Reversible overt nephropathy with Henoch-Schönlein purpura due to piroxicam

Even though newly developed effective antiarithmetic agents may initially be reported as causing only minor side effects, toxic reactions, which are often undetected in early studies, may occur. Piroxicam has recently been repeatedly shown to act as a strong inhibitor of prostaglandin synthesis and may be taken once a day because of its long plasma half-life of 36-56 hours.1 Non-steroidal anti-inflammatory drugs may cause nephrotoxicity as an effect secondary to their inhibition of prostaglandins;2 this differs from phenacetin-induced analgesic nephropathy. We report on two patients who as a result of hypersensitivity to piroxicam (Pfizer Inc, Karlsruhe, West Germany) developed acute nephropathy with characteristic features of Henoch-Schönlein purpura.3

Case reports

CASE 1

A 27-year-old male student with a two-year history of classical seronegative rheumatoid arthritis regularly attended the rheumatic disease service of our department. Active joint disease (American Rheumatoid Arthritis Association criteria) affected both hands, his fingers, knees, and ankle joints, with signs of synovitis rather than joint destruction. After treatment with aspirin and ketoprofen without improvement he began taking 20 mg piroxicam daily, which induced appreciable clinical remission. He observed painless macroscopic haematuria associated with a mild purpuric rash.

Clinical examination, renal x-ray films, echography, and scintigraphy showed no abnormalities except for a mild disseminated rash and peripheral oedema. The ratio of blood urea nitrogen to creatinine concentration and electrolyte concentrations and chemistry profiles were normal, but urine analysis showed macroscopic haematuria. Piroxicam was stopped and his nephropathy and rash had disappeared by the fourth day after admission. Treatment with piroxicam was not repeated.

CASE 2

A 51-year-old postmenopausal woman with no history of renal disease was admitted for treatment of an active phase of classical rheumatoid arthritis (American Rheumatoid Arthritis Association criteria). She took 20 mg piroxicam daily with an excellent clinical response. Prostaglandin E2 concentrations (measured radioimmunochemically) in synovial fluid aspirated from inflamed knee joints were reduced (see figure). She had painless macroscopic haematuria and complained of a rash and abdominal discomfort and so was readmitted to hospital, treatment with piroxicam alone was continued.

Clinical examination showed a purpuric rash, peripheral oedema, and gastrointestinal haemorrhage. Signs of nephropathy were macroscopic haematuria, proteinuria, and a reduced glomerular filtration rate (figure). The ratio of blood urea nitrogen to creatinine concentration, electrolyte concentrations, and further chemistry profiles were within normal limits. Concentrations of circulating IgA immune complexes (using the Raji-cell assay and direct fluorescein isothiocyanate-labelled antihume rabbit gamma-globulin method) were raised (figure). Thus she fulfilled the criteria for Henoch-Schönlein purpura.4 Her condition improved rapidly and completely after piroxicam was stopped, and IgA immune complexes fell to within normal limits (figure). When her condition had completely stabilised she was rechallenged with piroxicam 10 mg daily. She again showed signs of Henoch-Schönlein purpura and impaired renal function associated with increased IgA complexes.

Comment

The rapid improvement that occurred in case 2 when piroxicam was withdrawn, and the relapse of clinical symptoms on rechallenge, strongly suggest that piroxicam was causally related to the acute Henoch-Schönlein purpura.

Some features of Henoch-Schönlein purpura suggest a vasculitis caused by circulating immune complexes containing IgA, which in particular are deposited in the glomerular mesangium and in normal as well as affected skin.4 Thus the urinary symptoms in case 1 and the drug-induced multisystemic disease in case 2 closely resembled classical Henoch-Schönlein purpura, which principally affects children.

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Drugs that strongly inhibit prostaglandin synthesis do not reduce the glomerular filtration rate or sodium excretion in hypertensive patients.\(^2\) In contrast, acute nephropathy requiring peritoneal dialysis occurred in a patient with compensated congestive heart failure treated with indomethacin.\(^3\) Renal function deteriorated considerably after treatment with piroxicam in both our patients, which indicates a hitherto unrecognised adverse reaction to this drug. Since piroxicam seems a promising treatment for rheumatoid arthritis this possible association of prolonged treatment with Henoch-Schönlein purpura must be confirmed or refuted.

