.

In 1932 she had experienced an attack of pyelitis and cystitis which subsided in one month after the use of various urinary antiseptics. Since that time she had not been entirely free from frequency and urgency. Once or twice yearly an acute exacerbation occurred, incapacitating her for three or four weeks. In 1934 a severe attack of renal colic on the right side lasted several hours. A cystoscopic examination had been performed at that time and she was told an infection was present in the right kidney. Following this, she had taken various medications but the urine was never free from pus.

The attack which caused her to come to the Clinic began four days before admission and was manifested by pronounced frequency, urgency, dysuria, and nocturia. Slight discomfort was noted in the region of each kidney. Although she felt chilly at times, no definite chills were experienced. An examination of the urine had been made and the report was that it was loaded with pus and a few red blood cells were present.

In 1913 an appendectomy had been performed, and in 1918 a diagnosis of pleurisy had been made. For years prior to 1928, frequent attacks of tonsillitis had incapacitated the patient, so a tonsillectomy had been performed.

Physical examination revealed a well developed and nourished woman whose temperature was 98.6° F., pulse rate 90, blood pressure 120 systolic, 80 diastolic. No abnormal findings were noted except a small adenoma of the thyroid and tenderness on deep palpation over the kid-

neys. Moderate discomfort was elicited by percussion in the region of the costovertebral angles.

Laboratory findings: Examination of the blood showed 4,970,000 red cells, 9,700 white cells, and 92 per cent hemoglobin. The level of the blood sugar was 124 mg., and of the blood urea 33 mg. per 100 cc. The Wassermann test gave a negative reaction. The basal metabolic rate was minus 14 per cent.

A roentgenogram revealed the chest to be normal. The report of the initial roentgenogram of the abdomen was: The lumbosacral region is normal. There are no suspicious shadows in the urinary tract. The kidneys are normal in size, shape, and position. There is a small calcified area in the region of the urinary bladder.

Following a cystoscopic examination, the following report was given: The cystoscope was introduced without difficulty. The patient's bladder was quite irritable and the examination was somewhat painful to her. Urine extracted from the bladder appeared quite cloudy. The bladder capacity was limited and only 100 cc. of solution could be introduced before she complained of considerable pain. Examination of the bladder revealed it to be diffusely inflamed and small petechial hemorrhages were scattered over the bladder wall. There was considerable edema about both ureteral orifices. Catheters were passed unobstructed to both kidney pelves and specimens of urine which were collected appeared slightly cloudy. The catheters were left in situ as the cystoscope was removed. Five cc. of indigo carmine was injected intravenously; it appeared from the right kidney in 3½ minutes with 4 plus concentration and from the left kidney in 3 minutes with 4 plus concentration.

A bilateral pyelogram revealed normal kidneys with the exception of a duplex pelvis on the left side.

Examination of the specimens of urine secured by catheterization revealed:

1. Bladder urine: pH 6.5, loaded with pus cells, few red blood cells; stained smear of the sediment showed gram negative bacilli, and the culture revealed *Escherichia coli*.

2. Right kidney: pH 6.5, numerous pus cells, occasional red blood cells, stained smear of the sediment showed gram negative bacilli, and the culture revealed *Escherichia coli*.

3. Left kidney: pH 6.5, numerous pus cells, few red blood cells; stained smear of sediment showed gram negative bacilli and again the culture demonstrated *Escherichia coli* as the offending organism.

Diagnoses were: bilateral pyelitis due to the *Escherichia coli* and cystitis due to the same organism; adenoma of the thyroid; calcified ovary.

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Progress and treatment: The patient was sent to the hospital and told to remain in bed. A simple bland diet was prescribed and the fluid intake was limited to 1000 cc. daily. Therapy with mandelic acid was instituted and although it increased the discomfort in the bladder for a few days, this was controlled by opium and belladonna suppositories. Twelve grams of the medication were administered daily, three grams being taken after each meal and at bedtime. A careful check of the pH of the urine revealed that it was maintained at 5.3; therefore additional acidifying agents were not required. The patient responded well to treatment and in eight days culture of the urine from the bladder showed it to be sterile. The patient was dismissed from the hospital after a period of 10 days.

One month later while at home, a second course of mandelic acid was prescribed. The patient states that she is completely relieved from symptoms and culture of the urine has showed it to remain sterile.

DISCUSSION

In recent years two new chemotherapeutic agents have been added to our armamentarium in the treatment of infections of the urinary tract, namely, mandelic acid and sulfanilamide. The introduction of these drugs has stimulated more careful bacteriological study of the offending organisms in these conditions and more scientific approach to their eradication.

