EFFECTS OF TWO DIFFERING HALOTHANE CONCENTRATIONS ON THE METABOLIC AND ENDOCRINE RESPONSES TO SURGERY

S. LACOUMENTA, J. L. PATERSON, J. BURRIN, R. C. CAUSON, M. J. BROWN AND G. M. HALL

Various anaesthetic techniques have been used in attempts to modify the metabolic and hormonal responses to surgery (Traynor and Hall, 1981). The most efficacious are afferent neuronal blockade with extradural analgesia (Engquist et al., 1977) and central inhibition of catabolic hormonal secretion with high-dose opiate anaesthesia (George et al., 1974). In many of the reported studies the control group of patients were anaesthetized with varying concentrations of inhalation agents. However, Roizen, Horrigan and Frazer (1981) found that high doses of halothane prevented the neuroendocrine response to skin incision and concluded that comparisons of the "stress response" to surgery required quantification of the anaesthetic dose.

In the present study we have investigated the effects of two concentrations of halothane on the metabolic and endocrine responses to pelvic surgery. This surgical model has been widely exploited for the investigation of the effects of anaesthesia in modulating the metabolic response to surgery (Engquist et al., 1977; Hall et al., 1978) and is more typical than the surface surgery used by Roizen, Horrigan and Frazer (1981). The two halothane concentrations used were 1.2 MAC, or the expanded MAC₉₅ which is the dose that prevents the response to skin incision in 95% of patients (De Jong and Eger, 1975), and 2.1 MAC, or MAC BAR₅₀, which is the dose that inhibits the adrenergic response to skin incision in 95% of patients (Roizen, Horrigan and Frazer, 1981).

SUMMARY
The effects of two differing concentrations of halothane, 2.1 MAC or 1.2 MAC, on the metabolic and endocrine responses to abdominal hysterectomy were investigated. The changes in blood glucose and lactate values, and plasma glycerol, cortisol, insulin and catecholamine concentrations were similar in both groups. We conclude that high concentrations of halothane do not suppress the responses to pelvic surgery, and that accurate quantification of the dose of halothane, within the concentration range of 1.2 to 2.1 MAC, is not essential in studies of metabolic changes associated with surgery.

PATIENTS AND METHODS
Eighteen healthy women admitted for total abdominal hysterectomy were investigated. Patients with malignant disease were excluded from the study. All patients were allocated randomly to receive either 1.2 MAC or 2.1 MAC halothane. The nature of the study was explained to the patients and consent obtained for the collection of central venous blood.

The patients were not given any premedication. On arrival in the anaesthetic room the duration of starvation was determined and a central venous catheter was inserted percutaneously via a vein in the antecubital fossa to permit the collection of blood samples and the administration of fluids. After the patient had rested for 10 min, a control
blood sample was collected and the heart rate and arterial pressure recorded.

Anaesthesia was induced with thiopentone 3.5–5 mg kg\(^{-1}\), the trachea was intubated with the aid of pancuronium 0.1 mg kg\(^{-1}\) and the lungs ventilated with 60% nitrous oxide in oxygen. Halothane was then added to the fresh gas flow and maintained at either 1.2 or 2.1 MAC for the duration of the study, with appropriate corrections for age and 60% nitrous oxide (Gregory, Eger and Munson, 1969; Roizen, Horrigan and Frazer, 1981). The inspired halothane concentrations were in the range 0.50–1.29%. Ventilation was adjusted to maintain an end-tidal carbon dioxide concentration of 4.5%. The nitrous oxide concentration was determined indirectly by measurement of the oxygen concentration using a calibrated analyser (Datex, Vickers). The end-tidal halothane concentration was measured with a piezoelectric detector (Engstrom, EMMA). After a warm-up period of at least 60 min, the analyser was zeroed with the 60% nitrous oxide in oxygen gas mixture and again with the patient's expired gas, immediately before the addition of halothane, to compensate for the offset produced by nitrous oxide and water vapour (Hayes, Westenskow and Jordan, 1983). The accuracy of the detector was verified periodically against a Riken refractometer, using air as the carrier gas.