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Rebreathing aborts migraine attacks

Four patients have been described1 who hyperventilated during their migraine attacks, which made their symptoms worse and in one case produced carpopedal spasm. There have been further reports (personal communications) in which one subject produced an attack by blowing up balloons, and another, trying to assure the symptoms of hyperventilation including carpopedal spasm which accompanied some of her attacks, found that rebreathing also abolished the nausea and reduced the headache. I describe six patients who were able to abort many of their attacks by rebreathing their own expired air from a bag.

Case reports

Case 1—A 37-year-old accountant with a history of classical migraine since childhood presented at this migraine clinic at the onset of an attack. He had had a visual aura of patchy scotoma for approximately 20 minutes before presentation and parasthesiae affecting his fingers. His aura usually lasted 40 minutes and would then be followed by nausea, sometimes vomiting, and headache lasting roughly six hours. Examination showed a left-sided palsy which the patient had had since his early teens. Otherwise there were no findings of note. The patient was asked to breathe through a nylon mouth valve into a bag, 25 cm × 20 cm made from laminated polyethylene and polyethylene terephthalate, a combination of material resistant to highly diffusable carbon dioxide. After 20 minutes of slow, deep breathing, with only a small intake of fresh air, his nausea had not developed although he had a slight headache. Twenty minutes later, after further rebreathing, there was no visual disturbance, nausea, or headache. The patient commented that while he was surprised to be so much better, so quickly, the technique had left him feeling as if he had “run up a down escalator.”

Case 2—A 29-year-old overweight and bronchitic Post Office worker had a 19-year history of classical migraine. His attacks occurred up to twice a week, lasted about six to eight hours, and were heralded by tachypnoea and diplopia, which lasted 10 minutes. At the onset of the headache he developed a right palsy and his eye would become fully closed if the attack was severe. Using the aura as an indication to begin rebreathing he was able to stop those attacks in which he thought the nausea and pain would not be very intense. On two occasions he persevered with rebreathing for 20 to 30 minutes at the onset of what he considered were the beginnings of severe attacks, in these occasions he lapsed into a state of unconsciousness to awake without a headache or nausea one to two hours later. Because of this disconcerting effect he was reluctant to continue rebreathing for very long.

Cases 3-6—the table gives details of these cases.

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*Identical twins.

Comment

It has been shown2 that patients can prevent their migraine attacks from developing by breathing carbon dioxide-oxygen mixtures at the onset of their attacks, but not by breathing carbon dioxide-air mixtures. These studies suggest that oxygen be important in preventing the development of an attack, although more recently oxygen inhalation has not proved to be effective.

In the series reported here patients rebreathed air. In such a “closed circuit,” carbon dioxide pressure must rise and oxygen pressure should fall. Thus in this group of patients the rise in carbon dioxide pressure, or other associated changes, or both, seemed to be important in aborting their migraine attacks. In case 5 unconsciousness induced by rebreathing was probably due to lack of anoxic drive, which is well recognised in some subjects and indeed more common in those with chronic respiratory disease, such as this subject. If carbon dioxide is the active agent in preventing migraine attacks, its mechanism of action is hard to explain. The contemporary view is that the migraine aura is caused by intracranial vasosconstriction and that the headache phase is due to extracranial vasodilatation. Carbon dioxide, a powerful vasodilator, should therefore increase the head pain. Possibly rebreathing protects by reversing the initial vasoconstriction, halting the migraine process. Alternatively, if the concept of two types of migraine sufferers, “dilators” and “constrictors,” is correct, rebreathing should benefit the constrictors. Recently, however, it has been suggested3 that extracranial vasodilatation may not contribute appreciably to migraine pain.

While it is difficult to explain the possible therapeutic effect of rebreathing in migraine, it is possible that changes in the interelectroencephalograms of some subjects with migraine remain unexplained. If the carbon dioxide pressure is important this may explain why exercise and excitement with increased ventilation can provoke attacks and why sleep, perhaps due to reduced ventilation, can cut short attacks. Nevertheless, the beneficial effects of rebreathing may be due not to the raised carbon dioxide pressure but to other changes postulated4 that endorphins minimise the stress of chronic airway obstruction; perhaps rebreathing achieves its therapeutic effect in migraine through the release of endorphins secondary to the respiratory distress it causes. Whatever the mechanism by which rebreathing aborts migraine attacks, new light may be thrown by this near-ancient technique on to an even older problem.

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