SHORT REPORTS

Anaphylactic shock induced by diclofenac

Diclofenac is a non-steroidal anti-inflammatory agent used in degenerative joint disease, rheumatoid arthritis, and allied conditions.¹ Its commonest unwanted effects include gastrointestinal disorders, rashes, peripheral oedema, and abnormalities of serum transaminase activity. More rarely, melaena and haematemesis, myoclonic encephalopathy, and myoclonus of the lower limbs may occur.^{2,3} We report a case of anaphylactic shock induced by diclofenac, which as yet is an unreported complication of treatment with this agent.

Case report

An 80 year old man with mild diabetes was treated with diclofenac 50 mg three times a day for degenerative osteoarthritis. Six months later in January 1981 his treatment was changed to ibuprofen 0.2 g three times a day. In March 1981 his pain was worse and he restarted treatment with diclofenac. Twelve hours after the first dose he consulted his doctor with a fever of 38.5 °C and vomiting. He was treated with paracetamol and his symptoms subsided in 36 hours. After four days he took another tablet of diclofenac and six hours afterwards was referred to our department because of a temperature of 39 °C, rigors, and vomiting. Except for a blood pressure of 70/50 mm Hg physical examination was normal. There were no signs of dehydration. Urine output during the first 24 hours was 550 ml. Laboratory findings were: haemoglobin, 12 g/dl; white blood cell count, $17.0 \times 10^9/l$ with a normal differential count; serum aspartate transaminase (AST), 90 IU/l (normal, 20-45 IU/l), serum lactic dehydrogenase, 337 IU/l (normal, 160-220 IU/l), serum alkaline phosphatase, 263 IU/l (normal, 20-95 IU/l), serum bilirubin, 35.9 $\mu\text{mol/l}$ (2.1 mg/100 ml (direct, 18.8 $\mu\text{mol/l}$ (1.1 mg/100 ml)), and serum creatinine 265.2 $\mu\text{mol/l}$ (3.0 mg/100 ml). Urine analysis was normal. Sputum, urine, and blood cultures were negative. A chest radiograph showed a mild cardiomegaly and electrocardiogram at rest showed a right bundle branch block with left axis deviation.

Although no causative agent or possible source of infection was found, the patient was treated for septic shock. He received isotonic fluids, crystalline penicillin 10 million units, and gentamicin 240 mg a day. His temperature subsided within 10 days, and the liver and kidney function tests returned to normal. He was readmitted after four months when rigors, vomiting, and fever (38 °C) followed a single dose of 25 mg of diclofenac by mouth. Blood pressure on admission was 100/60 mm Hg and the remainder of the physical examination was normal. Laboratory findings were: erythrocyte sedimentation rate (Westergren), 72 mm/first hour; haemoglobin, 12.2 g/dl; white blood cell count, $9.6 \times 10^9/l$ with a normal differential count; serum aspartate transaminase, 65 IU/l; serum lactate dehydrogenase, 280 IU/l; serum alkaline phosphatase, 165 IU/l; serum bilirubin, 23.9 $\mu\text{mol/l}$ (1.4 mg/100 ml); serum creatinine, 123.7 $\mu\text{mol/l}$ (1.4 mg/100 ml); serum complement—C3, 0.98 g/l (normal, 0.55-1.2 g/l), C4, 0.38 g/l (normal, 0.2-0.5 g/l). Protein immunoelectrophoresis and urine analysis were normal. Sputum, blood, and urine cultures were negative. Macrophage migration test was inhibited by diclofenac but not by ibuprofen. Mast cell degranulation test was negative for both drugs. X ray examination of the chest and total body radioisotope scan with gallium 67 did not show signs of focal infection. At this stage a hypersensitivity reaction to the drug was suspected and no antimicrobial treatment was given. Fever subsided gradually within four days and the patient was discharged in good health with normal kidney and liver function tests.

Comment

Hypersensitivity reactions to non-steroidal anti-inflammatory drugs, manifested by asthmatic attacks, urticaria, or angioedema, have been described.⁴ These reactions have been attributed to prostaglandin synthetase inhibition. Anaphylactic shock and urticaria have been reported in patients with idiosyncratic reaction to pyrazoline drugs, and this type of hypersensitivity seems to have an immunological background.⁴

Our patient developed a shock like syndrome, accompanied by a high grade fever, which is similar to that described in patients with idiosyncrasy to pyrazoline drugs. The concomitant appearance of shock and diclofenac ingestion on three different occasions confirms their causal relation.

Both the clinical picture and the positive macrophage migration test suggest a type of hypersensitivity reaction.

