MIDAZOLAM MODIFIES PANCREATIC AND ANTERIOR PITUITARY HORMONE SECRETION DURING UPPER ABDOMINAL SURGERY

J. P. DESBOROUGH, G. M. HALL, G. R. HART AND J. M. BURRIN

SUMMARY
We have investigated the effects of midazolam on circulating concentrations of pituitary and pancreatic hormones in eight healthy patients during cholecystectomy and compared the changes with those in a control group of eight patients. Anaesthesia was induced either with midazolam 0.42 mg kg⁻¹ i.v. followed by an infusion of midazolam 0.125 mg kg⁻¹ for 1 h, or with a sleep dose of thiopentone. All patients received vecuronium, and the lungs were ventilated with 0.5–1.0% halothane and 70% nitrous oxide in oxygen. The use of midazolam was associated with a significant decrease (P < 0.05) in secretion of cortisol and insulin during surgery. Serum growth hormone secretion was augmented, but this did not reach statistical significance. There was little difference in the concentrations of circulating metabolites between the two groups, except for a significant decrease in blood glucose (P < 0.05) in the midazolam group after 60 min. There were no marked differences in cardiovascular variables between the two groups of patients.

KEY WORDS

Midazolam is an imidazobenzodiazepine used for induction and maintenance of anaesthesia, and for sedation. Its pharmacology and clinical effects have been reviewed by Reves and colleagues [1]. Central actions of benzodiazepines are mediated via multi-subunit GABA<sub>A</sub> receptors which have binding sites for the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Benzodiazepines facilitate the synaptic effects of GABA, which modifies chloride ion conductance. GABA<sub>A</sub> receptors have been demonstrated in the CNS and in the periphery [2, 3]. In addition, benzodiazepine receptors, not linked with GABA, are present in high concentrations in peripheral tissues and in the CNS [4].

The effects of GABA agonists, including benzodiazepines, on pituitary hormone secretion have been studied extensively [5]. In general, GABA agonists reduce the secretion of adrenocorticotropic hormone (ACTH) and consequently cortisol, and stimulate basal secretion of growth hormone (GH). Studies of the effects of GABA agonists on hormone secretion from the endocrine pancreas have shown contrasting results [6, 7], but indicate that GABA may also have a role in pancreatic endocrine function.

Several groups have investigated the modification by midazolam of the hormonal and metabolic response to surgery and these studies have been reviewed recently [8]. The results of some studies may have been influenced by the concomitant use of potent opioids [9–11] which are known to affect hypothalamic–pituitary hormone secretion [12]. The object of the present study, therefore, was to investigate further the specific effects of midazolam on the hormonal and metabolic responses to upper abdominal surgery.

PATIENTS AND METHODS
We studied 16 healthy patients admitted for elective cholecystectomy. None had a history of diabetes mellitus or other endocrine disorder. All
patients gave written informed consent to the study, which was approved by the Hospital Ethics Committee. Patients were allocated randomly to receive either midazolam 0.42 mg kg$^{-1}$ i.v. over 5 min followed by an infusion of 0.125 mg kg$^{-1}$ i.v. for 1 h, or an induction dose of thiopentone.

All studies were started before 10:00. Patients were premedicated with papaveretum 15-20 mg and hyoscine 0.3-0.4 mg i.m. 90 min before induction of anaesthesia. On arrival in the anaesthetic room, a central venous catheter was placed percutaneously via a vein in the antecubital fossa for sampling of blood and administration of drugs and i.v. fluids. Approximately 30 min before the start of surgery (−30 min), a control blood sample was collected and mean arterial pressure and heart rate were measured.

Anaesthesia was induced in the control group with a dose of i.v. thiopentone sufficient to abolish the eyelash reflex, and in the midazolam group with midazolam 0.42 mg kg$^{-1}$ i.v. In the midazolam group, an infusion of midazolam 1 mg ml$^{-1}$ at a rate of 0.125 mg kg$^{-1}$ for 1 h only was started before surgery commenced. All patients received vecuronium 0.1 mg kg$^{-1}$ to facilitate intubation of the trachea, and the lungs were ventilated with 0.5-1.0% halothane and 70% nitrous oxide in oxygen. Ventilation was adjusted to maintain an end-tidal partial pressure of carbon dioxide 4.0-4.5 kPa.

Sodium chloride 0.9% was infused at a rate of 6 ml kg$^{-1}$ h$^{-1}$ during surgery and 2 ml kg$^{-1}$ h$^{-1}$ after the end of surgery in all patients. After antagonism of neuromuscular block, increments of flumazenil 0.1 mg were given to patients in the midazolam group if necessary to restore adequate spontaneous ventilation. All patients received papaveretum 5 mg i.v. on demand for analgesia in the recovery period.

