A NEW SULPHONAMIDE IN GENITO-URINARY INFECTIONS

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The management of chronic urinary tract infection and the prevention of infection in the presence of an indwelling catheter at times presents a difficult problem. None of the urinary antiseptics have been found to be universally or even consistently efficacious (Pool and Cook, 1947). The sulphonamides, including sulphanilamide, sulphathiazole and sulphasuxidine are frequently without value in combating proteus or the colon bacillus and may be potentially dangerous (Narins, 1948). Penicillin is almost completely ineffectual against gram-negative bacilli (Pool and Cook, 1947). 3.4 dimethyl-5-sulphanilamido-isoxazole (NU-445) has proved to be effective against *B. Coli* and *B. Proteus* both in vitro and in vivo (animal experiment) and is reputed to be of extremely low toxicity (Narins, 1948). This drug is not easily available at present in this country.

Lucosil mitis (2-sulphanilamido-5-methyl 1, 3, 4-thiodiazole) is absorbed rapidly from the intestinal tract and is excreted quickly in the urine in the non-acetylated form. Anderson (1943) has used lucosil in doses of 1 gram six times daily. This dosage brings the concentration of lucosil in the urine up to a maximum of 700 mgm. per 100 cc. if the daily output of urine is between 900-1,500 cc. (Thune *et al.*, 1942). After treatment the urine was sterile in 88 per cent. of cases.

Schmith (1945) treated 35 patients with lucosil in small divided doses. Thirty received 0.1 gm. five times daily for five days, a total of 2.5 gm. The remaining five patients received 0.2 gm. five times daily for five days, a total of 5 gm. In 28 cases the urine was sterile at the termination of treatment. Three of the remaining patients exhibited a few *B. Coli* on culture but the repeated examination eight days later revealed a sterile urine.

Impressed by these results we decided to investigate the therapeutic value of lucosil. It was administered to 16 consecutive patients. For all patients routine urine analysis, complete blood

counts and smears of the urinary deposits were examined at frequent intervals. A loopful of urine was smeared on blood agar and the culture examined. To determine the rate of destruction of the organisms in the urine, daily colony counts were carried out. A drop of urine from a Pasteur pipette was dropped into 20 cc. of melted agar. After mixing, the agar was poured into a sterile Petri dish and cultured at 37° C. The next day the colonies were counted. The number of drops in a cc. of urine were estimated and the number of colonies per cc. of urine were thus determined.

Case Reports

Case 1. A.P., aged 49, a bus driver had a suprapubic lithotomy and bladder neck resection performed in May, 1947, for a vesical calculus and bladder neck obstruction. Healing was satisfactory and he was discharged cured. In March, 1948, he complained of increased frequency of micturition D/N = 8/10, scalding and sediment in the urine.

Investigation. Urine, heavy growth of *B. Coli*. Cystoscopy revealed an intense cystitis. W.B.C., 5,500 per cmm. A five-day course of lucosil mitis (0.1 gm. four-hourly) was given. The urine remained infected. There were no toxic reactions. Bladder wash-outs with $\frac{1}{2}$ per cent. acetic acid using a Duke's apparatus produced improvement which was confirmed by cystoscopy. A median bar was seen this time.

Remarks. In the presence of a mechanical obstruction lucosil did not produce any improvement either of the symptoms or of the pyuria.

Case 2. J.T., aged 63, a clerk, was admitted with an enlarged prostate and intermittent claudication. The urine was sterile and kidney function good.

16.4.48. 'Aseptic' prostatectomy and lumbar sympathectomy. Lucosil mitis (0.1 gm. six hourly and penicillin 100,000 units t.d.s.).

20.4.48 Urine :—moderate number of leucocytes and a few coliform bacilli.

21.4.48. 600 colonies of *B. Coli* per cc. of urine.

