Jaundice after multiple halothane anaesthetics administered during the treatment of carcinoma of the uterus

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SUMMARY Halothane is thought to cause hepatitis after multiple exposures in certain susceptible patients. Patients undergoing repeated anaesthetics for insertion of radioactive implants for gynaecological neoplasia appear to be particularly at risk. We are reporting three cases in which hepatitis has followed multiple halothane anaesthetics, and discuss them with reference to our present knowledge of this complication.

The significance of halothane anaesthesia as a cause of postoperative jaundice continues to be disputed (Simpson, Strunin, and Walton, 1971), but most diagnosed cases have followed repeated administration of the drug (Klion, Schaffner, and Popper, 1969). We report three further cases of jaundice following halothane anaesthesia. All occurred during the course of 12 months in the same regional radiotherapy unit, and followed exposure to halothane on three or four occasions within one month.

Case Reports

CASE 1

Mrs I.S., aged 51, was diagnosed as suffering from carcinoma of the body of the uterus in November 1971, following vaginal bleeding for two months. There was no significant previous history. On 24 November 1971, the patient underwent a diagnostic curettage to confirm the diagnosis. The patient had further anaesthesia on 29 November 1971 for insertion of radioactive caesium and for vaginal hysterectomy on 6 December 1971. On all three occasions the anaesthetic was induced with thiopentone sodium and maintained with nitrous oxide, oxygen, and halothane. No other drugs were received by the patient during this time.

The patient made an initially uneventful recovery although pyrexia was noted on the immediate postoperative day. On the ninth postoperative day the patient was icteric but asymptomatic. There were no abnormal physical signs.

Received for publication 29 March 1973.

Investigations gave Hb 11.9 g/100 ml, WBC 5000/cmm, ESR 55 mm/hr, platelets 260 000/cmm, urea 10 mg%, Na⁺ 135 m-equiv/l, K⁺ 2.7 m-equiv/l, HCO₃ 29.0 m-equiv/l; bilirubin 11.6 mg%; DVB positive; SGOT 630 IU/ml, SGPT 650 IU/ml, ICDH 85 IU/ml, alkaline phosphatase 19 KA/ml; protein 6.3 g/100 ml, albumin 3.3 g/100 ml; normal electrophoresis; Australia antigen negative. Liver biopsy 14 days after the onset of jaundice showed expanded portal tracts with a dense infiltrate of lymphocytes and macrophages which extended into the liver lobules. The liver cells showed cytoplasmic ballooning and necrosis, and there was cholestasis.

The patient was treated expectantly and within 14 days the transaminase concentrations had fallen to normal although the bilirubin and alkaline phosphatase, after an initial rise, were slower to fall.

The patient remains alive and well seven months after her illness.

CASE 2

Mrs A.H., aged 61, was found to have a large pelvic mass following an 11-month history of vaginal bleeding. On 5 October 1970 she was examined under an anaesthetic and biopsy taken to confirm the diagnosis of carcinoma of cervix. On 12 October 1970 she underwent a further examination under an anaesthetic and cystoscopy. A third anaesthetic was used for insertion of radioactive caesium on 26 October 1970. A postoperative pyrexia was noted after this operation but was short lived. On 2 November 1970, a further anaes-

thetic was administered for another insertion of radioactive caesium.

On the day following the fourth anaesthetic the patient was again noted to be pyrexial and she became jaundiced three days later. The patient was acutely ill with nausea, vomiting, anorexia, and abdominal pain. The patient received no known hepatotoxic drugs with the exception of halothane. This was used for all four anaesthetics in association with thiopentone sodium, nitrous oxide, and oxygen. There were no abnormal physical signs apart from icterus and minimal hepatomegaly.

Investigations showed Hb 16.6 g/100 ml, WBC 5000/cmm, ESR 1 mm/hr; a film showed eosinophilia; urea 16 mg%, Na 128 m-equiv/l; K⁺ 4.2 m-equiv/l, HCO₃ 26 m-equiv/l, bilirubin 22.8 mg%, direct van den Bergh test positive, SGOT 3200 IU/ml, SGPT 4950 IU/ml, alkaline phosphatase 67 KA/ml; proteins 5.7 g/100 ml, albumin 3.3 g/100 ml, normal electrophoresis; prothrombin index 35%. Liver biopsy was not carried out.

The patient remained very ill for several days, and there was a transient period of oliguria. The transaminases rapidly fell to normal within nine days but the bilirubin and alkaline phosphatase were elevated for a further two weeks.

The patient remains alive and well 20 months after the episode of jaundice.

CASE 3

Mrs F.B., aged 67, was diagnosed as suffering from an invasive carcinoma of the cervix in November 1971. There was no significant past medical history. On 2 November 1971, 15 November 1971, and 29 November 1971, the patient underwent an examination under an anaesthetic and biopsy in an attempt to confirm the diagnosis and ascertain its extent. Thiopentone sodium, oxygen, nitrous oxide, and halothane were used as anaesthetic on all three occasions. The only other drugs received during this time were nitrazepam, pethidine, and atropine. On the fifth postoperative day the patient was noted to be pyrexial and she became jaundiced on the seventh postoperative day.

