INDOCYANINE GREEN CLEARANCE AND HEPATIC FUNCTION DURING AND AFTER PROLONGED ANAESTHESIA: COMPARISON OF HALOTHANE WITH ISOFLURANE

J. M. MURRAY, B. J. ROWLANDS AND T. R. TRINICK

SUMMARY

Specific biochemical and physiological tests of liver function were used to assess 20 consecutive patients undergoing prolonged head and neck surgery with halothane or isoflurane anaesthesia. Hepatic function was assessed by measurement of serum concentrations of total bilirubin and albumin, and plasma activity of pseudocholinesterase, γ-glutamyl transferase (GGT), aspartate transaminase (AST), alkaline phosphatase (ALP) and hepatic glutathione S-transferase. Plasma clearance of indocyanine green was used as an estimate of hepatic blood flow. No major differences were observed in serum concentrations of GGT, ALP, bilirubin, albumin or pseudocholinesterase. Serum AST activity in those patients receiving halothane was increased at 24 h and at 48 h compared with those who received isoflurane (not statistically significant). Glutathione S-transferase activity was increased significantly in the halothane group throughout the period of study, compared with those who received isoflurane. Similarly, there was a significant difference between the two groups as measured by plasma clearance of indocyanine green: in the halothane group there was a slower disappearance rate of the dye from plasma at specific times than in the patients who received isoflurane. Our data support the use of isoflurane rather than halothane for prolonged anaesthesia.

KEY WORDS

The evidence incriminating halothane in liver damage has become clearer in the past decade [1, 2]. It has been shown that reductive metabolism of halothane occurs in patients receiving halothane anaesthesia under conditions of normoxia [3]. In contrast, isoflurane has not been implicated as a cause of hepatic damage [4]. Metabolism of isoflurane is minimal compared with halothane (20% for halothane and less than 1% for isoflurane) and, unlike halothane, isoflurane does not undergo reductive metabolism [5, 6], or lead to formation of free radicals [7]. Isoflurane tends to preserve autoregulation and hepatic arterial blood flow, whereas halothane decreases blood flow and autoregulation. Both agents have been shown to reduce portal venous blood flow [8, 9]. Duration of anaesthesia contributes to toxicity [10]; it has been demonstrated that prolonged anaesthesia with halothane resulted in a decrease in prothrombin time and Factor VII activity compared with isoflurane [11].

Even after short exposures, hepatic glutathione S-transferase (GST) activity was increased in patients receiving halothane compared with isoflurane [12]. Plasma GST has been shown to provide a more sensitive index of acute hepatocellular damage than aminotransferase activity and correlates better with hepatic histology, an important factor when inferring hepatotoxicity by suspected agents [13].

Indocyanine green is a tricarbocyanine anionic dye used to measure blood flow through organ systems. Hepatic uptake of the dye is an active process which depends on sinusoidal perfusion, membrane transport and secretory capacity. The dye is bound intracellularly to Y and Z proteins and is excreted into the bile without metabolic alteration, conjugation or enterohepatic circulation. It is removed rapidly from the circulation and its decay is usually exponential in nature. Indocyanine green clearance provides an estimate of liver blood flow. There are, however, some problems using this method. Calculation of clearance assumes 100% first pass extraction, inter-individual variation in extraction is large (range 50-95%), and both halothane and isoflurane are known to decrease hepatic extraction of drugs. However, indocyanine green remains a useful substance for estimating hepatic blood flow [14, 15].

We have investigated the effects of prolonged anaesthesia with halothane or isoflurane on specific biochemical tests of hepatic function, and the extent to which each of these agents affects liver blood flow during this period.

PATIENTS AND METHODS

We studied 20 adult patients, aged 20–75 yr, undergoing prolonged head and neck reconstructive surgery (approximately 10 h duration). They were allocated randomly to receive either halothane (n = 10) or isoflurane (n = 10). Ethics Committee approval and informed consent were obtained. Patients...
with evidence of liver damage, either clinical or biochemical, or who had received an inhalation anaesthetic within 3 months were excluded.

Precordication consisted of temazepam 20 mg 1 h before induction of anaesthesia. All patients received a similar anaesthetic comprising fentanyl 5 μg kg⁻¹, a dose of thiopentone sufficient to obtund the eyelash reflex and atracurium 0.5 mg kg⁻¹. After nasotracheal intubation, anaesthesia was maintained by controlled ventilation with isoflurane or halothane in air and oxygen (FiO₂, 0.35). End-tidal concentrations of halothane and isoflurane were measured using an Engstrom Emma agent monitor and MAC hours of each vapour calculated. Ventilation was adjusted to maintain normocapnia. Repeated doses of fentanyl and atracurium were given as required. Arterial blood-gas tensions and pH were measured at 5-h intervals during surgery and daily thereafter.

During surgery and after operation, the volume of fluid administered, including blood, was titrated carefully against haemodynamic status, urinary output and a desired PCV of 30–33%.

Monitoring included ECG, invasive arterial and central venous pressures, core and peripheral temperature, end-tidal carbon dioxide and vapour concentrations and pulse oximetry. Blood samples were taken before operation and 5 h after induction of anaesthesia and at 10 h, when surgery was completed. These measurements were repeated 24 h and 48 h after operation. This blood was assayed for total bilirubin, albumin, γ-glutamyl transferase (GGT), alkaline phosphatase (ALP) and aspartate transaminase (AST), using an Astra 8 (Beckmann Instruments, California), and for pseudo-cholinesterase. Hepatic glutathione S-transferase (GST) was also measured using HEPKIT, an ELISA method from Biotrin International, Dublin. Samples were batched together to reduce assay variability.