MANDELIC ACID

The introduction of the ketogenic diet by Clark¹ and Helmholtz² was a distinct advance in the treatment of infections of the urinary tract. Its administration frequently caused general and gastro-intestinal symptoms which rendered it objectionable to some patients. By its employment, however, infections associated with stasis which previously did not respond to other types of medication could be treated successfully.

Fuller³ later demonstrated that the bacteriostatic factor in the urine of patients on the ketogenic diet was Beta hydroxybutyric acid. When, however, this was administered by mouth, it did not prove effective as it was completely oxidized. Previously, Schotten⁴ and Knoop⁵ had demonstrated that mandelic acid when taken by mouth was excreted unaltered in the urine. Rosenheim⁶ showed that it was excreted in the urine by the kidneys in a concentration adequate for bactericidal action when the pH of the urine was sufficiently low. In 1935 he reported the results secured in a series of 12 patients with infections of the urinary tract. He stated that while the series was too small to draw definite conclusions, the results merited further and extensive trial.

Since this time, numerous publications have attested to the value of this drug and it has been demonstrated that in from 80 to 90 per cent of

uncomplicated cases of infections of the urinary tract the urine will be found bactericidal.

The institution of therapy with mandelic acid is indicated in the subacute and chronic infections, although I have employed it in the more acute stages of pyelitis and cystitis when extreme irritability of the bladder was not present. The organisms which have responded to treatment are *Escherichia coli*, *Aerobacter aerogenes*, *Streptococcus faecalis*, members of the genera *Salmonella*, *Pseudomonas* and *Shigella*. I have found that coccal infections, with the exception of *Streptococcus faecalis*, have been resistant to treatment with mandelic acid. Members of the genus *Proteus* likewise have not responded to mandelic acid therapy.

The drug most commonly prescribed is the ammonium salt in the form of the elixir or the syrup. As the percentage of the salt in the elixir and the syrup may be different, depending upon the type used, obviously the dosage of the drug must be varied. The elixir contains approximately 28 per cent of the salt and is administered in three fluid drachms (12 cc.) after meals and at bedtime. Approximately 12 gm. of the pure acid are required daily for satisfactory end results.

The pH of the urine must be maintained between 5.3 and 5.5. In the majority of cases, the mandelic acid reduces the pH of the urine to this level. If not, it may be accomplished by the use of ammonium nitrate or ammonium chloride. In addition, to increase the concentration of the drug in the urine, the fluid intake must be restricted to 1000 or 1200 cc. daily. The majority of bacilli in the urine are killed with a concentration of 0.5 per cent solution of mandelic acid in the urine at a pH of 5.5. If necessary, the concentration of the drug in the urine may be increased. As the mandelic acid is eliminated almost entirely in the urine, by knowing the 24 hour output of urine and the daily dosage we may increase the concentration to 0.9 or 1 per cent.

A simple bland diet is prescribed and if the infection is pronounced, the patient is told to go to bed.

Miscellaneous supportive measures are administered as necessary, relief of the bladder discomfort being secured by opium and belladonna suppositories or the use of the various barbiturates.

This medication is continued from ten days to two weeks unless complications arise which render its withdrawal advisable. If the urine is not sterile at this time, treatment with mandelic acid is discontinued for ten days or two weeks as the organism may have built up a resistance to the drug. Following this, a second course of treatment may be necessary to render the urine sterile.

Failure to secure good results may be due to several causes. If the organism has the power of splitting urea with the resultant formation of

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ammonia, it may be impossible to reduce the pH of the urine to 5.3 or 5.5. The patient may not tolerate the medication or, due to poor renal function, sufficient concentration of the mandelic acid in the urine may not be attained. The presence of chronic prostatitis which continues to reinfect the bladder may be conducive to securing an unsatisfactory result.

The presence of calculi, tumors, or foreign bodies as a nephrectomy tube may render sterilization of the urine difficult and finally, as stated by Braasch⁷, the presence of pyelonephritis with cicatricial changes in the pelvis and calices and residual urine may render a cure extremely difficult.

In patients whose renal function is not normal, careful observations should be made to avoid acidosis and similarly in children acidosis may occur unless due care is exercised in the administration of the drug. Elevation of temperature, although not pronounced, frequently occurs even in patients with normal kidneys.

Nausea and diarrhea may be present in a small percentage of cases but is not usually sufficiently pronounced to be very distressing.

In conclusion, the oral administration of mandelic acid will be efficacious in eradicating approximately 85 to 90 per cent of uncomplicated infections of the kidney and bladder. This does not infer that complete study of the urinary tract is not necessary, as coexisting pathology may be present which may ultimately destroy the kidney unless detected early and thus be responsible for failure in the use of this drug.

SULFANILAMIDE

The second drug, sulfanilamide, was introduced by Domagk⁸ in 1935 and used first in the United States by Long and Bliss⁹. Sulfanilamide administered by mouth is eliminated in the urine in the free state and the conjugated form, para-acetyl-amino-benzene-sulfonamide.