1.5.48. Urine :—acid, trace albumen. Deposit, numerous pus and red blood cells with a moderate number of coliform bacilli. 600 colonies of *B. Coli* per cc. of urine. Lucosil was discontinued and a course of sodium mandelate sterilized the urine in six days.

Remarks. Prophylactic penicillin and lucosil were of some value in this case. The urinary infection was kept under control. The persistent infection was mild. Changing the urinary anti-septic rapidly sterilized the urine.

'Aseptic' prostatectomy is the term applied by Wilson Hey (1945) to prostatectomy when complete asepsis of such a standard as is expected in operations upon the knee joint is applied. The various steps of the operation and the post-operative period have been described by Stock (1947). A suprapubic diathermy enucleation—dissection of the prostate and a wedge excision of the trigone is performed. Meticulous haemostasis of the prostatic bed is obtained by diathermy electro-coagulation. The bladder is drained by a rubber tube introduced from the bladder into the urethra by the railroad method. The tube is fixed by a Harris' stitch and the bladder carefully sutured in layers.

Case 3. J.J., aged 70, developed acute retention following cystoscopy. Thirteen years previously an enlarged prostate had been removed by the Harris technique.

Urine :—acid, trace albumen. Deposit, large number of pus cells and coliform bacilli. Blood urea, 47 mgm. per cent. Hb., 70 per cent. R.B.C.s, 3.6 mill./cmm. W.B.C.s, 8,500 per cmm. Kidney function good.

11.6.48. Bladder drained with an indwelling catheter. Lucosil mitis, 0.1 gm. four-hourly. Penicillin, 200,000 units intramuscularly t.d.s.

15.6.48. Culture of urine, colonies of *B. Coli* too numerous to count. 'Aseptic' prostatectomy performed. There was marked basal cystitis and pus around the internal urinary meatus.

16.6.48. Culture of urine, colonies of *B. Coli* too numerous to count.

19.6.48. Urine still infected. Urethral tube removed.

21.6.48. Suprapubic leak developed. Catheter inserted into bladder which was irrigated with $\frac{1}{2}$ per cent. acetic acid through a Dukes' apparatus.

22.6.48. Hb., 68 per cent. R.B.C.s, 3.6 mill./cmm. W.B.C.s, 21,000 per cmm.

28.6.48. Suprapubic fistula healed.

2.7.48. Discharged. Urine still infected with *B. Coli*. A few days after discharge from hospital

the patient had an attack of haematuria which did not entail admission to hospital. In August, 1948, the patient wrote that he was fit and passing urine well.

Remarks. Lucosil and penicillin may have prevented an ascending pyelonephritis and infection of the pelvic cellular tissue but did not cure the urinary infection.

Case 4. T.C.W., aged 68, a retired sea captain, was admitted on 20.8.48 with acute retention due to an enlarged prostate. He had been catheterized before admission.

Urine :—grossly infected, trace albumin. Deposit, large number of R.B.C.s and leucocytes. Culture, staph. aureus (coagulase positive). Hb., 80 per cent. W.B.C.s 13,000. Blood urea, 42 mgm. per cent. 'Aseptic' prostatectomy performed. Penicillin, 200,000 units t.d.s., and lucosil mitis, 0.1 gm. four-hourly.

21.6.48. Blood urea, 47 mgm. per cent.

25.6.48. Urethral tube removed.

28.6.48. Blood urea, 107 mgm. per cent. Urinary deposit, large number of pus cells, R.B.C.s and coliforms. Culture, *B. Pyocyaneus*. Colonies too numerous to count.

29.6.48 Rigors and anuria. Lucosil discontinued. Streptomycin, 1 gm. stat. and $\frac{1}{2}$ gm. four-hourly until 5 gm. given.

30.6.48. Passed urine. This was sterile.

7.7.48. Discharged cured.

When reviewed in August, 1948, he was passing urine freely and was symptom-free.

Remarks. Lucosil and penicillin cured the infection caused by staphylococci. It did not prevent infection by other (gram-negative) organisms.