Blood samples were collected at the start of surgery (0 min) and 30, 60, 90, 120, 240 and 360 min after the start of surgery. Heart rate and mean arterial pressure were measured at the same time as blood sampling. Blood samples were analysed in duplicate for PCV, glucose, lactate, non-esterified fatty acids (NEFA), cortisol, growth hormone (GH) and insulin concentrations as described previously [13]. Investigators were unaware of the sample identities at the time of analysis.

The samples were analysed for hormones in two batches. The intra-assay coefficients of variation for cortisol were 7% and 4% at 144 and 478 nmol litre$^{-1}$, respectively, for GH 5% and 8% at 4.4 and 11.8 mu litre$^{-1}$, respectively, and for insulin 10% at 9.2 mu litre$^{-1}$. The interassay coefficients of variation for cortisol were 11% and 8% at 144 and 493 nmol litre$^{-1}$, respectively, for GH 13% and 12% at 4.6 and 11.9 mu litre$^{-1}$, respectively and for insulin 10% at 9.4 mu litre$^{-1}$.

Results are shown as mean (SEM) or median (range) for GH data which were not normally distributed. Data were analysed by one- or two-way analysis of variance with Dunnett's test as appropriate, and by Wilcoxon rank sum test and Wilcoxon signed rank test for GH data.

**RESULTS**

There was no difference between the groups in age, weight, duration of surgery or dose of papaveretum received (table I). The mean time interval from the start of induction of anaesthesia

<table>
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<tr>
<th>TABLE I. Details of patients studied (mean or SEM)</th>
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<td>Control (n = 8)</td>
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<td>Age (yr)</td>
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<td>Weight (kg)</td>
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<td>Sex (F:M)</td>
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<td>Duration of surgery (min)</td>
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<td>Total dose of midazolam (mg)</td>
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<td>Post op. papaveretum (mg)</td>
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![Fig. 1. Mean (SEM) serum concentrations of cortisol in control and midazolam groups. 0 min = Start of surgery. Significant difference between groups: * P < 0.05.](https://academic.oup.com/bja/article-abstract/67/4/390/242176/1300242176)
to the start of surgery was 17.5 min in the control group and 20.6 min in the midazolam group. In patients receiving midazolam, surgery commenced 5.6 min after the infusion was started. The mean (SEM) induction dose of midazolam was 26.3 (1.6) mg and the total dose was 34.1 (1.1) mg. Three patients in the midazolam group received flumazenil on completion of surgery after antagonism of neuromuscular block: two received 0.2 mg and one received 0.5 mg. In all three patients, flumazenil was given after the 90-min blood sample had been collected. Blood loss did not exceed 300 ml in any patient and no patient received blood transfusion during the study.

Serum cortisol (fig. 1)

In the control group of patients, serum concentrations of cortisol increased significantly during surgery from 466 nmol litre\(^{-1}\) to 1155 nmol litre\(^{-1}\) \((P < 0.01)\) after 30 min and reached 1465 nmol litre\(^{-1}\) \((P < 0.01)\) after 90 min. This significant increase in serum concentration of cortisol \((P < 0.01)\) persisted to the end of the study. In the midazolam group, cortisol concentrations increased more slowly, from 364 nmol litre\(^{-1}\) to 830 nmol litre\(^{-1}\) \((P < 0.05)\) and to 1034 nmol litre\(^{-1}\) \((P < 0.05)\)

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**TABLE II.** Concentrations of blood glucose and lactate and plasma NEFA, and PCV. Within group differences from preinduction value \((-30\) min\): *P < 0.05; **P < 0.01. Between group differences: †P < 0.05

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<tr>
<th>Time of sample (min)</th>
<th>Blood glucose (nmol litre(^{-1}))</th>
<th>Blood lactate (nmol litre(^{-1}))</th>
<th>Plasma NEFA (nmol litre(^{-1}))</th>
<th>PCV (%)</th>
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after 90 min. Cortisol values were significantly less in the midazolam group at 60 min compared with the control group ($F = 5.61$, $P < 0.05$).

**Serum growth hormone (fig. 2)**

In the control group, GH values did not change significantly from preinduction values of 1.0 ($< 1-6.9$) to 1.4 ($< 1-8.3$) at the start of surgery (0 min), but increased to 16.4 (6.1-30.8) μlitre$^{-1}$ after 30 min of surgery. This significant increase ($P < 0.01$) persisted until 120 min after the start of surgery. In contrast, in the midazolam group, GH concentration increased significantly from preinduction values of 1.1 ($< 1-24.3$) to 4.0 ($< 1-38.6$) μlitre$^{-1}$ ($P < 0.05$) at the start of surgery (0 min) and increased further, to 23.2 (1.2- > 100) μlitre$^{-1}$, after 30 min of surgery. This significant increase ($P < 0.01$) was maintained until 90 min after surgery started. In spite of the augmented response in the midazolam group, there was no significant difference between the two groups at any time point studied.