When the required end-tidal halothane concentration had been maintained for 10 min another blood sample was collected and surgery commenced. Further samples were obtained 30 min, 1 h, 2 h, 4 h and 6 h after the start of surgery. At the same time as the blood samples were collected, arterial pressure and heart rate were measured. Sodium chloride solution 150mmol litre\(^{-1}\) was administered i.v. at a rate of 6 ml kg\(^{-1}\) h\(^{-1}\) during anaesthesia and surgery, and at 2 ml kg\(^{-1}\) h\(^{-1}\) in the postoperative period. A measured blood loss greater than 350 ml was replaced with an equal volume of Dextran 70 in saline. Analgesia was provided after surgery with papaveretum 15 mg i.m. on demand.

All samples were analysed in duplicate for glucose, lactate and glycerol concentrations, and haematocrit by methods described previously (Hall et al., 1980). Plasma cortisol and insulin concentrations were measured by radioimmunoassay techniques (Seth and Brown, 1978; Hall et al., 1980) on samples collected before the induction of anaesthesia and 30 min, 2 h and 6 h after surgery commenced. The intra- and inter-assay coefficients of variation were, respectively, 6.2% and 6.8% for cortisol and 4.6% and 10.8% for insulin. Plasma concentrations of noradrenaline and adrenaline were determined on samples collected before the induction of anaesthesia, immediately before and 1 h and 6 h after, the start of surgery. The catecholamines were measured by a double-isotope modification of the catechol O-methyltransferase (COMT) assay which permits high precision and sensitivity (Brown and Jenner, 1981). The intra- and inter-assay coefficients of variation were 4.6% and 9.8%, respectively.

On the 3rd day after operation, the skin-fold thicknesses of the patients were measured and the percentage of fat to body weight calculated (Durnin and Womersley, 1974).

The results are expressed as mean values (± SEM). Statistical evaluation of the results was undertaken using a two-way or one-way analysis of variance as appropriate.

RESULTS

Details of the patients studied are shown in table 1. There was no significant difference between the two groups.

**Blood glucose concentration (fig. 1)**

There was a small increase in blood glucose concentration in both groups of patients between the induction of anaesthesia and the start of surgery.
surgery: from 4.39 to 4.60 mmol litre$^{-1}$ in the 2.1 MAC group and from 3.7 to 4.30 mmol litre$^{-1}$ in the 1.2 MAC group. The onset of surgery was associated with a rapid increase in glucose concentration after only 30 min to 6.10 mmol litre$^{-1}$ in 2.1 MAC patients ($P < 0.001$) and to 5.41 mmol litre$^{-1}$ in 1.2 MAC patients ($P < 0.001$). The glycaemic response was sustained for the duration of the study with concentrations of 6.65 mmol litre$^{-1}$ and 5.60 mmol litre$^{-1}$ after 6 h in 2.1 and 1.2 MAC groups, respectively ($P < 0.001$). There was a significant difference ($P < 0.05$) between the two groups after 30 min of surgery.

**Blood lactate concentration (fig. 2)**

Blood lactate values showed little change before surgery, but increased significantly ($P < 0.01$) after 30 min and 1 h of surgery in both groups of patients. Lactate concentrations, however, declined at the end of surgery so that there were no significant changes from preinduction values in either group after 2, 4 and 6 h. There was no significant difference between the two groups.
Plasma glycerol concentration (fig. 3).

Plasma glycerol concentrations did not alter significantly during the period of anaesthesia before surgery. After 30 min of surgery the glycerol concentration increased significantly ($P < 0.01$) in both groups, from 97 to 190 umol litre$^{-1}$ in 2.1 MAC patients and from 126 to 193 umol litre$^{-1}$ in 1.2 MAC patients. The glycerol response was similar to that of lactate in that no significant change was found after 2 h in either group. There was no significant difference between the two groups.
Plasma cortisol and insulin concentrations (fig. 4)

Plasma cortisol concentration increased significantly after 30 min of surgery in both groups to 756 nmol litre\(^{-1}\) (P < 0.001) in the 2.1 MAC patients and to 559 nmol litre\(^{-1}\) (P < 0.001) in the 1.2 MAC patients. The hypercortisolaemia persisted throughout the study and reached 1167 nmol litre\(^{-1}\) in the 2.1 MAC group and 920 nmol litre\(^{-1}\) in the 1.2 MAC group after 6 h.

Plasma insulin values did not change significantly in either group of patients.

Plasma catecholamine concentrations (fig. 5).

