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Endocrinological Changes following Etomidate, Midazolam, or Methohexital for Minor Surgery

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Etomidate is known to inhibit adrenocorticosteroid synthesis. The extent and duration of the effects of etomidate (63 ± 6.4 mg) on spontaneous and stimulated corticosteroid levels, as well as on plasma concentrations of ACTH, β-endorphin, and catecholamines were examined and compared to those following administration of the new benzodiazepine, midazolam, or of methohexital. Twenty-nine healthy, young, male orthopedic patients were randomized into three groups receiving either etomidate/fentanyl (n = 12), midazolam/fentanyl (n = 8), or methohexital/fentanyl (n = 9). Etomidate caused cortisol levels to decrease from 12.5 ± 1.2 μg/dl preoperatively to 5.9 ± 0.8 μg/dl after operation ($P < 0.001$), compared to an increase from 12.0 ± 1.9 μg/dl to 18.5 ± 2.9 μg/dl in the group receiving methohexital. At 6 and 20 h postoperatively, all cortisol levels were normal. The cortisol decrease from 12.5 ± 1.7 to 7.6 ± 1.5 caused by midazolam was similar to that following etomidate, but the response to exogenous ACTH was significantly impaired in patients receiving etomidate as compared to those receiving midazolam. ACTH and β-endorphin levels increased in patients receiving etomidate, presumably as a result of the interruption of negative feedback due to cortisol synthesis inhibition. Midazolam on the other hand prevented the increase of ACTH and β-endorphin levels. Etomidate completely suppressed spontaneous aldosterone levels (from 33 ± 6.7 to 7 ± 2.1 pg/ml), as well as the response to stimulation with exogenous ACTH without affecting serum electrolytes. Etomidate had no influence on plasma catecholamines, but midazolam attenuated the stress-related epinephrine increase. (Key words: Anesthetics, intravenous: etomidate; methohexital; midazolam. Hormones, adrenal; adrenalcorticotrophic; aldosterone; cortisol. Hormones, pituitary: ACTH, β-endorphin. Sympathetic nervous system, catecholamines: epinephrine, norepinephrine.)

ETOMIDATE HAS BEEN SHOWN to suppress adrenocortical function, both *in vitro* and *in vivo*.[1–5] The mechanism of action has been identified as a dose-dependent, reversible inhibition of the conversion of cholesterol to adrenocorticosteroids.[2,3,6–8] A single induction dose of etomidate was found to be sufficient to prevent the increase of corticosteroid levels caused by surgery, and to impair the response to exogenous $ACTH_{1-24}$.[3,5,8,9] Larger doses led to more prolonged suppression.[3,10–13] On the other hand, cortisol levels have been shown to increase normally after etomidate in patients undergoing aorto-coronary bypass surgery.[14]

Ledingham and Watt[15] suggested a causal relationship between prolonged administration of etomidate and increased mortality in critically ill patients. It is, therefore, now unanimously acknowledged that etomidate is no longer acceptable for long-term sedation, but there is still some uncertainty regarding the advisability of its use as an induction agent for anesthesia; the cardiovascular stability described by Kettler *et al.*[16] might well be outweighed by its hormonal and metabolic side-effects. In an editorial, Longnecker announced his intention to refrain from employing etomidate until this question had been resolved to his satisfaction.[17]

The present study was designed to provide a more comprehensive basis than previous studies for evaluating the neuroendocrine effects of etomidate. Particular attention was given to the extent and duration of adrenocortical suppression. The study was conducted on patients undergoing minor operations in order to minimize the adrenocortical stimulation due to surgical stress and to isolate the adrenocortical effects of etomidate. Only male patients were included in order to eliminate possible gender influences, and to determine whether the results found in other studies conducted only with women[8–13] also applied to men.

Materials and Methods

This study was conducted with institutional approval. The participants were young, healthy male patients scheduled for superficial orthopedic procedures who gave prior written informed consent. All operations began between 8:00 and 11:00 A.M. to avoid the effects of diurnal rhythm.