We should, however, emphasise that in all three instances in our patient the diclofenac induced anaphylaxis was preceded by ibuprofen ingestion. When the patient took diclofenac for the first time before

treatment with ibuprofen anaphylaxis did not occur. Thus the role of this drug in the induction of hypersensitivity is still to be determined.

¹ Brogden RN, Heel RC, Pakes GE, Speight TM, Avery GS. Diclofenac sodium: a review of its pharmacological properties and therapeutic use in rheumatic diseases and pain of varying origin. *Drugs* 1980;20:24-48.

² Martindale W. *The extra pharmacopoeia*. In: Wade A, ed. London: Pharmaceutical Press, 1977:1749.

³ Alcalay M, Thomas P, Reboux JF, Bontoux D. Myoclonies au cours d'un traitement par le diclofenac. *Sem Hop Paris* 1979;55:679-8.

⁴ Szezklik A, Gryglewski RJ, Czerniawska-Mysik G. Clinical patterns of hypersensitivity to non-steroidal anti-inflammatory drugs and their pathogenesis. *J Allerg Clin Immunol* 1977;60:276-84.

(Accepted 10 March 1983)

Department of Internal Medicine "C," Sackler School of Medicine, Tel Aviv University, Israel

SHLOMO DUX, MD, chief resident

ITAMAR GROSLOP, MD, resident

MOSHE GARTY, MD, MSC, deputy chief

JOSEPH B ROSENFELD, MD, professor of medicine

Correspondence and reprint requests to: Dr S Dux, Department of Internal Medicine "C," Beilinson Medical Center, Petah Tiqva, Israel.

Rifampicin and adrenal crisis

Rifampicin, a potent inducer of hepatic enzymes, increases the metabolism of glucocorticoids.¹ We report two cases of adrenal insufficiency secondary to tuberculosis in which acute adrenal crisis was apparently precipitated by rifampicin.

Case reports

Case 1—A 65 year old man presented with a productive cough and weight loss. Examination showed generalised skin pigmentation. The chest radiograph showed minimal infiltration in the left upper lobe, and after four weeks of incubation the sputum contained a scanty growth of acid-fast bacilli. The serum sodium concentration was 135 mmol(mEq)/l, potassium concentration 5.14 mmol(mEq)/l, and urea concentration 5.6 mmol/l (33.7 mg/100 ml) and the blood pressure 140/90 mm Hg. Treatment was started with rifampicin 600 mg, isoniazid 300 mg, and ethambutol 1 g daily. Because of the pigmentation arrangements were made to investigate possible adrenal insufficiency. Before the arranged admission, however, he presented with dizziness and lethargy. He was clinically dehydrated and had a blood pressure of 100/60 mm Hg. The serum sodium concentration had fallen to 115 mmol/l and the potassium and urea concentrations increased to 5.4 mmol/l and 8.0 mmol/l (48.2 mg/100 ml), respectively. A tetracosactrin (Synacthen) challenge test was immediately performed and subsequently confirmed adrenal insufficiency: serum cortisol values were 95 nmol/l (3.4 $\mu\text{g}/100\text{ ml}$) before and 85 nmol/l (3.1 $\mu\text{g}/100\text{ ml}$) 30 minutes after 0.25 mg tetracosactrin. The patient was treated with intravenous saline and hydrocortisone, his condition rapidly improved, and the electrolyte values returned to normal. He subsequently remained well initially taking 37.5 mg cortisone acetate and 0.1 mg fludrocortisone daily. Plasma cortisol concentrations remained low (85 nmol/l two hours after cortisone acetate), however, and these doses were therefore doubled. The 6 β -hydroxycortisol excretion rate was 4379 $\mu\text{g}/\text{day}$.

Case 2—A 73 year old man with extensive pulmonary tuberculosis was admitted complaining of nausea, vomiting, and weight loss seven weeks after beginning treatment with rifampicin 600 mg, isoniazid 300 mg, and ethambutol 800 mg daily. He was clinically dehydrated. Blood pressure was 120/70 mm Hg and serum sodium concentration 127 mmol(mEq)/l, potassium concentration 4.3 mmol(mEq)/l, and urea concentration 17.8 mmol/l (107 mg/100 ml). Chemotherapy was discontinued. After 400 mg of hydrocortisone his general condition slowly improved, and four weeks later the antituberculous chemotherapy was reinstituted. Within 14 days he was again complaining of nausea and vomiting. There was mild generalised pigmentation, clinical dehydration with a blood pressure of 100/60 mm Hg, and the serum sodium concentration was 127 mmol/l, potassium concentration 5.2 mmol/l, and urea concentration 23.3 mmol/l (140 mg/100 ml). The basal cortisol value was 213 nmol/l (7.7 $\mu\text{g}/100\text{ ml}$) with no response to challenge with tetracosactrin. After treatment with intravenous saline and hydrocortisone he rapidly improved and subsequently remained well taking 37.5 mg cortisone acetate and 0.1 mg fludrocortisone daily.

