UNEXPLAINED JAUNDICE FOLLOWING NON-HALOTHANE ANAESTHESIA
A Case Report

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SUMMARY

A patient developed unexplained jaundice following repeated anaesthesia. The only inhalation anaesthetic agent used was nitrous oxide. The clinical and laboratory features are very similar to those of the jaundice which has been attributed to halothane anaesthesia.

On rare occasions, halothane anaesthesia, especially when repeated within a short space of time, is associated with the development of postanaesthetic jaundice and hepatitis (Lindenbaum and Leifer, 1963; National Halothane Study, 1966; Sherlock, 1964). Patients receiving radium treatment for carcinoma of the cervix are particularly at risk (Trowell, Peto and Smith, 1975; Wright et al., 1975). With a few possible exceptions (Belfrage, Ahlgren and Axelson, 1966; Combes, 1969; Klatskin and Kimberg, 1969), no clear cause-and-effect relationship has been demonstrated between halothane and liver damage following anaesthesia, the cause of which remains unexplained (Simpson, Strunin and Walton, 1971; Dykes, Gilbert and McPeek, 1972; Editorial, 1974). However, halothane continues to be suspect. Of the 130 reports of unexplained jaundice following anaesthesia, received by the Committee on Safety of Medicines from 1964 to 1972, and of the four reports received by the National Drugs Advisory Board from 1968 to 1973, halothane had been used in every case (Inman and Mushin, 1974; National Drugs Advisory Board, 1974). In addition, the clinical and laboratory features of such cases show a certain consistency, and histological evidence of hepatitis has been found invariably in those patients in whom a liver biopsy was carried out (Peters et al., 1969; Klion, Schaffner and Popper, 1969; Sharpstone, Medley and Williams, 1971; Sherlock, 1971). We report unexplained jaundice following non-halothane anaesthesia. While such cases have been reported by others (Dykes et al., 1965; National Halothane Study, 1966; Mushin, Rosen and Jones, 1971; Simpson, Strunin and Walton, 1973), this case is of interest because of features very similar to those said to be typical of the hepatitis which may follow halothane anaesthesia.

CASE REPORT

A 62-year-old male factory supervisor was admitted for investigation and treatment of a gangrenous ulceration of the left hallux.

Past medical history. Three years previously he had been admitted with acute claudication in his right leg and eventually a right Gritti-Stokes amputation was performed. Several anaesthetic agents were given during that admission, but no details are available.

Over the previous 4 yr he had been treated for arterial hypertension with methyldopa 250 mg given four times daily, frusemide 40 mg on alternate days and slow-release potassium chloride 600 mg daily. He was a maturity-onset diabetic, well controlled on a 2400 calorie diet and glibenclamide 20 mg daily. Three days before his present admission treatment with clindamycin 150 mg, thrice daily, was commenced.

Physical examination. The right leg had been amputated and there was evidence of extensive peripheral vascular disease in the remaining leg with ulceration of the hallux. Pyrexia of 37.4 °C was noted, which settled within 24 hr of admission. The arterial pressure was 150/90 mm Hg and no abnormality was found in the respiratory system.

Investigations. The serum electrolyte and blood urea concentrations, analysis of the urine, chest x-ray and e.c.g. were all normal. The haemoglobin concentration was 17.2 g/100 ml and the white cell count 9000/mm³ (neutrophils 83%, lymphocytes 14%, monocytes 2% and eosinophils 1%).

First anaesthetic. Premedication was atropine 0.6 mg given i.v. Anaesthesia was induced with thiopentone 200 mg followed by suxamethonium 75 mg for endotracheal intubation. Anaesthesia was
maintained with nitrous oxide (8 litre/min) and oxygen (4 litre/min) delivered from a Boyle’s apparatus fitted with a halothane vaporizer (Fluotec Mark 2) and a methoxyflurane vaporizer (Pentec 2). A further 225 mg of suxamethonium was given in increments of 25 mg and the lungs were ventilated manually using a Magill attachment. During the operation 200 ml of 5% dextrose was infused i.v. An attempted femoral angiogram was unsuccessful because of poor flow in the femoral artery and the procedure was abandoned after 30 min. Anaesthesia was uneventful and recovery normal.

