Phenazopyridine-induced hepatitis

Phenazopyridine is a commonly prescribed urinary analgesic, used either alone (Pyridium) or in combination with an antibiotic—for example, in Azo Gantrisin, Azotrex, Uro Gantanol. This report describes an addition to the three recorded cases of hepatitis due to phenazopyridine sensitivity^{1,2} and indicates that this agent may be unusual in causing both a hypersensitivity-mediated hepatitis and a direct toxic effect on the liver.

Case report

On four occasions a previously healthy Caucasian housewife developed symptoms of hepatitis after being given phenazopyridine for a urinary tract infection. There was no personal or family history of adverse drug reactions or allergy.

TREATMENT AND ADVERSE EFFECTS

When she was 22 the patient received sulfoxazole and phenazopyridine for dysuria, frequency, and pyuria. Ten days later she developed diarrhoea, nausea, epigastric distress, and fever (39°C), and she was found to be jaundiced with hepatomegaly. Haemoglobin was 11.6 g/dl, sedimentation rate 70 mm in 1h, white blood count $9.05 \times 10^9/l$ ($9050/mm^3$) (8% eosinophils), bilirubin 81.6 $\mu\text{mol/l}$ (4.8 mg/100 ml) of which 50% was direct-reacting, and alkaline phosphatase 10.6 Bodansky units. Rapid improvement followed discontinuation of her medication and she was discharged, asymptomatic, after 21 days.

When she was 31 a further urinary tract infection was treated with phenazopyridine and a "penicillin-like drug." Within three days she developed retrosternal and epigastric discomfort followed by jaundice. No laboratory results are available for this episode, but the jaundice cleared spontaneously within three weeks.

In 1975, when aged 37, she had a third episode of urinary tract infection, and was treated with phenazopyridine (Pyridium, Warren-Chilcott Laboratories) 200 mg three times a day and ampicillin 250 mg four times a day. Within a week she developed malaise and epigastric distress. Laboratory studies seven days after the onset of symptoms showed a serum aspartate aminotransferase concentration of 200 units (normal <40 units), alkaline phosphatase of 155 units (normal 30-85 units), with normal bilirubin and serum protein levels. Both phenazopyridine and ampicillin were stopped and replaced by a sulphonamide; her symptoms subsided within a few days.

Two weeks later, dysuria recurred and she took one tablet (200 mg) of phenazopyridine. Within a couple of hours nausea, malaise, and epigastric distress recurred and persisted for five or six hours. She then restarted

ampicillin and completed a 10-day course with no ill-effects. When reviewed four months later there were no residual clinical or laboratory abnormalities.

Comment

Generally drugs induce hepatic injury by either a direct toxic effect or an indirect hypersensitivity mechanism. The major differences between these two types of hepatic injury have been defined by Klatskin.³

A direct dose-related hepatic injury has been reported in dogs given average daily doses 1.5 to 46 times greater than the therapeutic dose of phenazopyridine, and three infants who received high doses of phenazopyridine subsequently showed evidence of hepatic dysfunction.^{1,2} Thus phenazopyridine may under certain circumstances act as a direct hepatotoxin.

By contrast, the case described here fulfills the most important criteria for a diagnosis of hypersensitivity hepatitis: the reaction was not dose-related (occurring on the fourth occasion after only one tablet). Despite widespread use, phenazopyridine has been implicated in hypersensitivity hepatitis in only three patients^{4,5}; the latent period varied from 10 days to a few hours; fever and eosinophilia were documented on at least one occasion.

Phenazopyridine therefore shares with a few other drugs—for example, isoniazid, sulphonamides, chlorambucil³—the ability to produce both a dose-related toxic hepatitis and hepatic damage mediated by a hypersensitivity reaction. The ability of a drug to produce dose-dependent liver damage does not preclude it from inducing hypersensitivity-mediated hepatic damage.

