STREPTOMYCIN POISONING IN RENAL FAILURE

AN INDICATION FOR TREATMENT WITH AN ARTIFICIAL KIDNEY

BY

K. D. G. EDWARDS*, M.B., B.S.

AND

H. M. WHYTE, D.Phil., M.B., M.R.C.P., M.R.A.C.P.

From the Clinical Research Department, Kanematsu Institute, Sydney Hospital, Sydney, Australia

It is well known that streptomycin can cause vestibular damage resulting in attacks of vertigo and loss of balance and that deafness sometimes occurs concurrently. Loss of vestibular function is usually permanent and may be completely disabling, although some patients, especially the younger ones, learn to use compensatory mechanisms and so reduce their symptoms (Cawthorne and Ranger, 1957).

There is considerable variation in the amounts of streptomycin reported to have caused toxic effects, but, being normally excreted in the urine, overloading and toxicity are much more likely to occur when renal function is defective. The first five cases we report here emphasize this. But the fact that the drug is normally eliminated from the body by glomerular filtration raises the possibility of removing it in an emergency by extra-corporeal haemodialysis. Tests carried out *in vitro* prove this to be effective, and we now regard streptomycin administration in an oliguric patient as a clear indication for early treatment with an artificial kidney. Freedom from the signs of streptomycin toxicity in five patients treated in this way suggests that the treatment might have some virtue.

Patients with Permanent Vestibular Damage

Five patients have been seen in the past two years with permanent vestibular damage due to streptomycin. All had evidence of renal disease.

Case 1.—A man aged 68 had been found to have a very high blood pressure one year previously. He had no symptoms for three months, then developed a severe infection of the renal tract. He was admitted to hospital, and treated with penicillin, sulphonamides, and 14 g. of streptomycin in one week. He noticed vertigo from the first time he sat on the edge of the bed, and when he was allowed to walk he was noticeably unsteady on his feet. Treatment with pentolinium and rauwolfia for hypertension aggravated the vertigo. The vertigo occurred with any sudden head movement and was often accompanied by migrainous headache. When admitted to Sydney Hospital for investigation he was found to have a blood pressure of 240/160 mm. Hg, he was slightly deaf, and he walked with great difficulty with a wide-based staggering gait. He spent most of the day in bed to minimize vertigo. Special tests showed bilateral perception deafness and absence of vestibular response to caloric stimulation. He had chronic renal failure, with a blood urea level of 110 mg./100 ml., and a specific gravity range of 1018 to 1001.

Case 2.—A woman aged 56 had been hypertensive for 16 years. For the last two years she had been treated for recurrent pyelonephritis with antibiotics, including one course of streptomycin. Ganglion blockade was begun in an attempt to relieve severe headache and breathlessness, but she had some hypotensive attacks, one of which was severe and led to acute oliguric renal failure. She passed

very little urine for seven days, during which time she was treated again with a course of streptomycin. When transferred to Sydney Hospital the blood urea level was 300 mg./100 ml. and diuresis began the same day. Convalescence was complicated by marked vertigo on moving her head, sometimes followed by nausea and vomiting. Caloric tests of vestibular function showed no response, although hearing was normal. This loss of balance sense threatened to keep the patient bedridden, but after several weeks she managed to walk slowly if she kept her head steady. When discharged home she was able to walk satisfactorily in this way, although she still became giddy if she moved her head suddenly, and she could not walk in the dark. Her renal function on discharge was severely impaired, with proteinuria and microscopic haematuria present, a blood urea level of 80 mg./100 ml., and a glomerular filtration rate of 17 ml./minute (15% of normal).

Case 3.—A woman aged 56 was admitted to hospital with severe colicky pain in the right loin, vomiting, dehydration, shock, fever, and oliguria. Laparotomy revealed no abnormality. She had injections of penicillin and streptomycin, and noradrenaline was given for 48 hours to maintain the systolic blood pressure above 100 mm. Hg. Urinalysis revealed proteinuria, haematuria, and pyuria. After four days the level of urea in the blood was 90 mg./100 ml., and she appeared to be improving but complained of buzzing noises in her ears. Streptomycin was suspended after 4 g. had been given. She became increasingly deaf in addition to the tinnitus and experienced vertigo whenever she moved her head. This was shown to be due to loss of vestibular function. Subsequent urological investigation showed urethral stenosis, chronic papular cystitis, and small, irregularly contracted kidneys with impaired function. Her acute illness was now thought to have been due to an exacerbation of chronic pyelonephritis. She was discharged home, but was disabled by loss of hearing, giddiness, and ataxia. Her final tests showed a level of urea in the blood of 44 mg./100 ml., and a urea clearance 44% of the standard normal.

