Comparison of the effects of sevoflurane, isoflurane and halothane on indocyanine green clearance†

N. Kanaya, M. Nakayama, S. Fujita and A. Namiki

Summary

We have examined the effects of inhalation anaesthetics on indocyanine green (ICG) clearance, as an index of hepatic function, in patients undergoing elective surgery. Recently, a new method has been developed to measure in real-time the disappearance rate of ICG from plasma. This method eliminates the multiple sampling and delay of the conventional ICG test. ICG clearance is displayed as two indices: $K$ (ICG disappearance rate) and $R_{15}$ (ICG retention rate 15 min after injection of ICG 0.5 mg kg$^{-1}$). This measurement was performed in patients before and after 1 MAC of sevoflurane ($n = 6$), 2 MAC of sevoflurane ($n = 6$), 1 MAC of isoflurane ($n = 6$), 1 MAC of isoflurane ($n = 6$), 1 MAC of halothane ($n = 6$) or 2 MAC of halothane ($n = 6$) without surgical stress. Although mean arterial pressure decreased significantly at 1 and 2 MAC of sevoflurane, 2 MAC of isoflurane, and 1 and 2 MAC of isoflurane, ICG clearance was maintained at awake levels, except at 2 MAC of halothane ($K = \text{mean} - 33 \%$ (SEM 3)\%). $R_{15} = + 90 (3)\%$ from awake values. We conclude that sevoflurane and isoflurane have a more favourable effect on liver circulation than halothane. (Br. J. Anaesth. 1995; 74: 164-167)

Key words

There have been several reports on the effects of halothane, enflurane and isoflurane on liver blood flow in animals. Halothane has been reported to exert a more deleterious effect on liver blood flow than isoflurane in dogs [1] or humans [2]. Recently, sevoflurane has been investigated for its effects on the hepatic circulation in animals [3-6]. Fujita and colleagues [3] reported that 1.5 MAC of sevoflurane caused significantly lower portal blood flow than 1.5 MAC of isoflurane in the beagle. In contrast, Bernard and colleagues [5] reported that sevoflurane preserved hepatic arterial blood flow even at high concentrations (2 MAC), which resulted in significant decreases in cardiac output and mean arterial pressure in the chronically instrumented dog. To our knowledge, there have been no studies on the effects of sevoflurane on hepatic blood flow in humans.

The indocyanine green (ICG) clearance test has been found to provide acceptably accurate estimates of hepatic blood flow [7]. Our previous studies have shown the efficacy of a new method of the ICG clearance test, the “finger piece method”, during spinal [8,9] and general anaesthesia [10]. This method eliminates the multiple sampling and delay of the original ICG test while providing an accurate and speedy estimate of hepatic function. The aim of this study was to evaluate the effects of sevoflurane, isoflurane and halothane with 67\% nitrous oxide on ICG clearance using the finger piece method in humans under clinical conditions.

Patients and methods

We studied 36 adult patients undergoing elective surgery. Ethics Committee approval and informed consent were obtained. The patients were allocated randomly to groups 1-6, who received 1 MAC of sevoflurane ($n = 6$), 2 MAC of sevoflurane ($n = 6$), 1 MAC of isoflurane ($n = 6$), 2 MAC of isoflurane ($n = 6$), 1 MAC of halothane ($n = 6$) and 2 MAC of halothane ($n = 6$), respectively. Concentrations of 1.7\% for sevoflurane, 1.3\% for isoflurane and 0.8\% for halothane were considered 1 MAC. Patients with evidence of liver damage, either clinical or biochemical, or who had received an inhalation anaesthetic within 3 months were excluded. All patients were premedicated with midazolam 2.5 mg i.m. and atropine sulphate 0.5 mg i.m. at least 1 h before operation. Anaesthesia was induced with thiamylal 5 mg kg$^{-1}$ followed by suxamethonium 1 mg kg$^{-1}$ to facilitate tracheal intubation. The lungs were ventilated mechanically with 67\% nitrous oxide in oxygen and the appropriate inhalation agent. End-tidal carbon dioxide concentration was monitored (Capnomac, Datex, Helsinki, Finland) and normocapnia maintained. End-expired concentration of inhalation anaesthetics were also measured (Normac, Datex, Helsinki, Finland).