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SHORT REPORTS

Amidopyrine agranulocytosis: drug inhibition of granulocyte colonies in the presence of patient's serum

Amidopyrine causes agranulocytosis by an antibody-mediated hypersensitivity. The demonstration of a drug-dependent leukagglutinin in sensitised individuals suggests that agranulocytosis follows agglutination and destruction of circulating neutrophils, causing temporary marrow exhaustion.¹ The technique of bone marrow culture lends itself to the investigation of drug neutropenia and the growth of adequate numbers of colonies from peripheral blood and umbilical cord blood² facilitated this study.

Case history, methods, and results

A 28-year-old woman presented in February 1975 with a history of sore throat, night sweats, and malaise, which had not responded to a course of tetracycline. She was febrile and ill with cervical lymphadenopathy and pharyngeal ulceration. The leucocyte count was $0.5 \times 10^9/l$ with total absence of neutrophils; Hb 13.5 g; reticulocytes 6%; platelets $750 \times 10^9/l$. A bone marrow aspirate showed absence of all granulocytes and reduced erythroid precursors and megakaryocytes. A month previously while in Italy she had taken an analgesic containing amidopyrine (Optalidon) for an attack of

influenza and had continued to consume the drug. We gave her gentamicin and penicillin and nursed with reverse barrier precautions. For five days she remained ill, although blood cultures were repeatedly sterile and no pathogens were isolated from the throat. On the sixth day her condition improved. Simultaneously her leucocyte count rose, initially owing to a monocytosis; followed after three days by a rising neutrophil count. Antibiotics were withdrawn, and 12 days after admission she became afebrile. When she was discharged five days later her leucocyte count was $6 \times 10^9/l$ with a normal differential count.

To investigate colony inhibition a mononuclear cell fraction from the patient's blood was incubated for two hours at 37°C in medium containing 10% fresh normal or patient's serum with or without amidopyrine. No other source of complement was used. The cells were washed and cultured in soft agar at 5×10^5 cells/plate using the colony assay technique.³ Cord blood leucocytes were treated in the same way but were cultured at a concentration of 2×10^5 cells/plate. The patient's serum inhibited colony growth only in the presence of amidopyrine. Normal serum did not show any comparable drug dependent inhibition (see table). The patient's serum taken at presentation, six months, and twelve months later were tested further. All sera contained an amidopyrine-dependent leukagglutinin. No lymphocytotoxicity was detected by the Terasaki method on lymphocytes from 11 normal subjects; indirect antiglobulin tests against pooled group O erythrocytes were negative.

Comment

Colony inhibition may be a further property of the leukagglutinin found in this condition, suggesting that a drug-antibody complex

Colony inhibition by serum and amidopyrine (sera were ABO-compatible with the cell samples used).

	Patient's colonies (Mean of three culture plates $\pm$ SD)	% of control
Patient's serum*	30 $\pm$ 2.3	100
" " + 1.0 μ g drug	10.3 $\pm$ 4.6	34
" " + 10 μ g drug	10.0 $\pm$ 4.5	34
Normal serum	12.3 $\pm$ 4.6	100
" " + 1.0 μ g drug	12.7 $\pm$ 3.05	102
" " + 10 μ g drug	12.7 $\pm$ 8.5	103
	Cord blood colonies (Mean of three culture plates $\pm$ SD)	
Patient's serum*	18 $\pm$ 2.6	100
" " + 1.0 μ g drug	5.3 $\pm$ 3.7	29
" " + 10 μ g drug	5 $\pm$ 2.8	27
Normal serum	16 $\pm$ 3.6	100
" " + 1.0 μ g drug	18.3 $\pm$ 6.3	114
" " + 10 μ g drug	12.5 $\pm$ 0.7	79

*Taken 12 months after the agranulocytic episode.

adheres to and damages granulocytes at all stages of maturation. This process did not affect lymphocytes or erythrocytes. The mechanism of colony inhibition may be similar to that caused by antilymphocyte globulin.⁴ A suppression of colony-forming cells by the drug-antibody complex would explain the 6-8 days interval between stopping amidopyrine ingestion and granulocyte recovery, but many factors may modify the effect in vivo.

Colony inhibition could be a useful additional test in suspected amidopyrine sensitivity.