Case 4.—A man aged 51 developed acute oliguric renal failure after transfusion of 100 ml. of mismatched blood during an orthopaedic operation. Diabetes mellitus had been discovered two months earlier and was controlled by diet. During the oliguric phase he received penicillin and 6 g. of streptomycin as routine post-operative prophylaxis before being transferred to this hospital. Haemodialysis in the artificial kidney was performed for 10 hours after 10 days of oliguria because of increasing distress from uraemia. Diuresis began and his renal failure was gradually corrected. Four weeks after the first streptomycin injections he noticed vertigo on moving his head, eyes, or arms, and difficulty in balancing. He preferred to be back in bed with his head quite still on the pillows. Caloric tests for vestibular function showed complete bilateral loss. With physiotherapy he gained sufficient confidence to learn to walk again, but he had complete loss of balance sense in the dark, and would fall over if he shut his eyes or suddenly turned his head or eyes. He was quite unable to return to work. When seen eight months later he was depressed and emotionally labile, with no further improvement.

Case 5.—A man aged 28 developed acute oliguric renal failure after a thoracotomy following a penetrating wound of the chest. Routine post-operative injections of penicillin and streptomycin were given, with a total dose of 4 g. of the latter. He was transferred to the clinical research unit, Sydney Hospital, after two weeks of conservative treatment. Haemodialysis was performed for 10 hours the next day because of severe uraemia, acidosis, and overhydration. The subsequent diuresis was uneventful from the biochemical aspect. Four weeks after the first injection of streptomycin he noticed vertigo on moving his head, and found difficulty in walking. He was anaemic, but a subsequent blood transfusion did not improve his symptoms. Caloric tests of vestibular function showed no response. Physiotherapy

*In receipt of a Fellowship from the Adolf Basser Research Fund of the Royal Australasian College of Physicians.

was effective in rehabilitation, and he was able to walk confidently with his head held steady, though he still experienced vertigo with sudden head movements and could not stand with his eyes closed. He continued to improve and was discharged home. Ten months later he still found difficulty in balancing, and caloric tests were still negative. While trout fishing on one occasion he had to travel two miles back to camp over rough country after dark. Walking was impossible because he kept losing his balance, so he crawled the whole way. He now makes sure of returning to camp before nightfall.

Dialysis of Streptomycin in Vitro

A simple, semi-quantitative test showed that streptomycin could be dialysed from blood across the same cellulose membrane as used in the artificial kidney. A small length of "visking" cellulose tubing containing 20 ml. of heparinized blood and 250 mg. of streptomycin was agitated for 18 hours in 500 ml. of 0.85% saline solution. Great care was taken with sterility. The streptomycin content of the bath fluid was measured by a modification of the method described by Mackie and McCartney (1953) in which serial dilutions of the test solution and of standard solutions of streptomycin were tested for their ability to inhibit the growth of the Oxford staphylococcus.

The results showed conclusively that streptomycin crossed the membrane to appear in the dialysing solution. By the end of 18 hours something between 100 and 250 mg. of streptomycin (40-100% of the original load) had been transferred from the blood to the bath fluid.

Patients Treated with Early Haemodialysis

Following these experiences it was decided to treat immediately by haemodialysis any further oliguric patients who had had a total dose of more than 1 g. of streptomycin.

Case 6.—A woman aged 30 developed acute renal failure following a severe ante-partum haemorrhage which necessitated a caesarean section and a blood transfusion. Streptomycin was begun two days later, but was stopped

after 1.5 g. had been given because she still had oliguria. She was transferred to Sydney Hospital on the eleventh day. Giddiness had appeared and was suggestive of vestibular damage. She had no nystagmus, but complained of vertigo unless she kept her head and eyes perfectly still. She was dialysed as soon as possible for 10 hours. Diuresis began the day after dialysis, and her recovery was uneventful. After five weeks the vestibular responses to caloric stimulation were normal, and she was discharged. Four months later she felt quite well and balance was normal.