Comment

Rifampicin is a potent inducer of hepatic microsomal enzymes and increases the oxidation of cortisol to 6 β -hydroxycortisol.² As the major pathway of cortisol metabolism involving tetrahydroreduction of the A ring is not thought to be altered this increased utilisation usually represents only a small percentage of the cortisol produced in patients with normal adrenal function. In patients with pre-existing adrenal insufficiency, however, a higher and probably critical percentage may be involved.¹

In both of our patients, who had adrenal insufficiency associated with tuberculosis, it is highly probable that rifampicin precipitated the acute adrenal crisis. In case 1 this occurred two weeks after beginning treatment (the time interval at which maximal enzyme induction is occurring)³ and unusually high doses of replacement therapy were required, while in case 2 the biochemical features of adrenal insufficiency improved when rifampicin was discontinued only to recur two weeks after it was reintroduced. Moreover 6 β -hydroxycortisol excretion in case 1 was three to four times greater than that usually produced by therapeutic doses of rifampicin.²

To our knowledge the patient described by Edwards *et al*¹ is the only other case in which rifampicin was thought to have induced an acute adrenal crisis. We emphasise the importance of considering adrenal insufficiency in all patients treated with rifampicin as adrenal crisis may occur within two weeks after beginning the drug even in those whose cortisol production is only mildly impaired (case 2). In addition, replacement therapy should be carefully monitored, as the standard doses of cortisone acetate and fludrocortisone may be inadequate (case 1).¹ Other workers have also emphasised that patients receiving therapeutic doses of corticosteroids may need an increased dose when starting rifampicin.⁴

We thank Dr C A Hopkins for allowing us to report the patient in case 2 and Dr K Park for measuring 6 β -hydroxycortisol excretion in case 1 and for helpful advice.

¹ Edwards OM, Courtney-Evans RJ, Galley JM, Hunter J, Tait AD. Changes in cortisol metabolism following rifampicin therapy. *Lancet* 1974;ii:549-51.

² Ohnhaus EE, Park BK. Measurement of urinary 6 β -hydroxycortisol excretion as an in vivo parameter in the clinical assessment of the microsomal enzyme-inducing capacity of antipyrine, phenobarbitone and rifampicin. *Eur J Clin Pharmacol* 1979;15:139-45.

³ Buffington GA, Dominguez JH, Piering WF, Herbert LA, Kauffman HM, Lemann J. Interaction of rifampicin and glucocorticoids. *JAMA* 1976;236:1958-60.

⁴ McAllister WAC, Thompson PJ, Al-Habet S, Rogers HJ. Adverse effect of rifampicin on prednisolone disposition. *Thorax* 1982;37:792.

(Accepted 18 March 1983)

Department of Thoracic Medicine, Fazakerley Hospital, Liverpool L9 7AL

E H ELANSARY, MB, MMED, registrar

J E EARIS, MB, MRCP, consultant physician

Correspondence to: Dr J E Earis.

Pasteurella multocida endocarditis

Pasteurella multocida is found in the oral flora of most animals,¹ living most of its time as a commensal but capable of causing fatal haemorrhagic septicaemia in cattle.² In recent years an increasing number of infections in man have been reported, causing a wide range of systemic illnesses. *P. multocida* is a rare cause of infective endocarditis, and the following case is apparently the first to be reported in Britain.

Case report

A 50 year old painter and decorator was admitted to this hospital with a five day history of fever, shortness of breath, anorexia, and vomiting. Two days before admission he had started to become confused and had intermittent rigors and chills. He had had a non-productive cough a few days before the onset of his illness. Apart from pneumonia 25 years previously he had never had a serious illness. There was no history of recent travel or use of intravenous drugs. He had given up smoking six months previously after smoking 30 cigarettes daily for 30 years. He owned a dog.

On physical examination he was noted to be confused and disorientated. He was breathless with an irregular pulse of 120 beats/min. Temperature was 39°C and blood pressure 120/70 mm Hg. He was not jaundiced and had no lymphadenopathy, haemorrhages, or petechial spots. His left knee was swollen with some effusion. His heart was enlarged; the apex beat was in the anterior axillary line, and there was a grade 4/6 pansystolic murmur radiating to the axilla. Examination of chest and abdomen showed nothing abnormal, and the neurological findings were normal.

