THE INCIDENCE OF POSTOPERATIVE JAUNDICE WITH SPECIAL REFERENCE TO HALOTHANE*

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A NUMBER OF PUBLICATIONS in the recent literature have drawn attention to hepatic necrosis in patients who have been anaesthetized with halothane [1-15] In these reports halothane has been indicted as the causative agent Reaction to these reports has varied from the dogmatic attitude that halothane should be abandoned as an anaesthetic agent to blind insistence that halothane cannot be responsible for hepatic damage These positions obviously represent extremes which so far fail to be supported by facts It is evident that the whole question of hepatic damage and hepatic failure following anaesthesia and operation requires careful examination Considering the current controversy concerning the role of halothane in the production of hepatic damage, such an examination should, of course, have particular reference to the role which this drug may play in producing hepatic failure

The approach to this problem which immediately suggests itself to most people is the examination of hospital records to determine whether the use of halothane has in fact been associated with an increase in clinical evidence of hepatic damage or death from hepatic failure It is appreciated that such a study will neither prove nor disprove the contention that halothane produces hepatic damage It is reasonable to believe however, that, providing all the patients who have shown clinical evidence of hepatic damage in the postoperative period can be identified, and providing that the statistical sample is large enough, the question as to whether the use of halothane is more likely to produce hepatic damage than the use of other agents and techniques may be answered with some certainty We are aware that many factors associated with the treatment of surgical patients may result in hepatic damage, and that there is at the present time no possible method of ruling out intercurrent viral infections of the liver

In the hope that we might provide a reasonable answer to this primary question, we have examined the records of those patients in the Toronto General Hospital who have developed clinical jaundice in the postoperative period during the years 1953 to 1956, when no halothane was used, and during the period 1960 to 1963, when a large proportion of the general anaesthetics administered to surgical patients employed halothane as one of the agents

METHOD

The primary problem in retrospective studies of this type is the location and identification of the patients to be included in the study Many approaches to a

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solution of this problem have been suggested In this study we have attempted to locate all patients who developed clinical jaundice in the postoperative period by reference to the records of the biochemical laboratory We have examined the records of all the patients who have been reported to have a serum bilirubin greater than 1 5 Vandenburg units While we cannot guarantee that this will identify every patient in our hospital who has had clinical jaundice, we are reasonably certain that the number who will be missed by this method is extremely small The record of each patient has been examined to determine whether or not he had an anaesthetic, and our present report is based on the records of those patients who had, and whose serum bilirubin was 1 5 mg per cent or higher postoperatively We have excluded all patients who were jaundiced at the time of operation, all obstetrical patients, and all patients who had regional anaesthesia Our report, therefore, is based on those patients who were not jaundiced at the time of operation, who developed jaundice postoperatively, and who received general anaesthetics for surgical procedures of all types

Results

During the periods of study, 1953–56 and 1960–63, a total of 92,920 general anaesthetics were administered at the Toronto General Hospital. There were 44,609 administered in the initial period and 48,311 in the latter, of which 21,461 or 44 per cent were with halothane

A total of 250 cases of postoperative jaundice (Table I) was found on reviewing

TABLE I

Postoperative Jaundice after General Anaesthesia

	No of anaesthetics	Cases of jaundice	Incidence per 1000
1953–56	44,609	49	1 1
1960–63	88,311	201	4 2

the medical records for these patients, 49 occurring during the 1953–56 period and 201 in the 1960–63 period This gives an incidence of 1 1 per thousand for the first period and 4 2 per thousand general anaesthetics administered for the second Of the 201 cases from 1960 to 1963 (Table II) 88 had halothane while

TABLE II

Postoperative Jaundice after General Anaesthesia, 1960–63

Agents	No of anaesthetics	Cases of jaundice	Incidence per 1000
Halothane	21,461	88	4 1
Other agents	26,850	113	4 2

113 had other agents, an incidence of 4 1 and 4 2 per thousand respectively The incidence for those anaesthetized with agents other than halothane (Table III)

TABLE III

POSTOPERATIVE JAUNDICE AFTER GENERAL ANAESTHESIA, 1960–63

Agents other than halothane	Cases of jaundice	Incidence per 1000
Nitrous oxide±relaxant	98	4 1
Ether	1	3 8
Cyclopropane	12	7 4

was 4 1 per thousand for nitrous oxide with or without relaxants, 3 8 per thousand for ether, and 7 4 per thousand for cyclopropane

