week. We noticed that large haemoptyses occurred shortly after the nebulised salbutamol. After substitution of the salbutamol by nebulised isotonic saline there was a pronounced reduction in haemoptysis with only streaks of blood in the sputum thereafter. To substantiate these observations nebulised salbutamol was reintroduced and caused a further large haemoptysis (300 ml). Bronchodilator treatment was therefore subsequently maintained with oral prednisolone and the nebulised salbutamol discontinued. The episodes of haemoptysis gradually subsided over the next 48 hours. There was no recurrence when inhaled salbutamol 200 µg four times daily was reinstituted one week later.

Comment

Although intermittent haemoptysis may occur in bronchiectasis and be exacerbated by intercurrent infection, in our patient the continued use of nebulised salbutamol appeared to increase the degree of haemoptysis. This effect may be dose related, since before admission and during two previous admissions for haemoptysis the patient had used a salbutamol inhaler 200 µg four times daily as well as an ipratropium inhaler without any apparent adverse effect. During the two previous admissions when nebulised salbutamol was not used the haemoptysis was much less severe, less persistent, and disappeared within 48 hours. We therefore suggest that nebulised salbutamol and other similar nebulised drugs should be used with caution in patients with chronic reversible airflow obstruction and haemoptysis.

Neither Allen and Hanburys Ltd nor the Committee on Safety of Medicines had any record of this side effect of nebulised salbutamol being notified to them.

¹ Crofton J, Douglas A. *Respiratory diseases*. 2nd ed. Oxford: Blackwell Scientific, 1975:382.

² Gibson DG, Coltart DJ. Haemodynamic effects of intravenous salbutamol in patients with mitral valve disease; comparison with isoprenaline and atropine. *Postgrad Med J* 1971;47:suppl:41.

³ Paterson JW, Woolcock AJ, Shenfield GM. Bronchodilator drugs. *Am Rev Respir Dis* 1979;120:1166.

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Exacerbation of chronic liver disease due to hepatitis B surface antigen after delta infection

Carriers of the hepatitis B surface antigen (HBsAg) appear to be at high risk of developing δ infection.¹ The δ agent is highly pathogenic and causes acute and chronic liver disease.² δ Antigen is detectable in serum only in acute hepatitis and indicates recent δ infection³; in chronic hepatitis δ antigen may be identified in liver specimens, but in the serum only the antibody to it (anti- δ) may be identified.⁴ Results of recent studies⁵ suggests that the δ agent is a factor in fulminant hepatitis in asymptomatic carriers of HBsAg; it could also be responsible for serious infections in patients with chronic HBsAg liver disease.

We report on three patients with a history of chronic HBsAg liver disease whose clinical condition worsened suddenly and who died; sera from the three patients were tested for the presence of markers of hepatitis B virus and the δ agent.

Patients, methods, and results

We examined three men admitted to hospital with jaundice. Their histories showed them to have been HBsAg carriers for at least two years with raised activity of alanine transaminase (from two to four times normal), slightly raised bilirubin concentration, serum albumin concentration >30 g/l, and gammaglobulinaemia <20 g/l. They had not had ascites, bleeding, or periods of disturbed consciousness. Only one had undergone liver biopsy: histology had shown chronic persistent hepatitis. None had had previous treatment, and none was alcoholic.

During admission alanine transaminase activity was three to five times normal and they had hyperbilirubinaemia (six or more times normal concentrations), low serum albumin concentrations, hypergammaglobulinaemia,

prolonged prothrombin times, ascites, bleeding, and disturbed consciousness progressing to hepatic coma. Death occurred three to five weeks after admission.

Sera of the three patients were tested for markers of hepatitis B virus and δ agent. HBsAg, antibody to HBsAg (anti-HBs), total antibody to hepatitis B core antigen (anti-HBc), hepatitis B e antigen (HBeAg), and antibody to HBeAg (anti-HBe) were estimated with commercial radioimmunoassays (Ausria II, Ausab, Corab, Kit HBe; Abbott, Chicago, Illinois). Anti-HBc of IgM class (IgM anti-HBc) was detected with a solid phase radioimmunoassay using the method described by Lavarini *et al*⁴ (the HBe reagent was kindly provided by Dr Rizzetto, and we used anti-HBc iodine-125 from kit Corab, Abbott). Serum δ antigen and anti- δ were detected with solid phase enzyme linked immunosorbent assay based on the technique described by Crivelli *et al*⁵ (IgG anti- δ conjugated with immunoperoxidase was kindly provided by Dr Rizzetto).

The three patients were positive for HBsAg, total anti-HBc, and anti-HBe and negative for anti-HBs, IgM anti-HBc, and HBeAg; they were positive for δ antigen and negative for antibody to it.

Comment

The δ agent is highly pathogenic; in asymptomatic carriers of HBsAg it usually produces acute hepatitis that can occasionally be fulminant and often becomes chronic. In the three cases described the δ agent did not produce the classical picture of acute hepatitis with very high alanine transaminase activity. The patients in fact had suffered for at least two years from an HBsAg hepatitis that had evolved slowly, as is usually observed in our area, and then their condition deteriorated unexpectedly, leading to death. The infection with hepatitis B virus was not recent since their sera were positive for anti-HBe and negative for IgM anti-HBc; the presence of δ antigen in the sera indicated current infection by the δ agent.

We therefore presume that in these three cases the δ agent played an important part in the sudden and fatal exacerbation of the patients' liver disease.

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³ Smedile A, Farci P, Verme G, *et al*. Influence of delta infection on severity of hepatitis B. *Lancet* (in press).