Case 5. F.C., aged 45, a labourer, was admitted on 28.2.48 with paralysis and retention of urine due to cervical cord injury. Tidal drainage of the bladder was commenced on admission. Penicillin, 30,000 units six-hourly, and sulphamethazine, 11 gm. stat. and 1 gm. four-hourly given. He developed a severe *B. Coli* cystitis and urethritis.

5.5.48. Suprapubic drainage. Lucosil, 0.1 gm. four-hourly. Hb., 70 per cent. R.B.C.s, 3.9 mill./cmm. W.B.C.s, 20,000/cmm. Urine, large number of pus cells and few R.B.C.s. Culture, Colonies of *B. Coli* too numerous to count.

8.5.48. W.B.C., 33,000/cmm. Urine, mixed growth of *B. Proteus* and *B. Pyocyaneus*. Colonies too numerous to count.

Remarks. The patient complained of abdominal pain 24 hours after the first dose of lucosil. The pain lasted for 12 hours. Subsequent observations suggested that the pain was due to the spinal lesion and not the drug. Lucosil cured the *B. Coli* in-

fection but did not prevent infection by other (gram negative) bacilli.

Case 6. E.G., aged 75, a housewife, was suffering from B. Coli cystitis present for several years.

Intravenous pyelography, no evidence of obstruction or calculus.

Cystoscopy, cystitis only. Urine:—slightly acid, trace albumin. Sugar, nil. Deposit, large number of pus cells and small number of epithelial cells. Moderate number of coliform bacilli. She was given a five-day course of 0.1 gm. of lucosil four-hourly. Her frequency and dysuria improved. Urine:—slightly acid, very faint trace albumin. Deposit, a few epithelial cells only. When reviewed a fortnight later she still showed the improvement and there was no recurrence of the B. Coli cystitis.

Case 7. O.P., aged 56, a farmer, had acute retention due to an enlarged prostate. He had been catheterized four times before admission. Urine:—reaction acid, small amount albumin. Deposit, R.B.C.s, pus cells and coliform bacilli. Blood urea, 60 mgm. per cent. Excretion pyelography normal.

11.6.48. Lucosil mitis, 0.1 gm. four-hourly, and penicillin, 200,000 units t.d.s. An 'aseptic' prostatectomy was performed.

Strips of Gelfoam were inserted into the prostatic bed. The urethral tube blocked but after washing it out with 5 per cent. sodium citrate the urine flowed freely.

12.6.48. Urinary deposit, small number of R.B.C.s, leucocytes and 100 colonies of B. Coli per cc. of urine.

14.6.48. 600 colonies of B. Coli per cc. urine.

15.6.48. Tube removed and passed urine without difficulty.

20.6.48. Collapsed and died from pulmonary embolism.

Remarks. The probable cause of the embolus was phlebothrombosis found at autopsy to be due to exceptional trauma to the basilic vein in conjunction with a stiff shoulder joint. No thrombosis was found in the pelvis or lower limbs. The bladder showed no evidence of gross infection. It appears in this case that lucosil was of value in controlling the B. Coli cystitis.

Case 8. J.B., aged 51, developed a urethral stricture following the use of an indwelling catheter after an abdomino-perineal excision of the rectum for carcinoma.

Urine, sterile. W.B.C.s, 6,000 per cmm.

7.5.48. External urethrotomy. A small urethral catheter was inserted into the bladder. Lucosil, 0.1 gm. four-hourly for five days.

8.5.48. 5,600 colonies B. Coli per cc. urine.

12.5.48. Moderate number of pus cells, small number of R.B.C.s. The colonies of B. Coli in the urine were too numerous to count. W.B.C.s, 7,000 per cmm.

Remarks. In the presence of some obstruction, an indwelling catheter and a perineal wound, the drug did not prevent a urinary infection.

Case 9. A.W., aged 41, developed an impassable urethral stricture following gonorrhoea.

