THE PROOF OF GUILT

A Study of Case Reports of Postoperative Jaundice

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SUMMARY

A retrospective study of eleven cases of unexplained postoperative jaundice revealed that in four cases anaesthesia did not include halothane. In all the cases there was difficulty in obtaining full details about the patient, and in some cases all relevant information was missing. Of the seven cases who were given halothane, in only two was there no other obvious cause of the jaundice than halothane. The incidence of postoperative jaundice is in fact very low, and does occur after non-halothane anaesthetics. In most cases, the cause can never be established with any degree of certainty from case histories and the liver function tests available at present.

Much evidence for the “hepatotoxicity” of halothane is based on retrospective studies of case reports of postoperative jaundice. In order to ascertain how much useful information could be obtained from such studies, some case reports of postoperative jaundice which occurred in the Liverpool area were investigated as soon after the onset of the jaundice as possible. The findings illustrate some of the difficulties in deciding confidently a cause for the jaundice.

METHOD

The administrative anaesthetists of the hospitals in or near Liverpool were circularized and asked for information about any case of postoperative jaundice for which there was no obvious cause such as gall bladder or pancreatic disease. When this information was received, the author visited the patients who were alive, and examined in detail the patient’s history and preoperative events. The liver function tests were studied, and further tests done or requested if necessary. The case was discussed with the doctors involved, especially the anaesthetist. Postmortem results were consulted.

Adequate information was obtained in eleven cases but this does not represent the true incidence of postoperative jaundice. The information received about four other patients was inadequate and was given too late for any study to be made. It also became apparent through conversation with colleagues that jaundice which occurred after an anaesthetic which did not include halothane was not considered to be of interest and was therefore not reported to the author. This study is therefore only of some of the cases of unexplained postoperative jaundice which occurred during the period of study and is almost certainly biased in favour of jaundice which appeared after a halothane anaesthetic.

RESULTS

The eleven cases of jaundice occurred between July 1963 and January 1966. They are summarized in figure 1, where it can be seen that four patients did not receive halothane.

<table>
<thead>
<tr>
<th>TOTAL NO. OF PATIENTS — 11</th>
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<tbody>
<tr>
<td>Halothane — 7</td>
</tr>
<tr>
<td>No Halothane — 4</td>
</tr>
<tr>
<td>Repeated Anaesthetics — 4</td>
</tr>
<tr>
<td>Thoracic Surgery — 2</td>
</tr>
<tr>
<td>Suspected Viral Hepatitis — 1</td>
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<tr>
<td>Combined with Radiotherapy — 1</td>
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<tr>
<td>Combined with Profound Hypotension — 1</td>
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FIG. 1. Number of cases, and main features of patients with postoperative jaundice.

Jaundice after anaesthesia without halothane.

It can only be said of one of these patients that he probably did not have halothane. He illustrates one of the cardinal difficulties in any retrospective study, namely, the paucity, or in this case complete absence, of relevant notes. There was no record of anaesthetic or operation, or of treatment given. The anaesthetist did not think that halothane had been given.

The second patient was investigated for gall bladder disease 10 days after the onset of jaundice. However, when the jaundice was first noticed, the anaesthetic was immediately suspected, but as halothane had not been used, another cause was sought. A history suggestive of gall bladder disease was then obtained, and radiological studies showed a non-functioning gall bladder. The anaesthetic and operation were entirely coincidental to the onset of the jaundice.

It is very probable that if halothane had been used, no other cause would have been considered and the case would have been viewed erroneously as one of “halothane jaundice”.

No cause for the jaundice is apparent in the other two patients, the only conclusive fact being that they were not given halothane. However, some possibilities suggest themselves.

One patient was a boy of 16—in the right age group for infectious hepatitis. The other, a lady of 50 who underwent hysterectomy, could have been hypoxic during her difficult 3-hour operation. She was obese, and a steep Trendelenburg position had to be used to facilitate the surgery. Her postoperative course was stormy with, in addition to jaundice, a wound infection, deep vein thrombosis and a pulmonary embolus.

Jaundice after halothane anaesthesia.

Of these seven patients, there were two who had two anaesthetics and in whom careful study revealed no other known possible contributory factors than halothane. The intervals between the anaesthetics were 10 days and 4 weeks. One of these patients stated that after an anaesthetic 4 years previously, her husband thought that she was jaundiced. There were unfortunately no records of this anaesthetic, which would have been particularly valuable in this patient.

