POSTANAESTHETIC LIVER COMPLICATIONS IN A GENERAL HOSPITAL: A STATISTICAL STUDY*

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WITHIN THE FIRST THREE MONTHS of 1963 there appeared reports¹⁻⁴ of about three times as many hepatic complications following halothane anaesthesia as during the three preceding years.⁵⁻⁷ While such a change of emphasis in the literature is part of the natural history of every drug until its place in the Pharmacopoeia becomes fully defined, the new information nevertheless poses questions that demand an urgent answer. The practising anaesthetist would first of all wish to know how great is the danger of hepatic damage to which his patients might be exposed. Then, is the risk uniquely associated with halothane anaesthesia or may there be other factors also involved? Finally, is there any particular group of patients who are more likely to be affected than others? The articles cited above yield no information in this respect and the large-scale co-operative study recently set up to study the problem⁸ will not bring in its report for quite some time. We have, therefore, thought it of interest to review the experience of our hospital and present our findings.

MATERIAL AND METHODS

Notre-Dame Hospital is a 1000-bed teaching institution. During the period under study the hospital has been enlarged, the medical records library has been reorganized, and there occurred a noticeable shift in the composition of our patient material, which became weighted during the last two years towards patients in poor hepatic status, attracted by surgeons and internists particularly interested in the treatment of cirrhosis and hepatic insufficiency. Furthermore, since the end of 1960 there has been a definite epidemic of virus hepatitis in the Montreal area. All these factors might argue against drawing universal conclusions from our data. The overriding argument in favour of presenting them regardless of these facts is that we are reporting on close to 50,000 anaesthetics, 35,000 of which, by conservative estimate, were halothane-nitrous oxide.

The mean anaesthesia time in our operating rooms is 93 minutes. The anaesthetics are administered by resident physicians (their number varied between 14 and 21 during the period under study) or by certified anaesthetists of the visiting staff (their number grew from 7 to 10 over the same period).

We have personally screened all charts between January 1, 1959, and December

*From the Anaesthesia Department of Notre Dame Hospital, Montreal. Read in part at the Annual Meeting of the Canadian Anaesthetists' Society at Montebello, Quebec, May 1963. The authors wish to express their gratitude to Dr. S. Lauzé of the Hospital's Pathology Department and to Mlle M. Lavergne of the Medical Records Library for their valuable assistance in this study.

31, 1961, that bore one or more of the following diagnoses (the numbers refer to the A.M.A. Standard Nomenclature):

680-911	Acute yellow atrophy of the liver
680-915	Acute diffuse hepatic necrosis
680-952	Coarse nodular cirrhosis
680-9X6	Hypertrophic cirrhosis
680-956	Laennec's cirrhosis
680-X42	Hepatic insufficiency
004	Jaundice
932	Coma

Since the machine-coding of the year 1962 has not yet been completed, we were limited for that year to the study of charts belonging to those patients who died in the hospital with one of the above diagnoses.

From the roughly 450 charts we have retained for closer scrutiny those of patients who were anaesthetized after the hepatic diagnosis was made or in whom the hepatic diagnosis was made within four months after the exhibition of an anaesthetic—105 charts all told. Ninety-four patients had a known—and usually fairly serious—liver condition prior to anaesthesia. In eleven, the charts show no clear-cut evidence of pre-anaesthetic liver damage. Although we have set the cut-off point arbitrarily at four months, the longest delay between anaesthesia and the onset of symptoms suggesting liver damage in this series is 25 days.

For the purposes of the present discussion we define a hepatic complication as the production of new symptoms (usually those of jaundice) or the aggravation of pre-existing symptoms following anaesthesia and surgery. Hepatic death is defined as one directly due to the breakdown of the metabolic function of the liver. Thus, for instance, fatal bleeding from oesophageal varices will not be classified here as hepatic death unless it is accompanied by histological evidence of extreme degenerative liver damage. Twenty-seven patients out of the 105 died or developed complications. In fifteen of these autopsy reports or biopsy material were available. These were again reviewed for this study.

RESULTS

Figure 1 shows the incidence and fate of this type of case in our hospital population during 1959-61. Table I provides a tabulation of all complications encountered. In Figure 2 this information is divided into two groups: 2A shows our experience with patients who were known to have liver disease, while 2B shows the hepatic complications encountered in the remaining surgical hospital population. Figure 3 divides our subjects according to sex, age, and site of surgery to indicate how these factors affect the incidence of complications.

COMMENT

It cannot be denied that among our patients hepatic complications have accompanied anaesthesia and surgery in presumably healthy subjects in ever increasing number over the past four years (Fig. 2B). In this group we have

FIGURE 1. Number and fate of "hepatic" cases per 10,000 admissions to Notre-Dame Hospital in 1959-61.