The onset of jaundice occurred within 14 days in over 80 per cent of the cases in both periods, regardless of the agents used (Table IV) Eighty per cent of all the

TABLE IV

POSTOPERATIVE JAUNDICE AFTER GENERAL ANAESTHESIA

Time (days)	1953–56 (%)	1960–63 (%)	
		Halothane	Other agents
0–7	60	5[illegible]	81
8–14	26	2[illegible]	10
15–21	—	7	4
22–28	—	6	1
>28	14	8	4

cases had temperatures of 100 5° F or greater within the first postoperative week. Blood transfusions were administered to 70 per cent of those in the 1953–56 period and to 88 per cent in the 1960–63 period In this latter period 85 per cent of the group anaesthetized with halothane and 91 per cent of those anaesthetized with other agents received blood In addition, many of those who did not receive blood were given drugs such as penicillin, tetracycline, and chlorpromazine, which have been shown to cause jaundice

The mortality rate for the period 1953–56 was 37 per cent and for 1960–63, 25 per cent (Table V) Of the 88 patients who had jaundice after receiving

TABLE V

POSTOPERATIVE JAUNDICE AFTER GENERAL ANAESTHESIA, MORTALITY RATES

	Cases of jaundice	Deaths	%
1953–56	49	18	37
1960–63	201	51	25

halothane (Table VI), 23 died, one quarter within the first week postoperatively Twenty-eight deaths occurred in the remaining 113 cases, one third of these within the first postoperative week The case mortality rate was therefore 26 per cent for those who had received halothane, and 25 per cent for those anaesthetized with other agents

TABLE VI

POSTOPERATIVE JAUNDICE AFTER GENERAL ANAESTHESIA, MORTALITY RATES 1960–63

Agents	Cases of jaundice	Deaths	%
Halothane	88	23	26
Other agents	113	28	25

The causes of death that could be ascertained as accurately as possible from the charts and post-mortem findings were varied (Table VII) Five deaths due to

TABLE VII

POSTOPERATIVE JAUNDICE AFTER GENERAL ANAESTHESIA, CAUSES OF DEATH 1960–63

	Halothane	Other agents
Haemorrhage	4	2
Pneumonia	3	2
Renal	3	9
Embolism	2	2
Cardiac	3	6
General toxicity	3	4
Hepatic failure	5	3

hepatic failure occurred in those anaesthetized with halothane, three in the non-halothane group Of these, primary carcinoma with widespread secondaries was found in one, and four had proven cirrhosis preoperatively There remained three cases, one in the halothane and two in the non-halothane group, which could not be explained (Table VIII)

TABLE VIII

POSTOPERATIVE JAUNDICE AFTER GENERAL ANAESTHESIA, HEPATIC CAUSES OF DEATH 1960–63

	Halothane	Other agents
Carcinoma	1	—
Cirrhosis	3	1
Unexplained	1	2

DISCUSSION

The increase in incidence of postoperative jaundice from 1 1 to 4 2 per thousand general anaesthetics administered during the two periods studied can possibly be explained by several factors

One must consider the changing operative pattern More complicated and prolonged procedures, necessitating the administration of blood and drugs more frequently and in greater quantities, are being carried out Heart–lung and neuro-

logical procedures accounted for over 12 per cent and 10 per cent respectively, of the cases during 1960–63, in contrast to 0 and 2 per cent in the 1953–56 series

The chance of transmitting the virus of serum hepatitis accidentally has been reported to vary from 1 per cent for those receiving one unit of blood to 3 per cent for those receiving four units [16] A recent Japanese report estimates that 64 5 per cent of their blood transfusions transmit the virus, with an incubation period varying from 2 to 11 weeks Their incidence of hepatitis was 38 per cent for those receiving 200 to 800 c c of blood, and 58 per cent for 1000 to 1600 cc, only 10 per cent of which developed clinical jaundice [17]

The threefold increase in incidence of infectious hepatitis, estimated on the basis of the number of reported cases,[18] for the 1953–56 to 1960–63 periods, no doubt has a contributing role as well No method is currently available to separate infectious hepatitis from serum hepatitis