Investigations showed Hb 11.5 g/100 ml, WBC 6000/cmm, ESR 20 mm/hr, urea 58 mg/100 ml, Na⁺ 144 m-equiv/l, K⁺ 4.5 m-equiv/l; HCO₃ 25 m-equiv/l; bilirubin 24.5 mg%, direct van den Bergh test positive, SGOT 805 IU/ml, SGPT 1200 IU/ml, alkaline phosphatase 13 KA/ml; protein 6.1 g/100 ml, albumin 3.5 g/100 ml, normal electrophoresis; Australia antigen negative. No liver biopsy was performed.

The patient ran a complicated course. Symptomatically she suffered from prolonged anorexia, nausea, and vomiting. Biochemically the trans-

aminases fell rapidly, but continued to be slightly raised for a further six weeks. They were completely normal on 17 January 1972 and remained so subsequently. The serum bilirubin after a rise to 34.0 mg/100 ml, fell more slowly but was 9.3 mg/100 ml by 17 January 1972, and 2.8 mg/100 ml by 1 February 1972. The alkaline phosphatase rose to a maximum of 35.0 KA units on 4 January 1972 and was still elevated at 33 KA units when the patient was discharged on 2 February 1972. The patient's progress was further complicated by the development of renal failure which persisted up to the time of discharge from hospital. She died outside hospital three months later and no necropsy was performed.

Frequency of Multiple Anaesthetic Exposure

During the 12-month period over which these cases occurred, 150 patients were admitted to Weston Park Hospital with a diagnosis of carcinoma of either body or cervix of the uterus. Of these, 37 had no anaesthetic and 29 had only one halothane exposure; anaesthetic records of 34 patients were incomplete; 23 patients had at least two halothane anaesthetics. The maximum possible number of cases with two or more halothane anaesthetics was therefore 57.

More recently the policy has been to avoid multiple halothane exposure and no cases of jaundice have occurred over the past year.

Discussion

Halothane was first suspected of occasional hepatotoxicity in 1958, two years after its introduction. The clinical features of the sometimes fatal virus hepatitis-like syndrome which can follow halothane administration have been well documented in numerous reports which have been reviewed recently by Sherlock (1971). The incidence of fatal hepatic necrosis is rare, as demonstrated by three large studies on postanaesthetic deaths (Slater, Gibson, Dykes, and Walzer, 1964; Mushin, Rose, Gibson, Dykes, and Walzer, 1964; Mushin, Rosen, Bowen, and Campbell, 1964; National Halothane Study, 1966), and the very existence of 'halothane hepatitis' is still disputed by some anaesthetists (Simpson *et al.*, 1971).

The three cases reported by us demonstrate the features of halothane hepatitis described in previous reports, particularly the association of jaundice with multiple halothane anaesthetics. In each of the cases we have described, the operations performed were all minor ones, with the exception of the vaginal hysterectomy in case 1. None had received

other known hepatotoxic drugs or blood transfusion, nor had they been in contact with infective hepatitis, but as always in this type of case it is impossible to exclude coincidental virus hepatitis.

The onset of the illness was heralded by pyrexia one to seven days after the last operation; icterus followed two to three days later and was accompanied by systemic disturbance to a variable extent in the different cases.

The liver function tests were typical of acute hepatic necrosis with a very high initial transaminase value which fell very rapidly; high serum bilirubin levels which fell more slowly and moderately elevated serum alkaline phosphatase. A mild eosinophilia was noted in case 2. The liver biopsy in the one case in which it was performed showed a picture similar to that of acute viral hepatitis, and as is usual there were no specific histological features.

Simpson *et al* (1971) have disputed the existence of jaundice as an idiosyncratic reaction to halothane partly because other features of hypersensitivity, such as rashes and eosinophilia, are absent. Halothane is not unique, however, in producing, albeit rarely, a hepatitis-like picture with no other features of hypersensitivity. Some of the monoamine oxidase inhibitor drugs produce, again rarely, a similar clinical picture. This was not generally accepted until unfortunate patients were described who again developed jaundice when inadvertently given a further course of the same or a related drug (Holdsworth, Atkinson, and Goldie, 1961). The reality of this type of drug reaction can only be established by careful clinical observation, particularly, in the case of an anaesthetic, in situations where repeated administration is liable to occur. The treatment of carcinoma of the body and cervix of the uterus is one such situation.

Over the 12 months when our three cases occurred, the maximum possible number of patients with carcinoma of the uterus exposed to more than one halothane anaesthetic during their hospital admission was 57. In addition some of the 29 patients who had one halothane anaesthetic may have had the

same anaesthetic at the referring hospital. A similar series of six cases was reported from the Royal Brisbane Hospital, Australia (Hughes and Powell, 1970). These cases all followed repeated insertion of radium for carcinoma of the cervix and there were two deaths. From the paper of Hughes and Powell it can be calculated roughly that these occurred among a series of 80 patients exposed to two or more halothane anaesthetics.

Statistics on these small numbers are not very reliable, but the incidence of jaundice after two or more halothane anaesthetics administered during the course of treatment of carcinoma of the uterus is similar in our series to that reported from Brisbane. We are fortunate that none of our cases was fatal, but our experience provides additional evidence to support the view that halothane should be avoided for repeated frequent anaesthetics and draws attention to the fact that this is particularly likely to occur during the treatment of carcinoma of the body and cervix of the uterus.

We are grateful to Dr F. E. Neale, consultant radiotherapist, Weston Park Hospital, Sheffield, for permission to report these patients who were initially under his care.

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