It is estimated that in a period of two or three days an equilibrium is established between the amount ingested and the amount excreted.

Sulfanilamide therapy has distinct advantages over mandelic acid:

1. Less distress follows its use than when mandelic acid is employed.
2. It exerts a bactericidal effect in alkaline urine. This is a distinct advantage over mandelic acid which exerts its best effect in strongly acid urine. Sulfanilamide can therefore be used in the presence of organisms which have the power of splitting urea with the resultant formation of ammonia, which renders the urine strongly alkaline.

The results, however, in eradicating the various strains of the *Proteus* group have not been as satisfactory in my hands as those of other authors.

Sulfanilamide will eliminate between 85 to 90 per cent of uncomplicated infections of the urinary tract. In cases associated with chronic prostatitis which reinfects the bladder, striking results are frequently observed. In the coccal group of infections, however, our results have not been so striking.

The dosage advocated varies with various observers. In treating urinary infections in adults, some authors report excellent end results by the use of 60 gr. (4 gm.) daily, 15 gr. being taken after each meal and at bedtime for a period of three days, then a total dosage of 40 gr. (2.65 gm.) daily for two days, and a maintenance total dosage of 30 to 40 gr. (2 gm. - 2.65 gm.) daily for a total period of 10 to 14 days. In children, the dosage is proportionally smaller. In infants, 5 to 10 gr. are given daily; from 2 to 5 years, 15 gr. daily; from 5 to 10 years, 15 to 20 gr. daily; and over 15 years to young adults, 20 to 25 gr. daily.

There is evidence that better results may be secured when the drug is administered at regular intervals day and night. In this manner it is possible to maintain a constant free sulfanilamide level in the blood of approximately 10 mg. per 100 cc. In one of our cases of septicemia this level rose to 17 mg. per 100 cc. without producing any deleterious effects. If the drug is prescribed at regular intervals, one-sixth of the total calculated dose should be administered every four hours. I have followed this method of treatment in the majority of cases of infections of the urinary tract, administering from 15 to 20 gr. every four hours with equal amounts of sodium bicarbonate.

Sulfanilamide is an acid substance and should be administered with corresponding doses of sodium bicarbonate in order to avoid producing an acidosis and likewise to minimize gastro-intestinal symptoms.

Fluids should not be restricted when this medication is prescribed; rather, an abundant amount of water should be taken as the drug is excreted in the urine and, since it has definite toxic effects, it is essential to maintain a free rate of excretion.

In patients with poor renal function extreme care should be exercised in the administration of this drug, for if impaired renal function is present the patient may not be able to excrete concentrations in the urine greater than 30 to 40 mg. per 100 cc. That a toxic influence is exerted upon the kidney is indicated by the elevation of the blood urea and lowering of the output of phenolsulphonphthalein. In the normal kidney, however, we have seen no permanent impairment of renal function following the use of sulfanilamide.

Various manifestations of toxemia may develop, namely, cyanosis, nausea, drowsiness, tinnitus, and headaches. These are not, however, an indication to discontinue the use of the drug.

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Coggeshall and Bauer¹⁰ noted no hemolytic anemias in their series. In six cases moderate to pronounced reduction in the number of red cells occurred. Four of these patients had a spontaneous reticulocytosis and a smear revealed marked macrocytosis. These anemias disappeared, however, without special treatment. In two cases, the leukocyte count fell to 1800 - 2800 two weeks after discontinuance of the drug, but again returned to normal.

Sulfhemoglobinemia, agranulocytosis, hemolytic anemia, and methemoglobinemia have similarly been reported. Careful check of the sulfanilamide content of the blood, however, and repeated blood studies minimize the development of such complications.

When prescribing sulfanilamide, saline cathartics and laxatives should not be prescribed.

Unsatisfactory results may be due to:

- (1) The patient is unable to tolerate the drug.
- (2) Poor renal function may prevent adequate excretion of the drug.
- (3) Coexisting pathology such as tumors, calculi, and foreign bodies.
- (4) Gross changes in the kidney with residual urine do not give as satisfactory results as in the normal organs.

In view of its less evident action in the presence of the coccal group, it is advisable to try neoarsphenamine when these organisms are the offending bacteria.

SUMMARY

1. Mandelic acid and sulfanilamide are valuable drugs in the treatment of infections of the urinary tract.
2. Careful classification of the bacteria is advisable to determine which drug should be administered.
3. A more scientific approach to the eradication of urinary infections has followed the introduction of these drugs.
4. In patients who do not respond promptly to treatment, complete examination of the urinary tract is advisable to rule out coexisting pathological lesions in the genito-urinary tract.

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