ACETAZOLAMIDE THERAPY WITH RENAL COMPLICATIONS

BY

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Acetazolamide ("diamox") is widely used in the treatment of heart failure, epilepsy, and glaucoma. Although this drug is chemically a heterocyclic sulphonamide, there have not been many reports of renal complications following therapy. A number of cases have been recorded with renal colic whilst receiving treatment, but some of these were shown to have renal calculi. Becker and Middleton (1955) reported a case with an exacerbation of renal colic, in a series of 70 cases of glaucoma treated for up to 15 months; and Scheie (1955) described two cases treated for glaucoma which had symptoms of renal calculi, but these might have been present before therapy was instituted. Persky *et al.* (1956) reported the cases of two patients on long-term therapy for glaucoma, who had renal calculi, and that of a third patient, who had renal colic after two weeks of treatment, but a calculus was not demonstrated. They also quoted a personal communication (Leopold) concerning two patients with calculi receiving this drug. Barraquer and Escribano (1957) recorded typical renal colic in 30 patients among 300 treated for glaucoma, and five of these had copious haematuria.

It seems appropriate to record a case in which the repeated administration of acetazolamide was followed by recurrent renal complications.

Case Report

The patient, a professional man aged 28, had been subject to major and minor fits for 12 years, attributable to idiopathic epilepsy, and had regularly taken various anti-convulsant drugs. In addition, acetazolamide, 250 mg. daily, was first prescribed in March, 1957, and the incidence of his fits diminished. Without any previous history of renal disorder, he developed severe colicky pain, radiating from the left loin to the left testis, five weeks after the institution of the new drug. This attack lasted half an hour, and no urinary abnormality was noted.

One week later a similar attack of left renal colic occurred for 12 hours, and this time a small quantity of blood-stained urine was passed. He was well for a further six days and then developed right renal colic, which recurred intermittently until his admission to hospital four days later. Between the spasms he had dysuria and a constant dull ache in the right loin and right testis. The urine was not blood-stained, and, as before, no calculus or gravel was passed.

On admission (May 13) slight tenderness in the right renal angle was the only abnormal physical sign. He was afebrile and the blood pressure was 130/80. A catheter specimen of urine was sterile, free from albumin, and normal on microscopy. An intravenous pyelogram showed that the dye was not concentrated by the right kidney, but the density of the right renal shadow appeared to be slightly increased. The dye was excreted by the left kidney in diminished concentration. Calcified mesenteric glands were noted in the central abdomen, but no calculi were seen.

Retrograde examination of the urinary tract was performed by Mr. D. B. E. Foster on May 14. Cystoscopy revealed a normal bladder. Following right ureteric catheterization and irrigation with normal saline, a coagulum (described as "a sludge") was dislodged, resembling altered blood, which appeared to be obstructing the urinary flow. Similar material was obtained from the left ureter, but less in quantity. Subsequent retrograde pyelography revealed no significant abnormality in either urinary tract, and there

was no evidence of renal or ureteric calculi. Sterile specimens of urine were collected from both ureters before and after irrigation. Crystals were not found on microscopy, and the only abnormalities seen were numerous red blood corpuscles and occasional leucocytes. Acetazolamide therapy was discontinued without recurrence of urinary symptoms in hospital. He remained afebrile, and his daily urinary output was normal. An intravenous pyelogram one week later showed normal dye concentration and excretion by the right kidney, whereas concentration by the left kidney was still deficient.

After discharge from hospital on May 28 he returned to his home in another part of the country. Acetazolamide was not used again until the end of July, when he was given 250 mg. daily because of unsatisfactory control of his epilepsy. Six days later he developed an aching testicular pain and the drug was discontinued, with subsequent relief from pain. He was finally given acetazolamide 65 mg. daily in another centre in November, and after 10 days similar aching testicular pain occurred, followed by an attack of left renal colic, which lasted 10 hours. The drug has not been used again, and he has had no further renal colic.

Discussion

The third case of Persky *et al.* (1956) had certain features in common with our patient. They described a woman with glaucoma, aged 63, who was admitted to hospital with left renal colic, two weeks after the beginning of acetazolamide therapy (250 mg. four times daily). She had haematuria and frequency, and was tender in the left flank. The only microscopical abnormality recorded was red blood cells in the urine. Intravenous pyelograms before ureteric catheter drainage showed delayed excretion on the left, but afterwards normal excretion was demonstrated. No calculi were seen, but it was presumed that a small calculus had been passed, as there was haemorrhage and oedema of the left ureteric orifice. A blood clot, however, could have caused ureteric obstruction, as in our patient.

Since our patient also did not have crystalluria, the case described by Glushien and Fisher (1956) is particularly significant. A course of acetazolamide (250 mg. thrice daily for four days) had been prescribed for oedema complicating Hodgkin's disease, and at necropsy, 24 days later, renal lesions attributable to the drug were discovered. He had not taken any other form of sulphonamide drug. Microscopy revealed crystals in the renal tubules which resembled crystals that were obtained by the recrystallization of acetazolamide in acid solution. In spite of these and other renal changes, there had been no evidence of significant nitrogen retention or urinary suppression, and urinalysis had been entirely normal.

Bertino *et al.* (1957) found similar crystals in the renal tubules at necropsy in a case of the nephrotic syndrome, in which a total of 3 g. of acetazolamide had been given over nine days, 11 weeks before death.

The alternation between left and right renal colic which occurred in our patient was also noted by Barraquer and Escribano (1957) in one of their 30 cases.