Case 7.—A woman aged 38 had acute renal failure caused by a septic abortion due to *Clostridium welchii*. After three days at home she was admitted to hospital, where treatment included an eight-day course of 10 g. of streptomycin. Following this she was transferred to Sydney Hospital. Dialysis was begun as soon as possible, and was continued for four hours; for technical reasons it was stopped earlier than usual. During the oliguric phase, which lasted 18 days, the average urinary output was 400 ml./day. Diuresis followed, and the patient recovered. She had no loss of balance when discharged after nine weeks in hospital. After some weeks at home she noticed giddiness if she moved her head suddenly. She fell twice while out shopping, and had some difficulty in walking, but attributed this to very painful heels. The giddiness passed off, and when seen after four months her balance was normal, and tests of hearing and vestibular function were normal.

Cases 8, 9, and 10.—These patients received injections of 3 to 6 g. of streptomycin during the oliguric phase of acute renal failure. The causes of the renal failure and other details are shown in the accompanying Table, but all resembled Cases 6 and 7 in that they were treated by dialysis and all have remained free of symptoms and signs of streptomycin poisoning.

Discussion

The toxic effects of streptomycin became all too well known in the early days of its use. Smaller doses have since been advocated and the danger of renal insufficiency is better appreciated. The drug is normally eliminated in the urine by glomerular filtration, most of an injected dose being excreted unchanged within 12 hours. However, in severe renal failure very little is excreted and the concentration of streptomycin in the

Patients Given Excessive Doses of Streptomycin

Case No.	Age in Years	Sex	Diagnosis	Streptomycin					Dialysis Day (Days after Beginning Streptomycin)	Return of Urine Flow Exceeding 1,000 ml. Daily (Days)	Signs of Toxicity
				Days	Total Dose (g.)	Indication	Daily Urine Volume (ml.)	Maximum Plasma Urea (mg./100 ml.)			
Patients in whom the danger of streptomycin toxicity was not recognized: permanent damage sustained											
1	68	M	Chronic renal failure and hypertension	7	14	Pylonephritis	Not known	110	—	—	Bilateral loss of vestibular function and impaired hearing
2	56	F	Acute renal failure due to hypotensive therapy; chronic renal insufficiency	6	6?	„	30	300	—	7	Bilateral loss of vestibular function
3	56	F	Acute exacerbation of chronic renal failure	4	4	„	400	90	—	5	Bilateral loss of vestibular function and impaired hearing
4	51	M	Acute renal failure; mismatched blood transfusion; laminectomy	3	6	Post-operative prophylaxis	100	320	10	12	Bilateral loss of vestibular function
5	28	M	Acute renal failure after thoracotomy	4	4	„	30	470	15	16	„ „
Patients treated with dialysis specifically to remove streptomycin: no permanent damage detected											
6	30	F	Acute renal failure; ante-partum haemorrhage and caesarean section	1	1.5	Prophylaxis	240	355	9	10	Vertigo after 8 days, lasting for 2 days. Caloric tests normal
7	38	F	Acute renal failure; septic miscarriage	8	10	Septicaemia due to <i>Cl. welchii</i>	400	525	9	15	Giddiness after 80 days, lasting for some weeks. Caloric tests normal
8	38	F	„ „ „ „ „	5	5	„	0	360	5	16	None
9	62	M	Acute renal failure due to obstruction and haemolysis after prostatectomy	6	6	Post-operative prophylaxis	30	320	8	12	„
10	40	M	Crush syndrome	2	3	Prophylaxis	60	600	3 and 15	17	„

plasma may remain elevated for a long time. With each additional dose the plasma level rises further, and serious toxic effects may appear. The damage sustained by the central nervous system is usually permanent, especially in older patients, and sometimes more incapacitating than the disease for which streptomycin was given (Goodman and Gilman, 1955).

More recently an increasing incidence of toxic effects has been reported as occurring in spite of the smaller doses of streptomycin used currently in clinical practice. A total dose as small as 3 g. in three days has been known to cause vestibular damage, so that a more drastic limitation of dosage, to 0.5 g. daily whenever possible, has been advocated by Cawthorne and Ranger (1957). These authors described 24 cases of streptomycin poisoning, in nine of which urological disorders were present, with impaired renal function in at least two of them. They stressed the danger of giving the drug when there is renal insufficiency, and it would be interesting to know whether abnormalities in renal function could have been detected in all their patients who suffered damage. All of our patients, though only five in number, had gross renal insufficiency. It is an important point, because "on it depends whether the risks of the treatment can be determined beforehand or not" (*Brit. med. J.*, 1957).