TABLE I
"HEPATIC" COMPLICATIONS AND DEATHS, NOTRE-DAME
HOSPITAL, 1959-61

	1959	1960	1961	1962*
T O T A L	4	6	7	>10
INCIDENCE PER 1,000 ANESTHETICS	.36	.61	.61	>.80
HEPATIC †	-	3	5	6
HEPATIC † PER 1,000 ANESTHETICS	-	.31	.43	.48
HEPATIC † AFTER HALOTHANE - N ₂ O	-	2	3	3

* DEATHS ONLY

encountered seven fatalities during the period in question, six of these following uneventful halothane-nitrous oxide anaesthesia and "major" but by no means extraordinary surgery. One or possibly two of these subjects might be considered as having slight liver damage (it is possible that they were operated upon in the very early stage of hepatitis). If these cases were transferred to the group represented in Figure 2A, we would still be left with five unexplained fatalities, four of them following halothane-nitrous oxide anaesthesia, an incidence of roughly 1 in 8000. This finding per se need not be taken to implicate halothane in any particular measure; it simply reflects the fact that during the period of study 80 per cent of our patients were anaesthetized with halothane. The fifth fatality, which followed a spinal anaesthetic, would implicate the latter technique as much as the halothane one or more if one prorated it to the total number of

FIGURE 2. Comparison of complications observed in patients with known hepatic disease (A) with those found in the remainder of the surgical hospital population (B). Note that the non-fatal complications that might have occurred in 1962 could not be included in this study.

FIGURE 3. Distribution of complications according to age, sex, and site of surgery.

spinals performed in our hospital. Nine of the eleven cases represented in Figure 2B received blood transfusions—two units in one case, one unit each for the remainder. The time of onset of the complications (maximum 25 days, minimum 2 days, average 8.5 days) would argue against a causal connection between transfusions and liver damage in this series.

One should also consider the possibility that *all* our unexplained fatalities were due to virus hepatitis complicated by surgery and anaesthesia. The reported incidence of this disease in Montreal approaches one person per 2000 per year and the reported mortality is around 2.5 per cent. We have made the following assumptions. If the incidence of hepatitis is 1:2000 population per year, if the average hospitalization lasts 20 days, and if the disease had 20 per cent mortality when complicated by anaesthesia and surgery, then the chances that an average surgical patient might develop fatal hepatitis in the hospital would be

$$1/2,000 \times 20/365 \times 20/100 = 1/180,000.$$

Even assuming that the disease becomes 100 per cent fatal when anaesthesia and surgery intervene, the expected death rate would not amount to more than 1/36,000 as opposed to the observed 1/8000. There is also the problem that if we assume the very considerable mortality rate of 20 per cent, which is actually higher than the observed postsurgical mortality rate of patients with established severe liver damage (cf. Fig. 1), then, for the observed fatalities we should also have encountered some twenty-five cases of postoperative jaundice of varying intensity. In fact we have found only four, all of them quite light, and three of these occurring before the hepatitis epidemic. It is inconceivable that such a striking complication should be regularly overlooked. The facts are more consistent with the assumption that virus hepatitis plays no more than a secondary role in the complications here discussed.

The evidence presented in Figure 2A is also of interest. It will be noted that this group of approximately 100 subjects* with known preoperative hepatic disease contributed three-fifths of all hepatic complications encountered in our practice. Yet in this group, where the incidence of liver complications was over 500 times as large as in the general hospital population, halothane proved as good an anaesthetic, if not a better one, than the other agents and methods employed. The reason that this group was anaesthetized less frequently with halothane than was the general hospital population is due to the preferences of one staff anaesthetist who developed a personal interest in many of the most serious operations represented in this group. The selection within the group therefore precludes further conclusions from these data.

The results in Figure 3 might be of some practical interest as they show that female sex, postmenopausal age, and abdominal operations appear to have a bearing on the incidence of complications. In fact, among the eleven cases that make up Figure 2B at least one factor was present in all eleven, at least two factors in ten, and all three factors in four patients.

Blaming one chemical agent or another for the incidence of post-anaesthetic

*The uncertainty arising from the fact that the patient material producing the 1962 fatalities could not be counted.

liver complications might not furnish the full answer to the problem; it seems to us that not enough attention has been paid in this respect to the possible changes in hepatic blood flow that almost certainly accompany anaesthesia and surgery. The subject has recently been reviewed in impressive detail⁹; we can add to it only by pointing out the increased incidence of complications following abdominal surgery in our series and by calling attention to such unexplored aspects as the proper positioning of retractors and packs in the abdominal cavity. The increased vulnerability of postmenopausal women to severe liver damage is generally accepted although we are not aware that any explanation of this fact has been offered.

The finding of so many hepatic complications in our patient material has come as a surprise to us; in fact we were not aware at all of two of the seven fatalities represented in Figure 2B or of the hepatic aspects of five fatalities all told, since these were brought out at autopsy and were added to the charts only after considerable delay. Thus, if this study had not started with the culling of hospital records for hepatic complications, we would probably have submitted a more optimistic report.

In discussion of our results with colleagues (whose helpful criticism is gratefully acknowledged) we found broad agreement on the following points:

1. Hepatic complications following today's surgical procedures, which are both extensive and leisurely, represent a real hazard.