The next patient, a lady of 34, had an uneventful 15-minute anaesthetic for excision of an anal fissure, and became jaundiced 12 days later. It is unlikely that such a short exposure to halothane could alone have resulted in the severity and persistence of the liver function changes that were seen in this patient. The jaundice recurred spontaneously 18 months after her discharge from hospital, and six months after this her liver function was only just within normal limits. She gave a history of not feeling well and having no appetite for a few days before her admission to hospital for her fissurectomy and this supports the view that there was some liver dysfunction before her operation and that any anaesthetic could have made it worse.

Another lady, 46 years old, is worthy of detailed description. She was described as a patient who had four anaesthetics, all using halothane, over a period of 4 weeks and whose jaundice must therefore have been due to halothane. However, examination of her case records revealed some facts which throw doubt on this easy assumption. She was jaundiced after her second and fourth anaesthetics, but not after her third, when she was also given halothane. Her second anaesthetic lasted 11 hours, and for at least part of this time her blood pressure was deliberately lowered to about 60 mm Hg. At the end of this operation, she had a cardiac arrest but the heart was restarted within 5 minutes. She had been given three drugs, all of which have been described as causing jaundice, namely erythromycin and novobiocin after her second anaesthetic and chlorpromazine after her third. It is interesting to note that these three drugs had all been given to the 16-year-old patient described earlier. She also had a liver biopsy which was reported on by two pathologists independently and conflictingly. One suggested that the “changes are consistent with a toxic type of damage” and the other that the changes were due to “drug-induced hepatic cholestasis”.

It seems unfortunate that out of this confused and confusing series of events, halothane should have been considered as the sole cause of the jaundice and the case reported to the Committee for the Safety of Drugs as an example of a toxic side effect of halothane.

In two of the remaining three patients pneumonectomy had been performed for carcinoma of the lung and both were in poor general condition before the operation.

One patient died on the second postoperative day, the jaundice coinciding with an intractable fall in arterial pressure. The second patient died 10 days after operation from Pneumococcal bronchopneumonia. This infection had been present from his second postoperative day when the jaundice first appeared.

Hypoxia is known to be associated with thoracic surgery, both during and after the operation (Nilsson, Slater and Greenberg, 1965; Hatch, 1966). A further contribution to the jaundice could have been made by chlorpromazine which was given to the second patient for a few days before the operation. Some consideration must be given to these factors and to the hypotension in the first patient, as well as to halothane, when assessing the cause of the jaundice in these patients.

The third patient who received halothane was anaesthetized twice with this agent for insertion of radium for carcinoma of the cervix. Thirteen days after the second of these two short procedures, she became jaundiced and complained of malaise, nausea and loss of appetite. This patient was studied by means of serial extended bromsulphthalein tests (Dodson and Richards, 1972), the
first test being carried out 7 days after the onset of the jaundice. This test showed a severe degree of liver dysfunction and her serum alanine aminotransferase was 850 King units (normal <30 units). A further b.s.p. test only 4 weeks later showed a remarkable degree of improvement and the serum alanine aminotransferase was now within normal limits. A hysterectomy was therefore undertaken confidently under general anaesthesia because of this remarkable degree of recovery. Halothane was not used and care was taken to avoid hypoxia. The liver function deteriorated slightly after this operation, but the patient felt well and was able to leave hospital at the usual time.

It is important to note that an increase in b.s.p. retention has been observed after a combination of insertion of radium and radiotherapy under spinal anaesthesia for carcinoma of the cervix (Snively, Bullington and Schlosser, 1953). There have also been reports of patients who became jaundiced after radium insertion or deep X-ray therapy under halothane anaesthesia (Beddard, 1963; Ashton, O'Connor and Williams, 1963). Hughes and Powell (1970) note that there were no cases of jaundice after radiotherapy during the years when halothane was not used for anaesthesia, but six cases occurred during the years 1964-66 when halothane was used as the main anaesthetic.

Incidence of postoperative liver complications.

The total number of operations carried out in or near Liverpool for the period of time during which the above patients were reported was approximately 220,000. Assuming that there were only the eleven cases of postoperative jaundice described above, and taking account of the four other cases for which there was inadequate information, the incidence of postoperative jaundice was approximately 1:15,000; that after halothane anaesthesia would be lower. As stated earlier, however, cases occurred which were not reported to the author, and therefore the incidence should probably be higher.

In this series two patients died and in neither case was there autopsy evidence of hepatic necrosis.