**Serum insulin (fig. 3)**

In the control group, serum concentrations of insulin did not change significantly during the course of the study, but in the midazolam group concentrations decreased significantly after induction of anaesthesia, from 14.1 μlitre$^{-1}$ to 7.1 μlitre$^{-1}$ at the start of surgery ($P < 0.05$) and remained less than preinduction concentrations during surgery. Serum concentrations of insulin were significantly smaller in the midazolam group compared with the control group at 0 min ($F = 8.94$, $P < 0.05$) and at 360 min ($F = 5.62$, $P < 0.05$).

**Circulating metabolites and PCV (table II)**

Blood concentrations of glucose increased in the control group from 4.79 mmol litre$^{-1}$ before induction to 7.30 mmol litre$^{-1}$ after 60 min of surgery ($P < 0.01$). In the midazolam group, glucose values increased more slowly, from a preinduction value of 4.90 mmol litre$^{-1}$ to 6.64 mmol litre$^{-1}$ at 90 min ($P < 0.05$). Blood concentration of glucose was significantly less in the midazolam group at 60 min ($P < 0.05$).

Blood concentrations of lactate changed little in both groups during surgery, but declined in the postoperative period. This decrease was significant only in the control group at 360 min ($P < 0.05$). There were no significant differences in lactate values between groups. There was no significant change in plasma NEFA concentrations in the two groups of patients. NEFA values were always smaller in the midazolam group than in the control group and this difference was significant at 360 min ($P < 0.05$).

There were no significant changes in PCV in each group during the study and no significant differences between the two groups.

**Heart rate and mean arterial pressure (fig. 4)**

Heart rate did not change significantly in the control group during the study. In the midazolam group, heart rate increased significantly from 65 to 75 beat min$^{-1}$ at the start of surgery ($P < 0.05$) and remained greater than preinduction values during the study, although this change was not significant. Heart rate was significantly slower in the control group at 120 min compared with the midazolam group ($F = 9.15$, $P < 0.05$). Mean arterial pressure did not change signifi-
cantly in the two groups during the study, and there was no significant difference between groups.

**DISCUSSION**

Induction of anaesthesia with midazolam 0.42 mg kg\(^{-1}\) i.v. followed by an infusion of midazolam 0.125 mg kg\(^{-1}\) h\(^{-1}\) for 1 h in addition to halothane anaesthesia, produced a significant decrease in serum concentrations of cortisol and insulin, together with an increase in serum concentrations of growth hormone. The control group received thiopentone induction and halothane alone. Blood concentration of glucose was significantly smaller in the midazolam group at 60 min; otherwise, there were no significant differences in the concentrations of circulating metabolites between the two groups. There were no major differences in cardiovascular variables between the two groups.

Oral benzodiazepines have been shown to suppress cortisol concentrations in human studies [14]. Recent work suggests that GABA agonists may reduce the secretion of ACTH, and subsequently cortisol, through an inhibition of the secretion of hypothalamic corticotrophin releasing factor (CRF) [15, 16]. However, a direct effect on the adrenal glands cannot be excluded, as peripheral benzodiazepine receptors have been demonstrated in the rat adrenal cortex [17].

We have demonstrated a decrease in serum concentrations of cortisol at 60 min after the start of surgery in patients receiving midazolam. This is in contrast with a study by Dawson and Sear [9] in which no effect on the adrenocortical response to surgery was demonstrated when midazolam 20 mg was used as an induction agent compared with thiopentone 4–5 mg kg\(^{-1}\), before fentanyl 3 μg kg\(^{-1}\), nitrous oxide and enflurane anaesthesia for hysterectomy. In their investigation, the induction dose of midazolam was smaller, no infusion was used and sampling was limited to preinduction, end of surgery and three postoperative samples. All these factors, particularly the absence of intraoperative samples, may be implicated in the failure of the study [9] to demonstrate any hormonal suppression with midazolam.

Our choice of dose of midazolam was based on a previous study by Nilsson and colleagues [10], in which midazolam was given in combination with large doses of alfentanil in a total i.v. technique. In their study the mean (SEM) dose of midazolam was 39 (4) mg and that of alfentanil 17.5 (2.1) mg. Serum concentrations of cortisol decreased after induction of anaesthesia, remained small during pelvic surgery and increased to approximately 800 nmol litre\(^{-1}\) only 4 h after the end of surgery. However, these results were not significantly different from the control group who received thiopentone and alfentanil (16.5 (2.4) mg). The use of alfentanil in this study may have masked any effect of midazolam on cortisol secretion, as opioids are known to inhibit the cortisol response to surgery [12].