Accumulating experiences certainly emphasize the importance of estimating renal function, at least roughly, before giving a course of streptomycin. It would be better to avoid giving it, unless absolutely necessary, when oliguria or shock is present, or when there is a possibility of acute renal failure occurring, as with septic abortions or crush injuries. It would be wise to take further thought and to make a full assessment of renal function before giving streptomycin for specifically renal conditions, or when there is a history of past or present renal disease, or when proteinuria or nitrogen retention is detected. Streptomycin therapy might well be regarded in similar light to the giving of potassium intravenously, where clinicians these days are rather acutely aware of the dangers involved and check that urinary excretion is adequate. Since becoming aware of the importance of asking about the use of streptomycin in anuric patients referred to us we have been surprised by the frequency with which it has been given. Often there has been no clear indication for its use and no awareness of the danger of continuing to administer it during a period of oliguria. The importance of avoiding streptomycin in the treatment of renal failure is not sufficiently well recognized, and finds no mention in recent accounts of the disease (Bull, 1955; Merrill, 1955).

Our own observations confirm the severity of the disability which streptomycin toxicity can induce, but an interesting and important feature is the long period of time which may elapse between administration of the drug and the appearance of symptoms. In both anuric patients symptoms were experienced 28 days after the first dose of streptomycin and 24 days after the treatment was stopped. This delay may be partly attributable to the fact that symptoms are less troublesome while lying in bed. Vestibular damage occurred in both of these men in spite of haemodialysis on the eleventh and sixteenth days and re-establishment of a daily excretion of urine in excess of 1,000 ml. soon after. It is possible that circulating streptomycin was insufficiently removed by dialysis and diuresis and continued to cause damage. Alternatively, the drug

could have become fixed in the tissues, or otherwise had time to cause damage which progressed even when streptomycin was removed or at least reduced in concentration.

This matter is not resolved by examining our experiences with other patients in acute renal failure in whom dialysis was deliberately used because they had been given streptomycin. One patient who had received 10 g. of the drug over eight days was not dialysed until the tenth day and yet remained free of symptoms. It must remain for further experience to demonstrate whether dialysis truly helps to prevent the development of vestibular damage due to streptomycin and the limits of safety in regard to dose and delay before dialysis.

There is no doubt, however, that streptomycin can be removed from the blood by dialysis. This fact has not been generally appreciated, and streptomycin could profitably be included in a list of drugs which can be removed by the artificial kidney (Merrill, 1957). Being confined to the extracellular fluid in the body, streptomycin should be more readily removed by dialysis than barbiturates and urea, which are distributed throughout the total body water. There is every reason to believe that early removal by dialysis should assist in preventing vestibular damage, and we now consider the administration of streptomycin in patients with renal failure to be one of the few conditions calling for immediate treatment with an artificial kidney (Edwards and Whyte, 1958).

Summary

Five instances of streptomycin poisoning in patients with renal insufficiency are described. In two of these with acute oliguric renal failure the symptoms of vestibular damage appeared 24 days after the last dose of streptomycin and after diuresis had occurred.

Tests *in vitro* showed that streptomycin can be removed from blood by dialysis, and early treatment with an artificial kidney is recommended for oliguric patients who have been given streptomycin.

Five patients with acute renal failure who had received 1.5 to 10 g. of streptomycin were treated by haemodialysis as early as was possible (three to nine days). None developed signs of toxicity.

Accumulating experience emphasizes the importance of estimating renal function before giving a course of streptomycin.

ADDENDUM.—The Commonwealth Serum Laboratories have kindly agreed to carry out streptomycin assays for us. Tentative conclusions reached for one of our recent patients who had received 3 g. of streptomycin were that dialysis reduced the concentration in the blood from 32 to 17 $\mu\text{g./ml.}$ Unfortunately, this woman developed signs of streptomycin toxicity. She is the only one to have done so of the eight patients who have been treated by dialysis specifically because they had received streptomycin.

REFERENCES

- Brit. med. J.*, 1957, 1, 1466.
Bull, G. M. (1955). *Lancet*, 1, 731, 777.
Cawthorne, T., and Ranger, D. (1957). *Brit. med. J.*, 1, 1444.
Edwards, K. D. G., and Whyte, H. M. (1958). *Med. J. Aust.* In press.
Goodman, L. S., and Gilman, A. (1955). *The Pharmacological Basis of Therapeutics*, 2nd ed. Macmillan, New York.
Mackie, T. J., and McCartney, J. E. (1953). *Handbook of Practical Bacteriology*, 9th ed. Livingstone, Edinburgh.
Merrill, J. P. (1955). *The Treatment of Renal Failure*. Grune and Stratton, New York.
— (1957). *J. chron. Dis.*, 5, 138.