The patients were randomly assigned to one of three groups: a group receiving methohexital/fentanyl/N_2O, a group receiving etomidate/fentanyl/N_2O, and a group receiving midazolam/fentanyl/N_2O.

Premedication in all three groups consisted of oral flunitrazepam 2 mg *h.s.* and promethazine 50 mg and piritramide 15 mg i.m. 45 min before transport to the operating room. In the operating room, an intravenous infusion was begun in a peripheral vein and 500 ml of

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balanced electrolyte solution was infused prior to induction to compensate for overnight fluid loss. The infusion was continued at the rate of 2 $ml \cdot kg^{-1} \cdot h^{-1}$ during the operation and the first 4 postoperative hours. After 4 h postoperatively, the patients were given oral fluids *ad libitum*.

After prior administration of 0.3 mg fentanyl and 2 mg pancuronium, anesthesia was induced with either 1.5 mg/kg methohexital, 0.3 mg/kg etomidate, or 0.2 mg/kg midazolam. Intubation was facilitated with 100 mg succinylcholine. Anesthesia was maintained in all three groups with 33% O_2, 67% N_2O, and repeated injections of 0.05–0.1 mg fentanyl whenever deemed necessary by the anesthesiologist. Ventilation was adjusted to keep end-expiratory CO_2 at 35–40 mmHg. Anesthesia was always given by the same two persons in order to minimize differences in management. Etomidate was supplied in 1 ml ampules containing 125 mg of the substance dissolved in ethanol. Thus, the effects of the standard solvent, propylene glycol, were avoided.

Etomidate was infused at a constant rate of 0.36 $mg \cdot kg^{-1} \cdot h^{-1}$ starting immediately after intubation and ending 15 min before the end of the operation. Midazolam was infused at a constant rate of 0.09 $mg \cdot kg^{-1} \cdot h^{-1}$ and discontinued 20–30 min before the end of the operation. The infusion rates were calculated according to published pharmacokinetic parameters and infusion models.[18,19] Methohexital was only given in the initial bolus injection; there was no methohexital infusion. The methohexital/fentanyl/N_2O sequence is our standard anesthetic technique for minor surgical procedures.

Venous samples were drawn on the day before operation at 3 P.M., after premedication but before induction of anesthesia, immediately after the operation in the recovery room, 6 h postoperatively, and on the following morning (20 h postoperatively). They were drawn into chilled tubes, kept on ice until centrifugation at 0° C, and then stored at −80° C until further processing.

Adrenocortical stimulation was performed with 0.25 mg synthetic $ACTH_{1-24}$ i.m. (Synacthen®, CIBA-Geigy) on admission day, immediately after operation, as well as 6 and 20 h postoperatively. We refrained from stimulating the patients receiving methohexital immediately after the operation, since we knew from previous experience, as well as from the literature,[12] that cortisol levels in these patients increased normally in response to surgical stress.

ACTH, β-endorphin, and aldosterone concentrations were determined using commercially available radioimmunoassay test kits (ACTH kit from CIS, Salluggia, Italy, sensitivity 2 pmol/l, coefficient of variation 5.2%; β-endorphin kit from Immuno Nuclear, Stillwater, U.S.A., sensitivity 3 pmol/l, coefficient of variation 12.6%; aldosterone kit from Serono Diagnostics, Freiburg, West Germany, sensitivity 5 pg/ml, coefficient of variation 8.5%). The aldosterone antibody had less than 0.01% cross-reactivity with corticosterone. Cortisol was determined by RIA using a highly specific cortisol antibody which had negligible cross-reactivity with 11-deoxycortisol and other adrenocortical steroids (sensitivity 30 pg/ml, coefficient of variation 3.7%). Plasma catecholamines were measured by HPLC with electrochemical detection (sensitivity 20 pg/ml, coefficient of variation 6.2%). All determinations were performed in duplicate. Normal values for our laboratories are: cortisol 15 ± 4 μg/dl in the morning; aldosterone 81 ± 30 pg/ml for prone patients; ACTH 4–14 pmol/l; β-endorphin 5–13 pmol/l; epinephrine 48 ± 23 pg/ml; norepinephrine 254 ± 53 pg/ml.