Urine:—acid, faint trace albumin. Deposit, moderately large number of pus cells and occasional R.B.C. Culture, sterile. Blood urea, 27 mgm. per cent.

2.7.48. Suprapubic cystostomy and excision of a stricture 3.4 cm. long in the bulbous urethra. The anterior end of the urethra was mobilized and the roof of the urethra was sutured with interrupted catgut sutures. A No. 4 soft rubber catheter was inserted along the urethra and left projecting through the suprapubic opening. The perineal wound was gently packed with vaseline gauze. The patient was kept dry by continuous suction through a sump drain in the bladder. Lucosil, 0.1 gm. four-hourly maintained sterility of the urine.

Case 10. R.L., aged 71, a retired medical practitioner had B. Coli cystitis for several months. The prostate was enlarged. Urine:—acid, faint trace albumin. Sugar, nil. Deposit, large number of pus cells and coliforms. The colonies of B. Coli were too numerous to count. Hb., 96 per cent. W.B.C.s, 7,000/cmm. After five days of lucosil, 0.1 gm. four-hourly, the urine was sterile and contained no pus cells. W.B.C.s were 8,000/cmm.

Case 11. G.B., aged 73, had an enlarged prostate and bilateral inguinal herniae.

Urine, sterile. Blood urea, 40 mgm.

Intravenous pyelography showed normal renal outline and function. 'Aseptic' prostatectomy performed and lucosil mitis, 0.1 gm. four-hourly, until sutures removed. Urethral tube removed on the fourth day, when urine was still sterile. This was confirmed by repeated daily mid-stream specimen of urine. The convalescence was complicated by a biniodide rash.

Case 12. A.B., aged 70, developed acute retention due to an enlarged prostate. The bladder was drained for two days with an indwelling catheter.

Hb., 96 per cent. W.B.C.s, 16,000/cmm. Urine:—acid, trace albumin. Sugar, nil. Deposit, small number of leucocytes, few R.B.C.s. Culture, atypical B. Coli. Kidney function, fair.

Intravenous pyelography revealed hydronephrosis with regurgitation up the ureters. Blood urea, 35 mgm. per cent.

2.7.48. 'Aseptic' prostatectomy. Pus was seen around the internal urinary meatus. Culture of the pus revealed the presence of numerous colonies of staph. albus. The urine was grossly infected with staph. albus. The urethral tube was connected to a Duke's apparatus and the bladder was washed out at two-hourly intervals with 5 per cent. citrate solution for the first day and then three times daily with $\frac{1}{2}$ per cent. acetic acid. Lucosil, 0.1 gm. four-hourly, and penicillin, 200,000 units t.d.s.

3.7.48. Blood urea, 35 mgm. per cent. Urea clearance, 67 per cent.

5.7.48. Blood urea, 67 mgm. per cent. 600 colonies of staph. albus per cc. of urine.

7.7.48. Blood urea, 24 mgm. per cent. Urine urea, 0.6 gm. per cent. Deposit, moderate number of R.B.C.s and few leucocytes. Culture, sterile. Tube removed and passed urine without difficulty.

10.7.48. Hb., 86 per cent. R.B.C.s, 4.7 mill./cmm. W.B.C.s, 11,000/cmm.

12.7.48. Blood urea, 28 mgm. per cent. Deposit, occasional leucocyte and R.B.C. Culture, sterile.

16.7.48. Discharged. Wound soundly healed.

Remarks. Lucosil was of value in preventing further infection. The organisms found in the urine were white staphylococci usually regarded as non-pathogenic.

Case 13. K.P., aged 56, had chronic retention due to an enlarged prostate. Urine:—acid, trace albumin. Deposit, pus cells and a moderately heavy growth of B. Coli. X-ray of renal tract showed a jack stone in the bladder.

Intravenous pyelography, bilateral hydronephrosis and poor concentration of the dye. Kidney function tests showed poor function.