Other factors that must be considered in the production of postoperative liver damage are the direct and indirect consequences of trauma These consist of injury to the bile ducts or hepatic blood vessels, prolonged retraction upon the liver, or secondary to pancreatic necrosis that may complicate upper abdominal surgery Traction alone upon upper abdominal structures can diminish hepatic blood flow by 50 per cent, thus leading to hepatic damage Prolonged shock, with or without the excessive use of vasopressors, has been noted to cause centrilobular necrosis All these factors may precipitate liver failure, especially in cases where disease of the liver already exists

The effect of drugs on the liver is assuming ever increasing importance as a possible causative factor in the production of hepatic damage and jaundice These drugs (and over 70 have been incriminated) include many of the commonly used antibiotics, sedatives, antidepressants, phenothiazines, and anticoagulants, many of these are used extensively in surgical patients pre- and post-operatively

Of the anaesthetic agents commonly used today, none comes under Klatskin's definition of a hepatotoxin [19] Yet, cyclopropane in our study and in that of Allen and Metcalf[20] had a higher association with postoperative jaundice than the other agents, i e halothane, nitrous oxide, and ether No one would condemn cyclopropane on this basis alone

The difference in incidence of postoperative jaundice in patients anaesthetized with halothane and with other agents is not statistically significant This does not necessarily mean that there may be no direct relationship between halothane and hepatic necrosis, but it does give less support to those who would associate the two

Summary

A retrospective study of 250 cases of postoperative jaundice following the administration of 92,920 general anaesthetics during the two periods 1953–56 and 1960–63 at the Toronto General Hospital revealed a marked increase in the over-all incidence, but no significant difference between those anaesthetized with halothane and those anaesthetized with other agents

Résumé

Rétrospectivement, nous avons fait une étude de 250 cas d'ictère postopératoire à la suite de 92 920 anesthésies générales administrées à l'hôpital Toronto General L'étude a porté sur deux périodes la première, de 1953 à 1956, la seconde, de 1960 à 1963

Au cours de la première période, nous n'avions pas employé d'halothane mais, au cours de la seconde période, nous l'avions employé dans 44 pour cent des 48 311 anesthésies régionales

La frequence de l'ictère postopératoire, au cours de la première période (1953–1956), a été de 1 1 par 1000 anesthésies et, au cours de la seconde période (1960–1963), de 4 2 par 1000 anesthésies (tableau I) Sur les 201 cas d'ictère survenus entre 1960 et 1963, 88 avaient reçu de l'halothane alors que 113 avaient reçu d'autres agents une fréquence de 4 1 et 4 2 par 1000 respectivement (tableau II) La fréquence chez ceux qui furent anesthésiés avec d'autres agents était de 4 1 par 1000 pour ceux qui avaient reçu du protoxyde avec ou sans myorésolutifs, de 3 8 par 1000 pour ceux qui avaient reçu de l'éther, et de 7 4 par 1000 pour ceux qui avaient reçu du cyclopropane (tableau III) Chez au-delà de 80 pour cent des cas, au cours des deux périodes, l'ictère est apparu avant le 14e jour, quel que soit l'agent utilisé (tableau IV) Le taux de mortalité pour la période de 1953 à 1956 a été de 37 pour cent, et pour la période de 1960 à 1963, de 25 pour cent (tableau V) Le taux de mortalité a été de 26 pour cent chez ceux qui avaient reçu de l'halothane, et de 25 pour cent chez ceux qui avaient reçu d'autres agents (tableau VI) Les causes de la mort ont été multiples (tableau VII) L'insuffisance hépatique a été la cause de la mort chez cinq malades qui avaient reçu de l'halothane, et chez trois malades dans l'autres groupe De ceux-ci, trois cas demeurent inexpliques un, parmi le groupe de l'halothane et deux, parmi l'autre groupe (tableau VIII)

Les facteurs qui peuvent expliquer l'augmentation de la fréquence de l'ictère postopératoire de 1 1 à 4 2 par 1000 anesthésies générales, au cours des deux périodes étudiées, peuvent se trouver dans le changement de la façon d'opérer, le risque de transmettre accidentellement le virus d'hépatite sérique à cause de l'usage plus fréquent des transfusions, la fréquence trois fois plus grande de l'hépatite infectieuse, la possibilité de traumatisme opératoire, le choc prolongé, et l'usage d'un ou plusieurs médicaments reconnus comme susceptibles de jouer un rôle dans la production de lésions hépatiques

Au cours de cette étude, nous n'avons pas observé de différence importante entre la fréquence de l'ictère postopératoire chez les malades anesthésiés à l'halothane et chez ceux qui furent anesthésiés avec d'autres agents

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