Details of our ICG clearance test have been reported previously [8-10]. ICG clearance was obtained from an ICG clearance meter (RK-1000, Sumitomo Electric, Japan), using the finger piece method.

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Effects of volatile anaesthetics on ICG clearance

Table 1 Mean (SEM) haemodynamic values and ICG clearance during sevoflurane, isoflurane and halothane anaesthesia. $K = \text{Plasma disappearance rate of ICG}; R_{15} = \text{ICG retention rate 15 min after injection of ICG.}$

Significant differences ($P < 0.05$) compared with: *awake state for corresponding anaesthetic; † 1 or 2 MAC of sevoflurane or isoflurane for corresponding stages; § 1 MAC of halothane for corresponding stages; $\dagger$ other groups for corresponding stages.

<table>
<thead>
<tr>
<th>Anaesthetic</th>
<th>Awake</th>
<th>1 MAC</th>
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<th>Awake</th>
<th>1 MAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (b/min)</td>
<td>77 (4)</td>
<td>78 (4)</td>
<td>67 (3)</td>
<td>76 (4)</td>
<td>74 (3)</td>
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<td>76 (4)</td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td>114 (3)</td>
<td>93 (3)*‡</td>
<td>50 (3)*‡</td>
<td>66 (3)*‡</td>
<td>96 (7)</td>
<td>57 (2)*‡</td>
<td>74 (3)*¶</td>
<td>57 (2)*‡</td>
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<td>57 (2)*‡</td>
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<td>57 (2)*‡</td>
<td>74 (3)*¶</td>
<td>57 (2)*‡</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>67 (6)</td>
<td>50 (3)*‡</td>
<td>71 (3)</td>
<td>57 (2)*‡</td>
<td>89 (4)</td>
<td>72 (6)</td>
<td>89 (4)</td>
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<td>89 (4)</td>
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<td>72 (6)</td>
<td>89 (4)</td>
<td>72 (6)</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>84 (5)</td>
<td>66 (3)*‡</td>
<td>89 (4)</td>
<td>57 (2)*‡</td>
<td>89 (4)</td>
<td>89 (4)</td>
<td>74 (3)*¶</td>
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<td>74 (3)*¶</td>
<td>89 (4)</td>
<td>74 (3)*¶</td>
<td>89 (4)</td>
</tr>
<tr>
<td>$K$</td>
<td>0.123 (0.008)</td>
<td>0.138 (0.012)</td>
<td>0.150 (0.045)</td>
<td>0.124 (0.019)</td>
<td>0.135 (0.010)</td>
<td>0.144 (0.006)</td>
<td>0.124 (0.014)</td>
<td>0.144 (0.006)</td>
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<td>0.124 (0.014)</td>
<td>0.144 (0.006)</td>
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<tr>
<td>$R_{15}$ (%)</td>
<td>17.1 (2.0)</td>
<td>14.1 (2.2)</td>
<td>19.0 (6.0)</td>
<td>18.5 (4.3)</td>
<td>14.2 (2.6)</td>
<td>11.9 (1.3)</td>
<td>18.4 (4.8)</td>
<td>18.7 (5.8)</td>
<td>17.1 (1.9)</td>
<td>19.6 (2.5)</td>
<td>14.3 (1.2)</td>
<td>27.2 (1.9)*†</td>
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Discussion

The ICG clearance technique may be used to measure hepatic blood flow (HBF) and has proved to be a satisfactory method to derive total hepatic blood flow (THBF) [7]. Because the conventional ICG clearance test requires multiple blood samplings, it is not suitable for practical and non-invasive clinical measurement. In our previous reports, the ICG clearance test using the finger piece method was shown to be easy to perform and non-invasive [8–10].