Plasma noradrenaline concentrations increased slightly during halothane anaesthesia before the start of surgery, but only became significantly different from preinduction values in both groups after 6 h (P < 0.05). In contrast, plasma adrenaline values decreased during anaesthesia from 0.44 to 0.16 nmol litre\(^{-1}\) in the 2.1 MAC group and from 0.47 to 0.27 nmol litre\(^{-1}\) in the 1.2 MAC group. After 1 h of surgery the adrenaline concentration had increased to 0.69 nmol litre\(^{-1}\) in the 2.1 MAC patients (P < 0.05 compared with presurgical value, P < 0.15 compared with preinduction value) and to 1.08 nmol litre\(^{-1}\) in 1.2 MAC patients (P < 0.01 compared with presurgical value, P < 0.05 compared with pre-induction value).
Arterial pressure and heart rate (fig. 6).

Mean arterial pressure decreased significantly \( (P < 0.01) \) during anaesthesia before surgery in both groups and this persisted for the duration of the study. Heart rate did not change during the period before surgery but declined significantly in both groups after 2 h \( (P < 0.001) \), 4 h \( (P < 0.01) \) and 6 h \( (P < 0.05) \). There were no significant differences between the groups for either arterial pressure or heart rate.

Haematocrit

The haematocrit declined progressively during the study in both groups, from 38.8% to 36.1% \( (P < 0.001) \) after 6 h in the 2.1 MAC group and from 38.3% to 35.4% \( (P < 0.001) \) after 6 h in the 1.3 MAC group. There was no significant difference between the groups.

DISCUSSION

The results show clearly that a high concentration of halothane, 2.1 MAC, had no beneficial effects on the endocrine and metabolic responses to pelvic surgery. This finding is in marked contrast to the results obtained by Roizen, Horrigan and Frazer (1981), who demonstrated that the neuroendocrine response to surgery could be prevented by increasing doses of anaesthetic agents including halothane. However, these investigators examined patients undergoing surface surgery and confined the sampling period to the 10 min following the surgical incision. It can be argued that, because the afferent stimuli produced by pelvic surgery are greater than those produced by surface surgery, an even higher concentration of halothane than 2.1 MAC would be needed to prevent the hormonal and metabolic response. We do not consider it justifiable to attempt to increase the halothane concentration to more than 2.1 MAC in such patients as the postoperative course in the present study was prolonged and unpleasant. Shivering and severe muscle spasms occurred frequently and all nine patients in the 2.1 MAC group vomited. Analgesic requirements were high and reached papaveretum 90 mg in the first 24 h after surgery in several patients.

The importance of this study lies in the observation that accurate quantification of the dose of halothane is not essential when this agent is used during studies of the hormonal and metabolic response to surgery. If we had shown a dose-related effect of halothane on the response to surgery, then much of the work concerned with extradural analgesia and high-dose opiate anaesthesia would have required re-evaluation. Although we did not investigate other volatile agents, there is no reason to suspect that they would behave differently.

Halothane anaesthesia before the start of surgery had little effect on circulating metabolites, but was associated with a decrease in plasma adrenaline concentration while the concentrations of noradrenaline were maintained. These changes are similar to those reported by Halter, Pflug and Porte (1977) and Pflug and Halter (1981) who also used a barbiturate-neuromuscular blocking drug-halothane anaesthetic technique. The cause of the decrease in plasma adrenaline concentration during anaesthesia alone is not clear, but both barbiturates and halothane have been shown to suppress adrenomedullary secretion \textit{in vitro} (Halter and Schneider, 1973; Roizen et al., 1974). If halothane is responsible for the inhibition of the secretion of adrenaline in the anaesthetized patient, it is evident that even a concentration of 2.1 MAC is unable to prevent stimulation of the adrenal medulla during hysterectomy.

Although there is evidence that halothane suppresses the insulin response to glucose stimulation \textit{in vitro} (Gingerich, Wright and Paradise, 1974, 1980), there is little \textit{in vivo} work to support this contention (Halter and Pflug, 1980). In the present study there was no significant difference between the two doses of halothane in their effect on circulating concentrations of insulin. It is extremely difficult, however, in the operative and postoperative period, to isolate the effects of halothane from other important factors that influence the secretion of insulin. In spite of these difficulties, the results suggest that high concentrations of halothane do not markedly affect insulin secretion in healthy patients undergoing pelvic surgery.

In conclusion, there were no differences in the metabolic and hormonal responses to hysterectomy between patients anaesthetized with 1.2 MAC or 2.1 MAC halothane, the higher concentration being equivalent to the MAC BAR\textsubscript{95} (Roizen, Horrigan and Frazer, 1981).
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REFERENCES