Indocyanine green clearance was measured at similar times. Single injections (0.5 mg kg⁻¹) of the dye were used to evaluate hepatic uptake. Clearance was calculated from serum dye concentrations obtained at 5, 10, 15 and 20 min after injection of indocyanine green into a large forearm vein. Percentage disappearance rate (PDR) was calculated using the formula:

\[
PDR = \frac{0.693}{T_1} \times 100
\]

where 0.693 is a constant.

Statistical analysis of the data was performed using one-way analysis of variance and Student's t test where appropriate. P < 0.05 was considered significant.

RESULTS

Both groups were similar with regard to gender and, although there was no significant difference in the ages of the two groups, the mean age of those receiving halothane was more than 10 yr greater than the isoflurane group (table I).

Arterial blood-gas tensions and pH remained within satisfactory limits. Mean exposure time was

<table>
<thead>
<tr>
<th>Time of measurement</th>
<th>Halothane group</th>
<th>Isoflurane group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>4.5 (0.9)</td>
<td>4.5 (0.9)</td>
</tr>
<tr>
<td>5 h</td>
<td>11.58 (3.18)</td>
<td>4.0 (1.30)</td>
</tr>
<tr>
<td>10 h</td>
<td>10.97 (3.9)</td>
<td>3.2 (0.55)</td>
</tr>
<tr>
<td>24 h</td>
<td>5.13 (2.2)</td>
<td>1.46 (0.28)</td>
</tr>
<tr>
<td>48 h</td>
<td>8.85 (2.98)</td>
<td>1.47 (0.26)</td>
</tr>
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</table>

19.5 (SD 0.3) MAC h for halothane and 20.1 (0.5) MAC h for isoflurane.

There were no significant changes in GGT, ALP, bilirubin, albumin and pseudo-cholinesterase. There was an increase in AST activity in both groups at 24 h and 48 h, with halothane producing the greater increase (not significant) (table II).

Serum GST activity was increased significantly throughout the study period in the halothane series compared with those patients who received isoflurane (P = 0.010) (table III).

In the isoflurane group, percentage disappearance rate of indocyanine green was significantly greater than in the halothane group between the 5- and 10-h measurements (P = 0.03). However, in the isoflurane group, the baseline value was greater and this difference was maintained at the 5-h interval and at 24 h and 48 h after operation. The differences between the two groups at these times were not significant. When expressed as percentage change from baseline, disappearance of dye was similar in both groups except at the 5–10 h interval (table IV).

DISCUSSION

There are two sub-types of unexplained hepatitis after halothane anaesthesia: Type I is mild, transient and often subclinical; Type II has features of hypersensitivity leading to necrosis, fulminant hepatic failure and death [16].
Estimation of liver enzyme activity is a common method of assessing hepatic damage from all causes. The relevance of increased ALP, GGT and AST activity to anaesthetic-induced liver damage is questionable [17]. It would appear that changes in these enzyme activities are insufficiently sensitive to detect mild subclinical hepatic dysfunction. Serial measurement of albumin, pseudocholinesterase and bilirubin concentrations would also appear to be unhelpful in addressing this problem.

It has been shown by analysis of plasma activity that there is some evidence for mild, often transient liver dysfunction after only brief exposures to halothane [18]. When isoflurane was administered to a similar group of patients, these changes did not occur.

A highly sensitive and specific ELISA has been developed for the detection and measurement of α-class GST (subunits B1 and B2) in plasma (Biotrin Laboratories Ltd, Trinity College, Dublin). The α-GST are located in the lobular and centrifibular hepatocytes. The latter are more susceptible to damage from anaesthetics such as halothane and toxins such as alcohol and paracetamol. GST has a short half-life (less than 1.5 h) which allows it to be used to follow the course of liver dysfunction.

After a single exposure to halothane and enfurane, but not to isoflurane, there was a significant increase in GST activity at 1 h and 3 h. A second increase in GST activity occurred in some patients 24 h after halothane, suggesting two mechanisms of hepatic injury, with the later increase being perhaps related to metabolism or to metabolites [19].

We have found significant increases in plasma GST activity in those patients who received halothane anaesthetic of long duration. Similar findings did not occur in those patients who received isoflurane. In the halothane group, the increase in GST was maximal at 5 h and returned to baseline values at 24 h, with a further late increase at 48 h. In the isoflurane group, GST activity remained within the upper limits of the assay (≤ 4.5 μg litre⁻¹) throughout the study.

Although the damage produced by prolonged halothane exposure was minor and subclinical, and evident only as increased GST activity, it is interesting to note the time intervals at which this occurred. The early and late increases in plasma GST activity may suggest two distinct mechanisms of halothane-induced liver dysfunction. Initially, there may be a direct effect of halothane on hepatic blood flow, followed by a secondary effect with halothane undergoing reductive metabolism [3] to unstable intermediates which may bind covalently to liver macromolecules to cause necrosis.

All anaesthetic techniques reduce liver blood flow. In patients exposed to volatile agents for brief periods, it is unlikely that any reduction has a significant effect on liver function. However, in the patient undergoing prolonged surgery, reduction in liver blood flow may be detrimental. It seems sensible, therefore, that if a patient required prolonged anaesthesia the technique and the agent used should be those that have the least effect on liver blood flow.

In this study we have demonstrated that both prolonged halothane and isoflurane anaesthesia reduced the clearance of indocyanine green in a linear fashion up to the first 5 h of surgery. However, from this point and to the end of the procedure, clearance of the dye was increased in the isoflurane group. These observations support the previously documented results on the effects of halothane and isoflurane on liver blood flow [10]. That is to say, isoflurane reduces hepatic arterial resistance and maintains total hepatic perfusion better than halothane and may also be advantageous for perfusion of the pre-portal organs, as it appears to reduce vascular resistances in this area slightly more than halothane.

### ACKNOWLEDGEMENT

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### REFERENCES