On the same evening the patient’s temperature was 39.3 °C (fig. 1). Although there was no obvious cause for pyrexia, cephalothin 1 g i.m. four hourly was commenced and the clindamycin was stopped. Pyrexia persisted for a further 6 days, during which the patient complained of nausea and upper abdominal discomfort.

Again the patient developed pyrexia (38 °C) after the procedure. Cephalothin 1 g six-hourly was continued.

Second anaesthetic. This was for a Gritti-Stokes amputation, 7 day after the aortogram and before the temperature had returned to the normal value. Pre-medication was morphine 5 mg and atropine 0.6 mg. Anaesthesia was induced with thiopentone 250 mg followed by suxamethonium 50 mg for endotracheal intubation; further muscle relaxation was provided by pancuronium 6 mg. Pulmonary ventilation was carried out with nitrous oxide (3 litre/min) and oxygen (1.5 litre/min) using a Cyclator ventilator with a semi-closed circuit and carbon dioxide absorber. The gases were delivered from a Boyle’s apparatus fitted with an unused Boyle’s ether vaporizer and a halothane vaporizer (Fluotec Mark 2). Anaesthesia was supplemented with droperidol 5 mg, and fentanyl 0.2 mg given in increments of 0.05 mg. Anaesthesia was uneventful and the arterial pressure remained normal throughout. During the operation 1000 ml of 5% dextrose in water was given i.v. The neuromuscular block was antagonized by neostigmine 5 mg preceded by atropine 1.2 mg.

The white cell count was 8000/mm³ (neutrophils 80%, lymphocytes 20%). The serum glutamic pyruvic transaminase (s.g.p.t.) was 11 mu./ml (normal range for our laboratory, 5–40 mu./ml) and the serum alkaline phosphatase was 31 mu./ml (normal range, 15–50 mu./ml).

Neuroleptanalgesia. Four days after the patient’s temperature had returned to normal and 11 day after the first anaesthetic, a translumbar aortogram was carried out under neuroleptanalgesia with droperidol 7.5 mg and phenoperidene 0.75 mg. No anaesthetic apparatus was involved. The contrast medium was sodium iothalamate (Conray 420). The aortogram confirmed the presence of extensive disease in the arteries of the leg.

Fig. 1. The patient’s temperature chart during admission in relation to the three procedures carried out and to the appearance of the jaundice.
On the evening following the operation the patient developed pyrexia (39 °C). Pyrexia continued, and on the eighth day after operation, jaundice appeared. As previously, during pyrexia following the first anaesthetic, the patient complained of nausea and upper abdominal discomfort, and, in addition, became very confused.

The results of serum analysis were: total bilirubin 5.6 mg/100 ml (normal range 0.1–1.2 mg/100 ml), alkaline phosphatase 70 mu./ml (15–50 mu./ml), s.g.o.t. 540 mu./ml (10–40 mu./ml), lactate dehydrogenase (LDH) 602 mu./ml (240–525 mu./ml), s.g.p.t. 200 mu./ml (5–40 mu./ml), and the prothrombin ratio was 1.4.

There was no evidence of gall bladder disease and a straight x-ray of the abdomen was normal. The patient had not received a blood transfusion. It was established that the patient had not received any injections or dental treatment for at least 1 yr before admission, nor had there been any known contact with a jaundiced patient. The amputation stump was clean and uninfected. No pathogenic organisms were cultured from the urine or sputum. Three attempts at blood culture were negative. The total white cell count was 12,000/mm³ and the eosinophil count was 55/mm³ (less than 0.5% of the total count). A liver biopsy was not taken because it soon became obvious that the patient was recovering.

The patient continued to receive glibenclamide, methyldopa, frusemide, slow-release potassium chloride and cephalothin in the same doses as previously. Two doses of methadone 5 mg i.m. were given within the first 24 hr of operation and nitrazepam 10 mg was given as night sedation on nine occasions during the first 2 week after operation and on a number of subsequent occasions.