Intergroup statistical analysis of demographic data, as well as data for steroid hormones, catecholamines, and electrolytes was performed with one-way analysis of variance. Temporal changes from baseline values were analysed with Student's *t* test for paired samples. It was not assumed that ACTH or β-endorphin levels were distributed normally, and these data were therefore analyzed with non-parametric methods: Kruskal-Wallis H-test or Mann-Whitney U-test, as the data required.

Results

Demographic Data

Nine patients received methohexital, 12 received etomidate, and eight received midazolam. Table 1 gives the means and standard errors for age, weight, duration of operation, fentanyl dosage (total and relative to weight and duration), and total, as well as relative, etomidate or midazolam dosage. There was no statistically significant difference between the groups regarding number of patients ($P > 0.4$ by χ^2), age, weight, or duration of operation ($P > 0.1$ by one-way ANOVA). There was a significant difference in the amount of fentanyl required in the three groups.

Cortisol

Preoperative cortisol levels were similar in all three groups. After operation the mean cortisol level in patients given methohexital had increased from 12.0 ± 1.9 to 18.5 ± 2.9 μg/dl (mean ± SEM), but had decreased in the group receiving etomidate from 12.5 ± 1.2 to 5.9 ± 0.8 μg/dl ($P < 0.0005$ for the latter change). The mean level in the group receiving midazolam decreased from 12.3 ± 1.7 to 7.6 ± 1.5 μg/dl ($0.05 < P < 0.1$). The difference between the groups receiving etomidate and midazolam on the one hand, and the group receiving methohexital on the other, was statistically significant at this time ($P < 0.0001$).

TABLE 1. Demographic Data and Drug Dosage (Means and Standard Error)

	Group			Comparison of All Groups with One-way ANOVA
	Etomidate	Methohexital	Midazolam	
Number of patients	12	9	8	$P > 0.4$ (by χ^2)
Weight (kg)	79 ± 3.8	77 ± 3	75 ± 1.4	$P > 0.1$
Age (yr)	28 ± 1.4	27 ± 2	23 ± 1.1	$P > 0.1$
Duration (h)	1.4 ± 0.1	2.0 ± 0.4	1.7 ± 0.3	$P > 0.1$
Etomidate (mg)	63 ± 6.4	—	—	
Midazolam (mg)	—	—	23 ± 1.4	
Fentanyl required				
(mg)	0.49 ± 0.078	0.79 ± 0.14	0.43 ± 0.046	$P < 0.05$
(μg/kg)	6.5 ± 1.2	10.5 ± 1.9	5.7 ± 0.6	$0.05 < P < 0.1$
(μg/kg/h)	4.8 ± 0.69	5.7 ± 0.6	3.8 ± 0.53	$0.05 < P < 0.1$

Six hours postoperatively, the mean level in the group receiving methohexital had decreased to 9.7 ± 2.9 μg/dl. Cortisol levels in patients receiving etomidate were still lower than preoperative values ($0.05 < P < 0.1$), but the diference between the groups was no longer significant. Twenty hours after operation, cortisol levels were the same in all three groups. Means and standard errors are given in table 2.

Cortisol levels responded normally to stimulation with synthetic $ACTH_{1-24}$ (Synacthen®) on admission day in all three groups. At the end of the operation this response was blunted in the patients receiving etomidate, but not in those receiving midazolam. At 6 h postoperatively, the stimulated cortisol increase in patients receiving etomidate was in the normal range, although it was still significantly reduced compared with the other groups. At 20 h postoperatively, the response to Synacthen® was the same in all three groups. The cortisol increases following stimulation are given in table 2.

ALDOSTERONE

Aldosterone levels were normal and comparable in all three groups at both preoperative sample points. After the operation, mean aldosterone levels in patients receiving etomidate decreased from 33 pg/ml to 7 pg/ml ($P < 0.0005$). This was significantly lower than in the patients receiving methohexital (67 pg/ml) or midazolam (38 pg/ml).

