HEPATIC FUNCTION AND INDOCYANINE GREEN CLEARANCE DURING AND AFTER PROLONGED ANAESTHESIA WITH PROPOFOL

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SUMMARY

We have studied the effects of propofol on hepatic function and clearance of indocyanine green (ICG) in 13 consecutive patients undergoing prolonged plastic and reconstructive surgery. Hepatic function was assessed using serum concentrations of liver-specific glutathione-S-transferase (GST). There were no significant changes in GST activity or plasma clearance of ICG throughout the study. (Br. J. Anaesth. 1992; 69: 643-644)

KEY WORDS

Renewed interest in the use of i.v. techniques to provide balanced anaesthesia has been prompted partly by concern on the potential of volatile anaesthetics to cause tissue and organ toxicity. Fulminant hepatotoxicity, although well documented, is rare. Recent reports have suggested that brief or prolonged exposure to halothane causes increases in liver-specific glutathione-S-transferase activity, which suggest a more subtle type of halothane-induced liver injury [1, 2].

The rate of removal of ICG from plasma may be used to estimate hepatic blood flow, as it is removed almost exclusively by the liver and its volume of distribution is close to that of plasma volume. The bolus method, although subject to errors, is adequate to detect changes in individuals. Clearance after peripheral bolus injection has been validated against hepatic vein catheterization in animals and normal subjects.

Having established that halothane and isoflurane may have particular disadvantages when administered over a prolonged period [2, 3], we designed this study to evaluate the effects of a continuous infusion of propofol on hepatic function and ICG clearance during and after prolonged anaesthesia.

METHODS AND RESULTS

We studied 13 adult patients, mean age 60.1 yr (range 40-70 yr) and weight 75.8 (SD 9.39) kg, undergoing prolonged head and neck reconstructive surgery (approximately 10 h duration). University Medical Ethics Committee approval and informed consent were obtained. Patients with evidence of liver disease, recent alcohol abuse, known hyperlipidaemia, or who had received an inhalation anaesthetic within the previous 3 months were excluded. No patient was taking drugs known to induce liver enzymes.

Premedication consisted of temazepam 20 mg, 1 h before induction of anaesthesia. All patients received a similar anaesthetic comprising an initial bolus of alfentanil 30 μg kg⁻¹ followed by an alfentanil infusion at 30-50 μg kg⁻¹ h⁻¹. Anaesthesia was induced with propofol 2.0 mg kg⁻¹ and maintained with a continuous infusion at an initial rate of 10 mg kg⁻¹ h⁻¹ for 10 min, followed by 8 and 6 mg kg⁻¹ h⁻¹ at 10-min intervals. Thereafter, the rate of propofol was adjusted to the clinical haemodynamic response. Atracurium 0.5 mg kg⁻¹, followed by increments if required, was used to facilitate nasotracheal intubation and provide neuromuscular block. Normocapnic ventilation was maintained with oxygen enriched air (FracO₂ 0.4). Arterial blood-gas tensions and pH were measured at 5-h intervals during surgery and daily thereafter.

During and after operation, the volume of fluid administered, including blood, was titrated against haemodynamic variables and urinary output. PCV was maintained at 30-33%.

Heart rate and rhythm, invasive arterial and central venous pressure, arterial oxygen saturation, end-tidal carbon dioxide concentration, temperature and urinary output were monitored throughout. The cumulative total dose of propofol administered was recorded every 1 h and the total infused noted at the end of surgery.

Blood samples were taken before operation and at 5 h after induction of anaesthesia and at 10 h when surgery was completed. These measurements were repeated at 24 h and 48 h after operation. This blood was assayed for hepatic glutathione-S-transferase 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) were
used to evaluate hepatic uptake. Clearance was calculated from serum dye concentrations obtained at baseline and at 5, 10, 15 and 20 min after injection of indocyanine green into a large forearm vein. These samples were centrifuged and their optical densities determined at 805 nm using the patient’s normal serum as a blank. Percentage disappearance rate (PDR) was calculated using the formula:

\[
PDR = \frac{0.693}{T_{1/2}} \times 100
\]

where \( T_{1/2} \) is the elimination half-life of ICG.

All values are expressed as mean (SD). The data were subjected to repeated measures analysis of variance. Statistical significance was inferred at \( P < 0.05 \).

The mean duration of anaesthesia was 10.1 h, and the dose of propofol given during this period ranged between 400 and 610 ml (mean 554.6 ml).

GST values did not exceed the normal range in any sample from any patient (table I).

Disappearance of indocyanine green at 5, 10, 24 and 48 h was expressed as a percentage change from baseline. After 5 h of anaesthesia, there was a 7.5% reduction in the disappearance rate of ICG (ns) and at 10 h this reduction had decreased to 3.7% (ns). Values calculated at 24 and 48 h showed no change from baseline.

COMMENT

Propofol, with its attractive pharmacokinetic profile, is used to maintain anaesthesia by continuous infusion. This study has examined the effects of a prolonged infusion of propofol on indocyanine green extraction and on a specific test of hepatic function.

Robinson and Patterson have outlined the effects of propofol on the commonly available liver function tests in patients undergoing minor surgery [4]. In their study, there were no major changes in liver enzyme activities. There is considerable doubt, however, regarding the usefulness and validity of standard liver function analyses in assessing hepatic injury from inhalation or i.v. anaesthetic agents.

The glutathione S-transferases are a complex group of enzymes that provide alternatives to measurement of plasma aminotransferase activity for detection of liver damage. The physical and chemical properties of GST are such that measurement of GST concentrations in plasma provides a very sensitive index of hepatic injury. When immunological methods are used to measure individual GST isoenzymes, it is possible to obtain considerable organ specificity. These advantages make the value of GST measurements particularly relevant in the clinical investigation of drug-induced liver damage.

Recent work has established the clinical benefits of GST measurement in assessing anaesthetic-induced liver injury during both brief and prolonged procedures [1, 2].

The rate of removal of the bolus doses of ICG from plasma, although subject to small errors, is adequate to detect changes in individuals. This has been validated recently by Cowan and colleagues, who demonstrated good agreement between measurements of hepatic perfusion from the peripheral disappearance curve alone and those that included hepatic vein catheterization [5].

Although propofol infusions have been shown to alter the extraction of some drugs, the small decreases in ICG clearance shown in this study may reflect the relaxant effects of propofol on smooth muscle which have been reported recently in isolated hepatic portal veins [6].

These data demonstrate that propofol, at a steady infusion rate of 6 mg kg\(^{-1}\) h\(^{-1}\), has no significant effects on the extraction rate of ICG during prolonged anaesthesia and causes no increase in GST activity greater than the upper limit of normal (6 ng litre\(^{-1}\)). In view of the sensitivity, but particularly the specificity of this isoenzyme assay, we can be certain that, in the selected group of patients who were studied, there was no suggestion of hepatotoxic effect of the propofol used for induction and maintenance of prolonged anaesthesia.

REFERENCES