**Immunological studies.** Hepatitis B antigen (HB Ag) was not detected and the Coombs test was negative. There was an increased γ-globulin fraction of the plasma proteins. An immunological screen was performed on a serum sample forwarded to the Anaesthetic Unit of the London Hospital. Antinuclear antibody was present to a titre of 1 in 20, smooth muscle antibody was present to a titre of 1 in 80, and liver/kidney microsomal antibody was not demonstrated.

The jaundice disappeared gradually over about 6 days and the pyrexia subsided in a further 7 days. The patient made a good recovery and on the 29th day after operation the serum bilirubin was 1 mg/100 ml, s.g.p.t. 7 mu./ml, s.g.o.t. 10 mu./ml, and LDH 344 mu./ml.

**DISCUSSION**

A history of repeated exposures to halothane is found in a high proportion of cases of unexplained jaundice and hepatitis occurring after halothane anaesthesia (Mushin, Rosen and Jones, 1971; Sharpstone, Medley and Williams, 1971; Reed and Williams, 1972; Inman and Mushin, 1974). The interval between the last anaesthetic and the appearance of the jaundice has been usually about 1 week. In 182 cases of liver damage following halothane anaesthesia, this interval averaged 6.2 days after a single exposure and 7.77 days after multiple exposures (McPeek and Gilbert, 1974). When jaundice results from blood transfusion reactions, severe sepsis and shock, or benign intrahepatic cholestasis (Schmid et al., 1965), the jaundice has been reported as appearing within the first 48 hr (Peters et al., 1969; Sherlock, 1971). A frequent finding in many cases of jaundice and hepatitis after halothane anaesthesia is the occurrence of unexplained pyrexia, often in excess of 38 °C, following the most recent anaesthetic and one or more of the earlier anaesthetics (Peters et al., 1969; Klion, Schaffner and Popper, 1969; Sharpstone, Medley and Williams, 1971; Reed and Williams, 1972; Inman and Mushin, 1974). Characteristically, pyrexia following the most recent anaesthetic precedes the appearance of the jaundice by several days.

The jaundice is usually accompanied by malaise, nausea and upper abdominal discomfort (Peters et al., 1969; Klion, Schaffner and Popper, 1969; Sherlock, 1971). In hepatitis occurring after halothane anaesthesia the serum transaminases are increased to concentrations similar to those found in viral hepatitis; the serum alkaline phosphatase is usually increased moderately; the one-stage prothrombin time is increased to a figure which parallels the severity of the illness, and the total white cell count is normal or may be moderately increased (Peters et al., 1969; Klion, Schaffner and Popper, 1969; Sharpstone, Medley and Williams, 1971; Reed and Williams, 1972). Eosinophilia may be present in the peripheral blood in some cases (Klion, Schaffner and Popper, 1969), but was not seen in any of the 11 cases reported by Sharpstone and colleagues (1971).

All of the features described above were present in our patient. The cause of his jaundice is not clear. Although the clinical and laboratory features of the jaundice are strikingly similar to those said to be typical of post-halothane jaundice, halothane was not administered.
When an anaesthetic machine has been used to deliver halothane, traces of the agent continue to be taken up by the anaesthetic gases from the antistatic rubber tubing, over a long period of time (Robinson, Barratt and Thompson, 1974). Leakage from a turned-off vaporizer may also be a source of halothane contamination. This possibility cannot be excluded.

There is some evidence (Paronetto and Popper, 1970) that a type of sensitivity reaction forms the basis of the hepatitis following repeated halothane anaesthesia. Halothane was, almost certainly, administered to the patient during his admission 3 yr previously. If such a sequence did occur, the jaundice was for practical purposes unavoidable, since all of the anaesthetic machines in this hospital are either fitted with a halothane vaporizer or have been used in conjunction with a portable halothane vaporizer.