Our technique was limited in accuracy as hepatic extraction of ICG was not measured to avoid the potentially traumatic insertion of a catheter. Measurement of hepatic extraction of ICG is necessary to measure quantitatively liver blood flow. Dye removal reflects blood flow, uptake, intracellular binding, metabolic transformation and biliary excretion. If any of these physiological functions deteriorates, systemic retention of the dye occurs. In fact, a few reports have suggested direct inhibition of hepatocyte function by halothane [11, 12]. Although isoflurane has been reported to cause a lesser degree of hepatotoxicity in hepatocytes than halothane [13], the direct action of sevoflurane on hepatocytes has not been investigated. From the data of the present study, we suggest that sevoflurane has a similar direct effect on hepatic function as isoflurane.

Because nitrous oxide potentiates the effects of anaesthetics, the combination of inhalation anaesthetics and nitrous oxide could affect ICG clearance. However, it is important to evaluate the effects of anaesthetics on hepatic function under clinical conditions. Similarly, the rapid sequence induction technique and drugs were selected to equalize the influences of tracheal intubation on the hepatic circulation. Thiopentone [14] and induction of anaesthesia per se may decrease HBF [2].
It has been reported that hepatic arterial blood flow exhibits autoregulation in the normal phase but not in the fasted state [15]. Under physiological conditions, changes in portal blood flow (PBF) modulate hepatic arterial tone to maintain THBF [16]. This phenomenon is termed the “hepatic arterial buffer response”. Halothane impairs this response and decreases HBF secondary to reductions in both PBF and hepatic arterial blood flow in animals [1, 4, 17–20].

Gelman, Fowler and Smith [1] reported that the hepatic arterial buffer response was maintained during isoflurane anaesthesia; the decrease in PBF was compensated for by an increase in hepatic arterial blood flow. Bernard and colleagues [5] observed no significant change in HBF during isoflurane anaesthesia in chronically instrumented dogs. Frink and colleagues [4] observed a significant decrease in PBF and THBF, although isoflurane had less effect than halothane in greyhounds [1, 4, 17–20].

In the present study halothane induced a significant delay in ICG clearance (caused mainly by reduction in HBF) in a dose-related manner, although neither 1 or 2 MAC of isoflurane caused any deterioration. Our results are similar to previous findings in animals and humans. Sevoflurane appears to undergo limited biotransformation and has little or no systemic toxicity in human volunteers [21]. However, the effect of sevoflurane on the hepatic circulation has not been well defined in humans. In pigs, both 1 MAC (2.66%) and 1.5 MAC (3.99%) of sevoflurane caused a significant increase in hepatic artery blood flow (+154% and +123%, respectively) measured by radionuclide-labelled microspheres [6]. The addition of 50% nitrous oxide to sevoflurane reduced liver blood flow at both concentrations of anaesthetic. In a recent study in rats it was shown that 1 MAC of sevoflurane was associated with an increase in hepatic arterial flow, but no change in portal tributary blood flow [22]. Bernard and colleagues [5] also reported in chronically instrumented dogs that 2 MAC (4.6%) of sevoflurane caused an increase of 33% in hepatic arterial blood flow, whereas PBF decreased by 33%. They suggested that the effect of sevoflurane on the hepatic circulation was similar to that of isoflurane and desflurane. Frink and co-workers [4] reported that sevoflurane maintained hepatic arterial blood flow and reduced PBF at 1.5 MAC (3.4%) and 2 MAC (4.6%) in chronically instrumented greyhounds. These two investigations indicate that high concentrations of sevoflurane cause a reduction in total hepatic blood flow secondary to a non-compensated decrease in PBF.

Fujita and colleagues [3] investigated in the hepatic artery ligated beagle the reduction in PBF during 1.5 MAC (3.54%) of sevoflurane anaesthesia compared with equipotent concentrations of isoflurane. They observed a significant increase in ICG clearance during sevoflurane anaesthesia compared with halothane. This result agrees with the findings of the present study in humans. However, they did not find any significant differences between halothane and isoflurane anaesthesia, as observed in our study.

References