⁴ Lavarini C, Crivelli O, Smedile A, *et al*. Radioimmunoassay detection of IgM antibodies to the hepatitis B core antigen in HBsAg liver disease. *Boll Ist Sieroter Milan* (in press).

⁵ Crivelli O, Rizzetto M, Lavarini C, Smedile A, Gerin JL. Enzyme-linked immunosorbent assay for detection of antibody to the hepatitis B surface antigen-associated delta antigen. *J Clin Microbiol* 1981;14:173-7.

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Chlormezanone poisoning

Chlormezanone is a tranquilliser with muscle relaxant properties that was first introduced into clinical practice in 1958. There is, however, only one published report of an overdose due to this drug.¹ We report a further case of chlormezanone intoxication.

Case report

A 36 year old woman was admitted to hospital after ingesting 7 g chlormezanone (Trancopal) five hours previously. On admission she was comatose (grade 3, Edinburgh scale) and hypotensive (95/60 mm Hg) and had a positive gag reflex, equal and reactive pupils, normal fundi, flaccid muscle tone, and reflexes that were generally difficult to elicit. Over the next 15 hours she regained consciousness and her blood pressure rose to 115/70 mm Hg. No evidence of respiratory depression was observed, and renal and hepatic function remained normal. The patient made an uneventful recovery.

The figure shows plasma chlormezanone concentrations, estimated by a

Plasma concentrations of chlormezanone in patient who had taken overdose.

specific high pressure liquid chromatographic method. A drug screen was negative for all other drugs. The terminal half life of chlormezanone was estimated to be 29 hours, and only 217 mg (3% of estimated overdose) was excreted unchanged in urine over 90 hours.

Comment

Marks¹ has described the case of a 28 year old woman who had ingested 9 g chlormezanone. She became "sleepy" and vomited, but her pulse, blood pressure, and respiration remained normal and she recovered completely within 24 hours.

McChesney *et al*² have reported that in man a single 400 mg oral dose of chlormezanone gave peak plasma concentrations, one to two hours after dosing, of 5-6 mg/l and that the mean half life was 24 hours. Only about 1% of the dose was excreted unchanged in the urine during the next 48 hours. The plasma concentrations in our patient were therefore in keeping with the ingestion of a substantial overdose of chlormezanone. The patient nevertheless made an uneventful recovery.

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² McChesney EW, Banks WF Jr, Portmann GA, Crain AVR. Metabolism of chlormezanone in man and laboratory animals. *Biochem Pharmacol* 1967;16:813-26.

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Incidence of liver cancer and trichloroethylene manufacture: joint study by industry and a cancer registry

Trichloroethylene, a high tonnage solvent widely used for degreasing metal and other purposes, has been manufactured at Runcorn since 1909. In 1975 the National Institute of Occupational Safety and Health issued a background information document which characterised trichloroethylene as a potent liver carcinogen in mice. The Employment Medical Advisory Service and Imperial Chemical Industries agreed that a study using data from a cancer registry was the best way to assess the incidence of liver cancer among past employees of the industry. A proposal was drafted with the Mersey Regional

Cancer Registry and permission to proceed was granted by the ethical committee of the Mersey Regional Health Authority.

Methods and results

The Mersey Regional Cancer Registry provided details of all their cases of liver cancer for 1951-77. An alphabetical list was compiled of the 55 subjects with a diagnosis of primary liver cancer and an address near Runcorn. The data for each case were name, address at registration, and dates of birth and registration. Two members of the personnel department at Imperial Chemical Industries compared the tens of thousands of past employees of the Runcorn site during 1934-76 with the registry list. The comparison would produce almost certain matches, probable matches (when only addresses differed), and possible matches.

The comparison produced one probable match and one possible match. The cancer registry sent details to the Department of Health and Social Security at Southport, where they were positively identified as referring to four separate men. It was concluded that none of the subjects had ever worked at the Runcorn site.

Comment

The observation of liver tumours in mice ingesting high doses of trichloroethylene came from a single study. No cases of liver cancer were found by Axelson *et al*¹ in a cohort study of 500 subjects or by Malek *et al*² in a small group of highly exposed dry cleaning operatives in Prague. Novotna *et al*, who studied 63 men with liver cancer in Prague, found that none had a history of occupational exposure to trichloroethylene.³

Basing this study on data from a cancer registry was selected from several alternatives. Exposure to trichloroethylene is perhaps highest and least complicated in user industries, but a cohort study of them was considered impracticable because of the many small establishments concerned. A survey of registry records in areas with user industries was not chosen because of the meagre occupational information. A cohort study of the 1000 or so trichloroethylene workers at Runcorn was considered inefficient because it would have meant reviewing over 100 000 personnel department records. Primary liver cancer is so rare that follow up of a population of 10 000 since 1936 would be needed for a satisfactory chance of detecting a doubling of risk. A rough calculation showed that the expected number of cases of primary liver cancer during 1951-77 among Runcorn workers was about 0.3. As a further check the files in the company's computerised medical records system (MORAS) were searched for past employees dying with liver cancer as the underlying cause. One was found, and there was another at a neighbouring works. The cancer registry records showed that the first of these had suffered a primary cancer of the oesophagus with a secondary liver tumour; the other patient had had multiple secondary deposits from an unknown primary tumour.

Determining the incidence of rare forms of cancer in groups of workers by matching cancer registry and employment files could have wide application. Errors are avoidable if one list is alphabetical and short. As two matches are a significant cluster and one suggests a problem no elaborate statistical tests are necessary.

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³ Novotna E, David A, Malek B. An epidemiological study of the hepatic tumour incidence in persons working with trichloroethylene. I—The negative result of retrospective investigations in persons with primary liver carcinoma. *Pracovní Lékařství* 1979;31:121-3.

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