Crozier and colleagues [11] showed that induction of anaesthesia with midazolam 0.2 mg kg\(^{-1}\) followed by an infusion of midazolam 0.09 mg kg\(^{-1}\) h\(^{-1}\) during minor body surface surgery decreased serum concentrations of cortisol and ACTH to an extent similar to etomidate 0.3 mg kg\(^{-1}\) followed by infusion of etomidate 0.36 mg kg\(^{-1}\) h\(^{-1}\). In contrast with etomidate, midazolam did not impair subsequent secretion of cortisol stimulated by exogenous ACTH. Midazolam attenuated β-ENDORPHIN secretion and ACTH secretion, which suggested a central site of action rather than an effect on adrenal steroidogenesis.

Flumazenil is a specific benzodiazepine antagonist. There are conflicting reports of its effects on hypothalamic–pituitary hormone secretion. *In vitro* studies have demonstrated that flumazenil may antagonize the inhibition of secretion of CRF induced by benzodiazepines [15]. Although we cannot exclude an effect of flumazenil on postoperative cortisol concentrations in our study, there were no marked differences in cortisol values in the three patients who received flumazenil compared with other patients in the midazolam group. Nilsson [8] reported no difference in postoperative concentrations of cortisol in patients receiving flumazenil after total i.v. anaesthesia with midazolam and alfentanil, compared with a similar group of patients who did not receive flumazenil. Furthermore, in a study in which flumazenil (mean dose 0.84 mg) was used to antagonize sedation after midazolam (mean dose 11.0 mg), no increases in β-endorphin or catecholamine concentrations were found compared with a control group [18].

The finding of a greater serum GH response, although not statistically significant, in patients receiving midazolam in the present study is consistent with many previous reports in which GABA agonists, including benzodiazepines, have
been shown to regulate secretion of GH in humans [19, 20]. In most studies, GABA agonists have a stimulatory effect on basal GH secretion, but inhibition of exercise-induced secretion of GH has been demonstrated, suggesting a dual role [20]. The precise mechanism is not fully understood, but GABA may modulate the actions of neurotransmitters involved in GH secretion.

The decrease in serum concentrations of insulin to 50% of resting values after induction of anaesthesia with midazolam 0.42 mg kg⁻¹ was interesting. It is tempting to speculate that this might be caused by a direct effect of midazolam on insulin secretion from the pancreas. GABA has been demonstrated in animal and human pancreatic islets [21, 22] and more recently has been shown by immunocytochemistry to be localized with insulin in the β-cells of the rat pancreas [23]. A mechanism whereby GABA co-secreted with insulin may modulate glucagon secretion via GABA₁ receptor stimulation has been reported [24]. Peripheral type benzodiazepine receptors also exist in rat pancreatic tissue [17], although numbers are much smaller than in the adrenal cortex. Human and animal studies have produced conflicting results of the effects of GABA agonists on insulin secretion [6, 7]: however, the findings suggest that GABA agonists may modulate endocrine pancreatic function. To our knowledge, a clinical effect of midazolam on secretion of insulin during surgery has not been reported previously, and this finding requires confirmation.

The marked changes in concentrations of cortisol, GH and insulin in the midazolam group had surprisingly little effect on the concentrations of circulating metabolites. Blood concentrations of glucose tended to be smaller throughout the study in the midazolam group, but this difference was significant only at 60 min. Control of glycaemia during surgery is influenced mainly by the extent of stimulation of the sympathetic adrenergic system. Crozier and colleagues showed that midazolam attenuated adrenaline concentrations during minor surgery [11]. It is possible that this was a direct effect, as GABA has been demonstrated in adrenal chromaffin cells and GABA receptors have been identified in the adrenal medulla [25].

The absence of significant changes in mean arterial pressure after the large dose of midazolam used in this study confirms previous reports showing minimal cardiovascular changes after induction of anaesthesia with midazolam. Haemodynamic effects after midazolam 0.25–0.3 mg kg⁻¹ are similar to those seen with thiopentone 3–4 mg kg⁻¹ [26, 27].

In conclusion, we have shown that midazolam, when given in a large dose, modifies the endocrine response to surgery. Unlike potent opioids which have only an inhibitory effect on many pituitary hormones [12], midazolam has a mixed inhibitory and stimulatory effect on pituitary secretion, together with an inhibitory effect on pancreatic function.

REFERENCES

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