ETOMIDATE AND ADRENOCORTICAL SYNTHESIS IN MAN

Sir,—We read with interest the report on the effects of a bolus dose of etomidate on cortisol and ACTH secretion (Duthie, Fraser and Nimmo, 1985). We cannot, however, accept the conclusion that “a bolus dose of etomidate 0.3 mg kg\(^{-1}\) causes no significant adrenocortical suppression”.

Other studies have noted an increase in cortisol secretion which occurs about 1 h after the induction of anaesthesia with thiopentone (Fragen, Shanks and Molteni, 1983; Yeoman et al., 1984; Moore et al., 1985) which was not seen in comparative groups given etomidate for induction. The two studies in patients undergoing “minor” surgical procedures (diagnostic laparoscopy—Fragen, Shanks and Molteni; inguinal hernia repair—Yeoman and others) indicated that the cortisol response in the thiopentone groups was decreasing at 3 h after induction. As blood sampling was not performed by Duthie, Fraser and Nimmo between 1 and 4 h after induction, it is hardly surprising that a cortisol stress response was not seen. The prolonged cortisol response reported by Moore and colleagues in patients undergoing abdominal hysterectomy was probably related to the longer duration of surgery and the greater surgical “stress”.

In conclusion, we feel that the authors are not justified in their assertion that boluses of etomidate do not cause significant adrenocortical suppression, because they did not sample during the time that a cortisol response would be expected.

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REFERENCES

Sirs,—I read with interest the paper by Duthie, Fraser and Nimmo (1985). The authors failed to demonstrate significant differences in cortisol, corticosterone or ACTH concentrations when either etomidate or thiopentone was given to induce anaesthesia. They also suggest that the incomplete inhibition of cortisol synthesis was probably compensated for by an increase in ACTH secretion. They did not find a significant increase in ACTH, but it is true that there is a marked variability in ACTH concentrations. However, if their hypothesis is correct (that ACTH compensates for partial inhibition of cortisol synthesis) should not they demonstrate a significant decrease in cortisol concentrations first, since one would expect plasma cortisol concentration to decrease first and then the ACTH concentrations to increase (feed back mechanism)?

Their results, however (no significant difference in cortisol concentrations between etomidate and thiopentone patients), can be explained easily on the basis that their patients had minor or surface surgery.

We do know that etomidate inhibits steroid synthesis (Fry and Griffiths, 1984), but we also know that the type of surgery influences markedly plasma cortisol concentrations (Clarke, Jonhston and Sheridan, 1970). So in some operations, like laparotomy, cortisol is expected to increase as a response to surgical stress. This increase will not occur after etomidate as the drug inhibits the adrenal cortex at the enzyme level. Indeed, Fragen and colleagues (1984) noted, in patients submitted to gynaecological laparotomy, that plasma concentrations of cortisol and aldosterone 1 and 2 h after induction were significantly lower with etomidate than with thiopentone. In contrast, Wagner and White (1984) studied patients who had minor surgery (cervical biopsy) and found similar cortisol and aldosterone concentrations before, during and after operation with either thiopentone or etomidate, but the adrenocortical response to exogenous ACTH stimulation was blunted in the patients receiving etomidate.

Owen and Spence (1984) point out that further similar clinical studies will offer no more than reconfirmation that etomidate suppresses the adrenal cortex.

It appears that the type of surgery accounts for the significant or not significant differences in cortisol concentrations between the etomidate and thiopentone groups reported in the above mentioned studies and not a different degree of inhibition of adrenal cortex by an i.v. bolus injection of etomidate. So an i.v. bolus injection of etomidate produces a “silent” inhibition of the adrenal cortex, but it significantly prevents the response of the adrenal cortex to an “increased stress” such as that caused by major surgery.

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REFERENCES
Sirs.—The recent paper by Duthie, Fraser and Nimmo (1985) suggests that the induction of anaesthesia with a single bolus dose of etomidate 0.3 mg kg$^{-1}$ is not associated with significant depression in cortisol concentration. In support, they cite the data of Sebel, Verghese and Makin (1983), while quoting our data (Sear et al., 1983) to show an effect when the drug is given by continuous infusion for the maintenance of anaesthesia. A re-examination of our data reported elsewhere in three separate studies (Sear et al., 1983; Moore et al., 1985; Sear, Atherden and Edwards, 1985) does not support their argument.

Thirty-five premenopausal women undergoing abdominal hysterectomy were studied. All were premedicated with diazepam 10 mg by mouth 2 h before operation. Anaesthesia was induced in all patients between 08.00 and 10.00 h. Patients were randomly allocated, within the separate studies, to receive one of three anaesthetics:

**Thiopentone group**: Thiopentone 4 mg kg$^{-1}$ for induction of anaesthesia, and maintenance with 67% nitrous oxide in oxygen supplemented with 0.5% halothane ($n = 14$).

**Etomidate bolus group**: etomidate 0.3 mg kg$^{-1}$ for induction, and maintenance as in the previous group ($n = 10$).

**Etomidate infusion group**: etomidate 0.3 mg kg$^{-1}$ for induction, and maintenance with an infusion of etomidate 10 μg kg$^{-1}$ min$^{-1}$ to supplement 67% nitrous oxide in oxygen ($n = 11$).

All patients received alcuronium 0.25 mg kg$^{-1}$ to produce neuromuscular blockade, and fentanyl 3 μg kg$^{-1}$ for additional analgesia. Blood samples were taken before induction, at the end of surgery, and 4 h after induction; cortisol and glucose concentrations were measured in all patients, and aldosterone concentration in 25 patients. Blood-glucose concentration was measured, as the magnitude of the increase during surgery has been equated with the severity of the surgical trauma (Hall, 1985).

Table I shows blood-glucose concentrations and serum cortisol and aldosterone concentrations in the three groups of patients. There were no significant differences in the glycemic response between the patients. There were, however, significant differences in the cortisol responses between the groups. At the end of surgery, and at 4 h after induction, the cortisol concentrations in the thiopentone group were significantly greater than in either of the other two groups ($P < 0.001$). There were no differences in cortisol concentrations between the two groups receiving etomidate, perhaps indicating that, if the drug does have a dose–response relationship on cortisol suppression, both doses in this study were probably acting maximally.

On the other hand, the three groups showed a difference in response when the effect on aldosterone secretion was studied. In the thiopentone group, a significant increase occurred both at the end of surgery and at 4 h while in the etomidate groups there was a dose-related inhibition of aldosterone secretion. In the bolus group, there was no increase in hormone concentrations at the end of surgery, but a significant increase by 4 h ($P < 0.05$). In the infusion group, aldosterone concentrations decreased by the end of surgery ($P < 0.01$), and were still lower than the preinduction value by 4 h. We also observed a differential effect on aldosterone precursor