While pyrexia following the first anaesthetic might possibly have resulted from the inhalation of gases contaminated by halothane, this could not have been the case following the aortogram under neuroleptanalgesia, as no anaesthetic apparatus was involved.

Some degree of sepsis, for which the patient was receiving clindamycin, was present in the gangrenous toe. The temperature of the patient was 37.4 °C on admission, and was in the normal range until after the first anaesthetic, as was the white cell count. Movement and trauma, a lowering of resistance to infection (Fenster, 1965), and suppression of the immune responses by anaesthesia and surgery (Park et al., 1971) would encourage a spread of infection which could have been responsible for pyrexia following each anaesthetic.

It is known that even minor infections can cause abnormal liver function (Carney and Van Dyke, 1972). However, sepsis would appear to be an unlikely cause of jaundice and liver damage in this case. S.g.p.t. and the serum alkaline phosphatase were normal after the second anaesthetic and continued to be given to the patient at night when required, can hardly be implicated in this case.

The clinical and laboratory features of viral hepatitis may be indistinguishable from those of hepatitis occurring after halothane anaesthesia (Dykes, Gilbert and McPeek, 1972; Simpson, Strunin and Walton, 1973). Under light microscopy the histological changes in the liver which result from viral hepatitis on the one hand, and drug-induced hepatitis on the other, are rarely, if ever, conclusive (Review by an International Group, 1974). The fact that hepatitis B antigen (HB Ag) was not detected in our patient does not exclude serum hepatitis (Simpson, Strunin and Walton, 1973), nor does the absence of a history of recent injections, as serum hepatitis can be spread by nasopharyngeal secretions (Krugman and Giles, 1970) and excreta (Chalmers and Alter, 1971). There is no history of contact with infectious hepatitis but subclinical occurrences of the disease are more frequent than open cases (Simpson, Strunin and Walton, 1973).

The results of the immunological screening tests for the detection of autoantibodies found in association with certain liver diseases are difficult to assess in our patient. Antinuclear antibody is found in a high proportion of unselected people and indicates a non-specific autoimmune response (Walker, 1972). The moderately high titre of smooth muscle antibody in our patient is consistent with the presence of a viral hepatitis, but smooth muscle antibody is also found in other viral diseases and in the patients with neoplasms (Walker, 1972). The absence of liver/kidney microsomal antibody (Smith et al., 1974) is of some interest, since this antibody has been found in some cases of unexplained hepatitis following exposure to halothane, studied as part of the London Hospital Postoperative Jaundice Survey (Walton B., personal communication).

Whatever the cause of the jaundice, the features of the case emphasize the need for caution in associating unexplained postanaesthetic jaundice and hepatitis with any one factor.
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References


Jaunisse Inexpliquée a la Suite d’Une Anesthésie Non Effectuée a l’Halothane:
Rapport sur un cas précis

Résumé

Une jaunisse inexpliquée s’est déclarée sur un opéré ayant été plusieurs fois anesthésié. Le seul agent anesthésiant par inhalation qui ait été utilisé est le protoxyde d’azote. Les caractéristiques cliniques et de laboratoire ressemblent beaucoup à celle de la jaunisse qui a été attribuée à l’anesthésie par l’halothane.
ZUSAMMENFASSUNG

Ein Patient entwickelte eine unerklärte Gelbsucht, nachdem er wiederholt narkotisiert worden war. Das einzige dabei verwendete Inhalations-Narkosemittel war Stickstoffoxyd. Klinische und laboratoriumsmässige Merkmale waren dabei sehr ähnlich denjenigen Gelbsuchtfällen, die man sonst einer Halothannarkose zuschreibt.

UNA ICTERICIA INEXPLICABLE DESPUES DE ANESTESIA NO-HALOTANA:
Informe de un caso

SUMARIO

Un paciente reveló una ictericia inexplicable después de una anestesia repetida. El único agente anestésico utilizado fue óxido nitroso. Las características de laboratorio y clínicas son muy similares a las de la ictericia que se han atribuido a la anestesia por halotano.