13.4.48. 'Aseptic' prostatectomy and removal of vesical stone. There was a small diverticulum in the bladder. Penicillin, 20,000 units t.d.s., and sulphamethazine, 1 gm. four-hourly.

15.4.48. Heavy growth of B. Coli in the urine.

17.4.48. Heavy growth of B. Coli in the urine. Urethral tube removed.

22.4.48. Developed a suprapubic fistula. A catheter was passed. Examination of the urinary deposit revealed a large number of R.B.C.s and pus cells and a heavy growth of B. Pyocyaneus.

29.4.48. The urine was still heavily infected with B. Pyocyaneus in spite of repeated wash-outs with $\frac{1}{2}$ per cent. acetic acid. Lucosil, 0.1 gm. four-hourly. W.B.C.s, 23,000 per cmm.

1.5.48. Urine, no change. W.B.C.s, 17,000 cmm.

20.5.48. No improvement. Lucosil discontinued. W.B.C.s, 14,000 per cmm. Sodium mandelate, 20 gr. t.d.s. A rectal examination revealed the presence of a pelvic cellulitis. W.B.C., 14,000/cmm. Hb., 62.

30.5.48. Streptomycin, course of 5 gm., produced a marked improvement but five days later the urine became infected again.

4.7.48. On discharge from hospital, the urine was still infected and the pelvic cellulitis had completely resolved.

19.8.48. Attended follow-up clinic. Appetite good. Increased frequency of micturition, D/N = 6/3-4. No incontinence, urgency or haematuria. Urine occasionally cloudy. Hb., 74 per cent. Blood urea, 57 mgm. per cent. Deposit, moderate number of pus cells and B. Proteus.

Remarks. None of the urinary antiseptics apart from streptomycin proved of any value. The small diverticulum probably was the continued source of the infection.

Case 14. J.E.W., aged 72, had acute retention due to an enlarged prostate. He had been catheterized twice. The urine was sterile and the blood urea 36 mgm. per cent.

27.5.48. 'Aseptic' prostatectomy.

28.5.48. Blood urea, 36 mgm. per cent. Urine sterile.

29.5.48. Blood urea, 28 mgm. per cent. Urine urea, 1.6 gm. per cent.

31.5.48. Blood urea, 29 mgm. per cent. Urine, sterile. Lucosil mitis, 0.1 gm. four-hourly. Penicillin, 100,000 units six-hourly.

1.6.48. Urethral tube out.

11.6.48. Urine:—neutral, trace albumin. Sugar, nil. Moderate number of leucocytes and R.B.C.s. Culture, scanty growth of staph. albus.

Intravenous pyelography showed poor excretion on both sides but those parts shown appeared to be normal. The wound was soundly healed.

Case 15. J.B., aged 84, had an attack of haematuria. Four years previously had had acute retention and a transurethral resection of the prostate had been performed in another hospital. This had to be repeated as the retention was not relieved.

Clinical examination revealed a diffuse enlargement of the prostate.

Cystoscopy, lateral lobes of the prostate markedly enlarged. No evidence of papilloma found.

Urinary deposit, pus cells. Colonies of B. Coli too numerous to count.

Intravenous pyelography, no hydronephrosis and good concentration. Kidney function tests,

good. Hb., 66 per cent. R.B.C.s, 4.8 million. W.B.C.s, 10,000 per cmm.

14.5.48. 'Aseptic' prostatectomy and excision of papilloma which was $\frac{3}{4}$ in. wide. Gelfoam strips inserted into the prostatic bed. Owing to the presence of a urethral stricture the catheter could not be passed retrograde. Lucosil, 0.1 gm. four-hourly, and penicillin, 100,000 units t.d.s.

16.5.48. 6,000 colonies of *B. Coli* per cc. of urine.

18.5.48. Small number of leucocytes and R.B.C.s. Colonies of pyocyanus too numerous to count.

25.5.48. Hb., 45 per cent. R.B.C.s, 3.9 mill./cmm. W.B.C.s, 15,000/cmm.

29.5.48. Discharged. Urine clear.

Case 16. W.J.B., aged 63, had chronic retention and cystitis due to an enlarged prostate.