There seems to be no doubt that the administration of acetazolamide to our patient caused his repeated attacks of renal colic. This is strongly suggested by the sequence of events, the absence of symptoms when the drug was withheld, and the negative previous history. There was evidence neither of calculus nor of infection of the urinary tract. The patient was most impressed by the beneficial effect of the addition of acetazolamide

to his anticonvulsive therapy, and he is disappointed that he has been unable to continue to take this drug.

ADDENDUM.—Since this paper was submitted, a man aged 57, with glaucoma, has been admitted to Llandough Hospital with typical right renal colic, which occurred during long-term acetazolamide therapy (250–500 mg. daily for three months). The pain lasted 36 hours and there was no oliguria. The previous history and physical findings were not suggestive of renal disorder. Numerous red blood corpuscles and occasional leucocytes were seen on microscopical examination of the urine, which was sterile, and an intravenous pyelogram was normal. My thanks are due to Mr. D. B. E. Foster for inviting me to see this patient.

Summary

A case of recurrent renal colic attributable to the repeated use of acetazolamide is described. One episode of unilateral suppression of urine was successfully treated by ureteric catheterization. Similar cases in the literature are discussed in brief.

I am indebted to Dr. Byron Evans for his permission to publish this case and for his advice. My thanks are also due to Dr. G. de B. Hinde for his help in the interpretation of the radiographs.

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Medical Memorandum

Acute Dystonic Reaction to Perphenazine

Phenothiazine derivatives of increasing variety are now in use as tranquillizers and anti-emetics and in the treatment of psychiatric disorders. The toxic effects of these drugs may occasionally cause alarm and diagnostic confusion to the uninitiated, and we are prompted to report the following case in which a dramatic picture suggestive of tetanus followed the use of a small dose of perphenazine ("trilafon").

CASE REPORT

The patient, a girl aged 18, had been treated unsuccessfully with dimenhydrinate for vomiting of pregnancy. At 10 weeks, treatment was begun with perphenazine, 4 mg. twice daily. At 6 a.m. the next day she complained of aching at the root of the jaws and difficulty in opening her mouth, but as the vomiting had been relieved she took a third tablet.

A few hours later she reported in the surgery. Her head was tilted backwards and to one side and her jaw was held open. Her facies was immobile and vacant. Although she could talk, she could not maintain her mouth in the closed position. She said her eyes were trying to roll upwards and she still had aching in the jaws. Her gait was normal and there was no tremor. She had no vertigo or headache and was mentally normal, alert, and acutely embarrassed by her "foolish appearance."

The diagnosis of a drug reaction was made. Pethidine, 50 mg., was given intramuscularly, and after 30 minutes the posture had relaxed and the facies had improved. During the next six hours, however, the symptoms of dystonia returned in spasms of increasing severity alternating

with partial relaxation. The features were now clenching of the jaws and head retraction. At 7 p.m. she was found in a position of opisthotonos, with strong spasm of all the spinal muscles. There was severe trismus and risus sardonius, the eyes were deviated upwards, and the brow was corrugated. She was fully conscious and anxious, and intimated that she had pain in the neck.

Apart from the upward deviation of the eyes, the picture was now typical of tetanus, and there was a recent history of chronic sepsis in the leg. Confidence was shaken in the diagnosis of an iatrogenic disorder, and after another dose of 100 mg. of pethidine she was transferred to hospital.

The pethidine again appeared to induce rapid relaxation. On arrival in hospital an hour later she was drowsy and depressed, but there was no trace of dystonia, and she could touch her toes. Full neurological examination was negative. As her story was reminiscent of an oculogyric crisis, signs of extrapyramidal disorder were particularly sought, but were absent.

Subsequently the use of phenothiazine drugs was avoided and there was no further evidence of any abnormality of physical or mental behaviour.

COMMENT

Perphenazine ("trilafon"; 1-[3-(2-chloro-10-phenothiazinyl) propyl]-4(2-hydroxyethyl) piperazine) is closely related to prochlorperazine ("stemetil"; 1-[3-(3-chloro-10-phenothiazinyl) propyl]-4-methyl piperazine). Various bizarre reactions which were thought to be peculiar to stemetil have been reported by the manufacturers. These include lip tremors, athetotic movements, trismus, and torsion of the spine with painful spasms of spinal muscles which may amount to opisthotonos. Hare (1958) has drawn attention to the very rare occurrence of similar symptoms, including head retraction, due to chlorpromazine. In addition mild features of Parkinsonism may occur with all drugs of the phenothiazine group. Although the more dramatic manifestations may be aggravated by stress and partly alleviated by commands, there is no doubt that they represent a true drug reaction and are not hysterical in nature. They appear to be related to high dosage and to be entirely reversible.

Acute dystonia following perphenazine has been noted previously (Shanon *et al.*, 1957). Other reports, however, have stressed its low toxicity in a dose range of 8–16 mg. daily, mild features of Parkinsonism occasionally occurring with daily dosage above 40 mg., while 72 mg. has been given for long periods in psychiatric practice (O'Reilly *et al.*, 1957; Schultz and Henderson, 1957). The reaction we have described after a total dose of 12 mg. is therefore remarkable. Although no other features of Parkinsonism were present, it appears to represent an exaggerated oculogyric crisis, with involvement of the muscles of the jaw and spine presumably through the medium of the extrapyramidal system.

A question of further interest, therefore, is the exact site of induction of this combination of trismus and opisthotonos, and its possible bearing on the unexplained predominance of these features in tetanus.

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