Results of initial laboratory evaluations included a haemoglobin concentration of 13.6 g/dl and white cell count of $18.3 \times 10^9/l$ with predominant neutrophils; platelet count was $84 \times 10^9/l$. Blood urea concentration was 8.1 mmol/l (48.8 mg/100 ml), bilirubin concentration 22 μ mol/l (1.3 mg/100 ml), and albumin concentration 22 g/l (total protein 56 g/l, α_1 and α_2 -globulins decreased) and serum alkaline phosphatase and aspartate aminotransferase activities normal. Electrocardiogram showed atrial fibrillation with rapid ventricular response and left ventricular hypertrophy. Chest x ray film showed cardiomegaly without any effusion or infiltrations.

A clinical diagnosis of acute infective endocarditis was made and specimens of blood (six sets), a throat swab, and midstream specimen of urine collected for culture. He was given digoxin to control ventricular rate. His blood cultures grew Gram negative coccobacilli, which were identified as *P. multocida* (later confirmed by the reference laboratory in Colindale). Initial sensitivity tests suggested treatment with ampicillin and gentamicin: later tests of minimal inhibitory concentrations of these drugs gave values of 0.25 and 2.0 mg/l respectively. He was treated with these antibiotics intravenously for three weeks, followed by intramuscular penicillin for one month. He required intermittent blood transfusions for his anaemia. Unfortunately, his left knee was not aspirated. The swelling in this joint gradually disappeared and a radiograph showed changes of osteoarthritis. Rheumatoid and antinuclear factors were not detected. His echocardiogram showed mitral incompetence with substantial regurgitation and left ventricular and left atrial enlargement.

After a prolonged illness his strength gradually increased and he was discharged from hospital after two months. Six weeks later he was seen in the outpatient clinic: his murmur was much less pronounced but he was still in atrial fibrillation with a ventricular rate of about 70 beats/min. He was followed up regularly, and one year after discharge he was quite well, mitral incompetence was stable, and there was no evidence of cardiac decompensation. He was still in atrial fibrillation and was taking digoxin and hydrochlorothiazide.

The patient lived near a farmyard, where he had handled sheep in the six months before the onset of his illness, so the source of infection might have been either his dog or the sheep. So far as we know these animals were quite well.

Comment

In 1878 Kitt first isolated a bacterium of the *Pasteurella* group during an epidemic in wild hogs.² Two years later Pasteur described the organisms that caused fowl cholera, and subsequently the organism indistinguishable from those causing fowl cholera was found in rabbit septicaemia, swine plague, and haemorrhagic septicaemia of cattle.² This organism is a small Gram negative coccobacillus which shows bipolar staining.

The range of infection falls into three main types. The first is that where there is a definite history of animal bite or scratches—most commonly a cat bite. The usual manifestation is cellulitis with lymphadenitis, but osteomyelitis and distant metastatic infective foci may occur.¹ The second type is that associated with exposure to an infected animal. *P. multocida* has been known to cause respiratory problems—for example, pneumonia—particularly in patients suffering from chronic respiratory illnesses such as chronic obstructive airways disease or bronchiectasis. Cases of peritonsillar abscess, empyema,³ fatal pulmonary abscess, and acute epiglottitis have been reported. The infection results from airborne or vector contact with the organism. A traumatic exposure to animals has also led to pelvic and abdominal infection due to this organism causing peritonitis in the setting of cirrhosis, appendicitis, cervicitis, vaginitis, and chorioamnionitis.¹ The route of infection in this category is not known. The third category is where *P. multocida* infection has occurred without any animal exposure. This is the least common but, again, a wide variety of infection has been reported—for example, bronchitis, empyema, meningitis, cerebellar abscess, endocarditis, osteomyelitis, and polyarthralgia.¹ A unique outbreak of this infection in a chronic disease hospital was reported where epidemiological studies failed to determine the source.¹

Person to person spread may occur since the organism may be part of normal human respiratory flora³; the infection appears to be due to opportunism rather than virulence. Penicillin is the drug of choice but strains resistant to penicillin have been reported.³ Erythromycin may be used in those patients allergic to penicillin.

¹ Furie RA, Cohen RP, Hartman BJ, Roberts RB. *Pasteurella multocida* infection: report in urban setting and review of human disease. *NY State J Med* 1980;80:1597-602. (80 refs.)