DISCUSSION

In most case notes of patients who enter hospital for operation little information is found that is relevant to the liver and its functions. Even the best case records rarely contain any information about the preoperative state of the liver, or the patient's nutrition or alcohol consumption. Surgical notes provide no comment on the liver unless a laparotomy has been performed. The anaesthetic notes give no measurements of arterial oxygen tension, and no data on liver blood flow and function during operation. Postoperative notes are limited and comments on the cause of postoperative pyrexia may not be informative even when a known cause has been treated. Hence the only obvious cause of postoperative jaundice is drug therapy, and even here the records relating to the drugs used, their dosage, route and time of administration, may be incomplete.

Halothane should only be incriminated as the primary cause of jaundice in an individual case when there are no other apparent causes. In this study, in only two of the eleven patients was there no suggestion that any other factor than halothane was responsible for the jaundice. Yet even in these patients there may be an unrecorded or unknown cause for the liver dysfunction. It is as well to recall that postoperative liver complications were well known before halothane was used and, more recently, cases of postoperative jaundice after anaesthesia without halothane have been recorded by Henderson and Gordon (1964), Mushin, Rosen and Jones (1971), Dykes and associates (1965); and the National Halothane Study (1966). Suggestions for possible contributory factors other than drugs in the aetiology of postoperative jaundice is provided by the prospective study of postoperative liver function changes carried out by Dodson and Richards (1972). They found evidence of deterioration in liver function after apparently uncomplicated anaesthesia and surgery and in the absence of any suspected hepatotoxin. The only associations shown were a greater degree of liver dysfunction after intraoperative hypoxia and in patients with a high preoperative alcohol consumption.

Unless case reports of postoperative jaundice are examined more critically, halothane will continue to be automatically, and often erroneously, linked with the jaundice. Case reports of jaundice after halothane have been used to prove that halothane is a hepatotoxic drug and to support the view that multiple halothane anaesthesia is particularly dangerous in this respect (Tornetta and Tamaki, 1963; Trey et al., 1968; Klion, Schaffner and Popper, 1969; Mushin, Rosen and Jones, 1971; Sharpstone, Medley and Williams, 1971). From experience of the difficulties encountered when attempting to elicit all the facts relevant to the liver function of patients with postoperative jaundice, the author considers that in many cases, great weight cannot be given to evidence of this kind. It is hoped that future studies in relation to postoperative jaundice will be directed towards the elucidation of the postoperative changes which occur irrespective of administered drugs, and
towards obtaining more direct evidence of the effects of halothane on the human liver.

Postoperative hepatic necrosis will continue to be a rare, unfortunate and sometimes fatal complication, whatever the anaesthetic given. In a few cases, the cause will be obvious, but in most instances, the aetiology must at present remain obscure.

Acknowledgements

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References


La preuve de culpabilité: étude portant sur une série d'observations d'ictères post-opératoires

Sommaire

Une étude rétrospective ayant porté sur une série de onze cas d'ictères post-opératoires demeurés inexplicés, a montré que dans quatre cas, l'anesthésie ne comportait pas l'administration d'halothane. Dans tous les autres cas, il a été très difficile d'obtenir tous les détails concernant les malades et dans certains cas, on ne disposait d'aucun renseignement utile valable. Sur les sept cas où l'halothane fut administré, il n'y en eu que deux, pour lesquels il n'existait aucune autre cause évidente d'ictère, que cet agent anesthésique. La fréquence des ictères post-opératoires est en fait très basse et une telle complication survient également à la suite de l'administration d'anesthésiques autres que l'halothane. Dans la plupart des cas, il n'est jamais possible d'établir, avec un certain degré de certitude, la cause de ce type d'incident à partir de l'historique des diverses observations et des tests fonctionnels hépatiques dont on dispose actuellement.

Die Schuldfrage: Zwei Falle von postoperativem Ikterus

Zusammenfassung


La prueba de culpabilidad: un estudio de comunicaciones de casos de ictericia posoperatoria

Resumen

Un estudio retrospectivo de once casos de ictericia posoperatoria no explicada reveló que en cuatro casos la anestesia no incluyó halotano. En todos los casos hubo dificultad en conseguir datos completos sobre el paciente y en algunos casos no había ninguna información pertinente. Solamente faltaba alguna causa evidente de ictericia, aparte del halotano, en dos de siete casos que recibieron este gas. La frecuencia de ictericia posoperatoria es en realidad muy baja y puede ocurrir después de anestesias sin halotano. En la mayoría de los casos no se puede establecer la causa con certeza basándose en las historias clínicas y pruebas hepáticas disponibles actualmente.