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Prosthetic endocarditis treated with ampicillin and gentamicin in a penicillin-hypersensitive patient

Prosthetic cardiac valve endocarditis has a high death rate,¹ and the cure depends on early diagnosis, effective bactericidal chemotherapy, and often surgical removal of the prosthesis. We report a case of prosthetic valve endocarditis in a penicillin-hypersensitive patient caused by *Streptococcus faecalis* and treated with ampicillin and gentamicin without further surgery.

Case report

After the insertion of a Braunwald-Cutter valve prosthesis for severe aortic stenosis a previously fit 51-year-old man developed a generalised erythematous rash that cleared when cloxacillin, the postoperative prophylactic antibiotic, was stopped. Further inquiry showed that he had previously

developed a rash when taking penicillin. His postoperative course was further complicated by a coliform infection of the urinary tract that responded to co-trimoxazole, and a small purulent discharge from the sternotomy site from which *Str faecalis* was cultured. This healed and he was well when discharged on the 16th postoperative day.

Ten weeks later he was admitted to another hospital with backache and fever with rigors. Blood cultures grew *Str faecalis*. He improved with erythromycin 1 g six-hourly given by mouth, but fever returned when this was stopped, and he was transferred to our care. Clinical examination showed splenomegaly but no sign of valve dysfunction or cardiac failure. Further blood cultures grew *Str faecalis*, and, because of the results of disc-sensitivity tests and his penicillin hypersensitivity, treatment with erythromycin 500 mg six-hourly intravenously and co-trimoxazole by mouth was begun. The bactericidal effect of his serum (measured as the greatest dilution completely killing 10⁶ organisms/ml of the infecting strain)² was present only to a dilution of less than 1/2, however, and when results of tube-sensitivity tests became available treatment was changed to ampicillin and gentamicin. Although the organism was not completely sensitive to either drug alone, a combination of both was totally bactericidal.

Prednisone 60 mg and chlorpheniramine 24 mg daily were given by mouth, and hydrocortisone 100 mg was given intravenously before ampicillin 62.5 mg intravenously. Thereafter, intravenous doses of ampicillin two-hourly were given as follows: 125 mg, 250 mg, 500 mg, 1000 mg, 2000 mg without reaction, resuscitation equipment being at hand. Ampicillin, 2000 mg for five doses on the first day, then four-hourly, and gentamicin 0.8 mg/kg (60 mg) eight-hourly were injected into an intravenous cannula in the superior vena cava inserted via the subclavian vein. The in-vitro bactericidal effect of his serum was unsatisfactory until doses of both antibiotics were adjusted and probenecid 1 g six-hourly was added (see figure). The patient suffered transient pruritis and flushing, an ampicillin-like rash which resolved, an inguinal rash caused by *Candida* that responded to gentian violet, and later glycosuria, which disappeared when prednisone was withdrawn. There were no major side effects and he completed eight weeks of treatment, the dose of prednisone being reduced as shown (see figure). Chlorpheniramine was continued for four days after antibiotics were stopped to prevent late sensitivity reactions. Fever and splenomegaly resolved and further blood cultures were sterile. After 14 months he remained well.

Time chart in days showing dosage of antibiotics, clinical features, and dosage of prednisone. Serum bactericidal effect was tested immediately before each ampicillin dose.

Comment

Despite the risk of anaphylaxis, ampicillin was used in the treatment of this patient since tube-sensitivity testing indicated that it would be an effective bactericidal agent combined with gentamicin. The adequacy of treatment for bacterial endocarditis should always be monitored by measuring the bactericidal effect of serum against the infecting organism.³ Although the strains of *Str faecalis* isolated during the two previous hospital admissions were not available for comparison, the source of infection was probably the minor postoperative sternotomy sepsis, and the initial six-week course of oral erythromycin only suppressed the organism. A history of hypersensitivity to penicillin does not necessarily imply adverse reactions when one of this group of drugs is used later.^{4,5} Corticosteroids with an antihistamine may reduce the severity of hypersensitivity but there is little evidence