2. While one hepatic death in about 8000 "uneventful" anaesthetics is a fact in this series, its relation to the use of halothane is no more than conjecture. The complications occur later than one would expect from chloroform poisoning,¹⁰ a different age group seems to be affected preferentially, on the other hand the pathology is strikingly similar. It would be particularly wrong to assume that by abandoning halogenated inhalation agents one could eliminate all future hepatic complications in a patient population such as ours. What, if any, 'excess risk' halothane represents over other agents, we are unable to tell.

3. Note should be taken of the fact that of the various complications thus far reported, only one occurred after the exhibition of halothane in oxygen. This technique has been warmly advocated by its proponents.¹¹ It was shown experimentally that it protects the liver against halogenated hydrocarbons^{9,12,13} and it might perhaps deserve special consideration when postmenopausal women are anaesthetized for abdominal surgery.

4. Compared with the estimated incidence of one hepatic death in about 8000 anaesthetics in previously healthy subjects, the hepatic death rate rose to 1 in 13 in a selected group of patients with pre-existing serious liver disease. Yet, in this group, patients receiving halothane showed fewer complications than those anaesthetized by a variety of other techniques. We must conclude that the liver diseases that we have studied do not sensitize their bearers against halothane.

SUMMARY

1. We have studied the hospital records of patients who were anaesthetized while suffering from certain liver conditions or who developed such conditions

following the exhibition of an anaesthetic. One hundred and five such cases turned up in four years in a 1000-bed teaching hospital.

2. Eleven postanaesthetic complications (seven of these fatal) were diagnosed in patients with no known pre-anaesthetic liver disease. Six fatalities followed halothane-nitrous oxide anaesthesia, the seventh patient received a spinal. This distribution does not differ significantly from the ratio of halothane to other anaesthetics employed in our hospital.

3. Sixteen postanaesthetic complications (eleven fatal, seven of these classified as hepatic deaths) were encountered among the 94 cases with known hepatic disease. In this group halothane anaesthesia was associated with proportionately fewer complications than other anaesthetics.

4. Calculations and considerations are presented to show that blood transfusions or concurrent virus hepatitis are not likely to account for the observed complications. On the other hand, interference with the hepatic blood flow either by the surgeon or by the anaesthesia cannot be excluded from the aetiology.

5. We conclude that: (a) Serious post-anaesthetic hepatic complications will occur rarely but regularly, affecting particularly postmenopausal women undergoing abdominal surgery; (b) some doubt must exist about the role of halothane⁴ in the production of such complications; (c) pre-existing liver disease increases the chances of hepatic complications more than five-hundred-fold but does *not* appear to sensitize the bearer against halothane; (d) special risk cases should receive halothane on theoretical grounds not in nitrous oxide but in 100 per cent oxygen.

RÉSUMÉ

Nous avons étudié les dossiers d'hôpital de malades qui ont été soumis à une anesthésie alors qu'ils souffraient de certains troubles hépatiques ou qui, à la suite d'une anesthésie, ont présenté des troubles semblables. Dans un hôpital d'enseignement de 1000 lits, au cours de quatre années, nous avons dépisté 105 cas de ce genre.

Chez onze malades qui n'avaient pas de troubles hépatiques avant l'anesthésie, il a été posé un diagnostic de complication hépatique postanesthésique et sept de ces malades sont morts. Six sont morts à la suite d'une anesthésie à l'halothane et protoxyde d'azote; le septième, après une rachianesthésie. Cette proportion ne diffère pas beaucoup de celle de l'halothane et des autres agents anesthésiques employés dans notre hôpital.

Parmi les 94 cas porteurs de troubles hépatiques connus avant l'anesthésie, 16 ont présenté des complications postanesthésiques, onze sont morts et sept ont été classifiés comme morts de troubles hépatiques. L'anesthésie à l'halothane, dans ce groupe, a compté moins de complications que les autres agents anesthésiques.

Nous présentons des chiffres et des arguments qui montrent que les transfusions ou l'hépatite virale simultanée ne semblent pas être responsables des complications observées. D'autre part, la diminution de la circulation hépatique soit par la chirurgie, soit par l'anesthésie, peuvent avoir joué un rôle dans l'étiologie de ces complications.

Nous concluons: (a) qu'il surviendront des complications hépatiques postanesthésiques sérieuses rarement, mais de façon régulière s'observant particulièrement chez les femmes ménopausées soumises à la chirurgie abdominale; (b) que le rôle que joue l'halothane dans l'apparition de ces complications demeure douteux; (c) que les porteurs de troubles hépatiques connus ont 500 fois plus de chance que les autres de présenter des complications hépatiques mais, selon toute apparence, leurs troubles ne les rendent pas plus vulnérables à l'halothane; (d) que théoriquement, les mauvais risques devraient recevoir de l'halothane avec 100 pour cent d'oxygène plutôt qu'avec du protoxyde.

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