Intravenous pyelography, kidney function poor. Right kidney hydronephrotic. Urine:—alkaline, trace albumin. Sugar, Nil. Deposit, leucocytes and coliform bacteria.

11.5.48. 'Aseptic' prostatectomy. Lucosil mitis, 0.1 gm. four-hourly. Penicillin, 100,000 units six-hourly.

12.5.48. Urethral tube blocked twice. Cleared by irrigation with 5 per cent. citrate solution.

14.5.48. *B. Coli* and pyocyanus in urine. Colonies too numerous to count.

15.5.48. Urine:—neutral, large amount of albumin. Large number of pus cells, R.B.C.s and organisms. Culture. *B. Coli* too numerous to count.

21.5.48. Pelvic abscess.

25.5.48. Abscess burst into bladder. Culture of urine overgrown with *B. Proteus*.

On discharge the urine was still infected.

Discussion

This investigation confirmed the value of lucosil mitis in *B. Coli* infections provided there is no mechanical obstruction in the genito-urinary tract. There were no toxic symptoms due to the drug. Vomiting, nausea, leucopenia, agranulocytosis, lymphadenopathy did not occur. Case 4 developed anuria but this was due to ascending pyelonephritis. Case 2 developed a rash but the patch test and distribution led us to believe that this was due to biniodide. Cases 13 and 16 took the drug for nearly a month without showing any ill effects from it.

B. Proteus and pyocyanus infections were not

controlled by it. In these cases streptomycin proved of value.

With regard to penicillin, R. Cruickshank (1945) and other speakers in a discussion at the Royal Society of Medicine, indicated that the sulphonamides and other antiseptics are more helpful in most urinary infections for these are commonly due to *B. Coli*. H. F. Helmolz and C. Sung (1944) tested the penicillin susceptibility of the common organisms in infected urine. They found that coliform infection was resistant to a dosage of 100,000 units of penicillin a day. This should give a concentration of 60 units per cc. of urine. *Staph. aureus* was inhibited at a concentration of 0.033 units of penicillin per cc. urine and *str. faecalis* at 3 units. In our experience, we have not been able to sterilize the urine in *B. Coli* infections even when using massive doses of penicillin ($\frac{1}{4}$ -1 million units daily).

Lucosil mitis appears, therefore, to be a valuable addition to the sulphonamide group, being active, well tolerated and of low toxicity.

Summary

Sixteen genito-urinary cases were treated with lucosil mitis. There were no toxic manifestations or discomfort due to the drug. In the absence of mechanical obstruction *B. Coli* infections were cured in five days.

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The streptomycin was obtained through the Medical Research Council.

The preparation referred to as 'Lucosil Mitis' is not at present available in this country. We understand that Messrs. William R. Warner & Co., expect shortly to issue a similar preparation under the name 'Urolucosil.'

BIBLIOGRAPHY

- ANDERSON, T., THUNE, K., SCHMITH, K., and SOBYE, P. (1942), *Ugeskr. f. Laeger*, **104**, 215.
ANDERSON, V. (1943), *Ugeskr. f. Laeger*, **105**, 177.
CRUICKSHANK, R. (1945), *Proc. R. Soc. Med.*, **38**, 650.
HELMHOLZ, H. F., and SUNG, C. (1944), *Amer. J. Dis. Child.*, **68**, 236.
HEY, WILSON H. (1945), *Brit. J. Surg.*, **33**, 41.
NARINS, L. (1948), *J. Urol.*, **59**, 92.
POOL, T. L., and COOK, E. N. (1947), *J.A.M.A.*, **133**, 584.
SCHMITH, K. (1945), *Nordisk Medicin*, **28**, 1393.
STOCK, F. E. (1947), *Brit. J. Urol.*, **19**, 206.