Aldosterone remained suppressed following etomidate at 6 and 20 h postoperatively with values of 6 pg/ml and 7 pg/ml respectively ($P < 0.0005$ compared to baseline in both cases). It reached a maximum at the end of operation in the group receiving methohexital ($P < 0.05$ against baseline), and at 6 h postoperatively in the group receiving midazolam ($P < 0.05$ against baseline). At 20 h postoperatively, there was no difference between the mean aldosterone levels of the three groups. Means and standard errors are given in table 3.

Synacthen® stimulation on admission day revealed no

TABLE 2. Serum Cortisol (Mean and Standard Error)

	Group			Comparison of All Groups with One-way ANOVA
	Etomidate	Methohexital	Midazolam	
Unstimulated levels (μg/dl)				
Sample points				
Admission day	7.8 ± 0.8	10.2 ± 1.9	11.0 ± 1.8	$P > 0.1$
Before induction	12.5 ± 1.2	12.0 ± 1.9	12.5 ± 1.7	$P > 0.25$
After operation	5.9 ± 0.8‡	18.5 ± 2.9	7.6 ± 1.5*	$P < 0.0001$
6 h after operation	8.3 ± 2.4*	9.7 ± 2.9	7.7 ± 2.1*	$P > 0.25$
20 h after operation	10.9 ± 1.3	10.3 ± 2.3	6.7 ± 1.1	$P > 0.1$
Stimulated increase of serum cortisol after 0.25 mg $ACTH_{1-24}$ i.m. (μg/dl)				
Sample points				
Admission day	17.6 ± 1.8	16.3 ± 1.6	14.2 ± 2.5	$P > 0.1$
After operation	4.9 ± 0.6†	n.t.	13.1 ± 3.4	$P < 0.01$
6 h after operation	8.5 ± 1.6†	15.8 ± 2.3	17.6 ± 1.3	$P < 0.01$
20 h after operation	13.3 ± 2.5	18.2 ± 1.9	21.0 ± 2.3	$0.05 < P < 0.1$

Symbols denote statistical significance of changes relative to pre-induction levels determined by Student's *t* test for paired samples.

n.t. = not tested.

* = $0.05 < P < 0.1$; † = $P < 0.05$; ‡ = $P < 0.0005$.

TABLE 3. Serum Aldosterone (Mean and Standard Error)

	Group			Comparison of All Groups with One-way ANOVA
	Etomidate	Methohexital	Midazolam	
Unstimulated levels (pg/ml)				
Sample points				
Admission day	41.0 ± 12	50.0 ± 21.7	46.0 ± 15.7	$P > 0.25$
Before induction	33.0 ± 6.7	29.0 ± 7.8	26.0 ± 13.3	$P > 0.25$
After operation	7.0 ± 2.1‡	67.0 ± 16.2†	38.0 ± 10.4*	$P < 0.005$
6 h after operation	6.0 ± 1.9‡	30.0 ± 13.7	62.0 ± 21.7†	$P < 0.05$
20 h after operation	7.0 ± 1.6‡	10.0 ± 3.1†	17.0 ± 5.5	$P > 0.1$
Stimulated increase of serum aldosterone after 0.25 mg $ACTH_{1-24}$ i.m. (pg/ml)				
Sample points				
Admission day	174.0 ± 26.3	156.0 ± 30.9	124.0 ± 18.9	$P > 0.1$
After operation	−1.0 ± 3.9‡	n.t.	114.0 ± 33	$P < 0.0005$
6 h after operation	10.0 ± 1.3‡	140.0 ± 27.7	116.0 ± 21.7	$P < 0.0001$
20 h after operation	24.0 ± 5.1‡	119.0 ± 37	119.0 ± 29.8	$P < 0.001$

Symbols denote statistical significance of changes relative to pre-induction levels determined by Student's t test for paired samples. n.t. = not tested.
* = $0.05 < P < 0.1$; † = $P < 0.05$; ‡ = $P < 0.0005$.

difference between the three groups regarding aldosterone response. Etomidate literally abolished the aldosterone increase, even at 20 h postoperatively, at which time cortisol response had already returned to normal (table 3).

ELECTROLYTES

In spite of the suppressed aldosterone levels, there were no significant changes in serum electrolytes. Serum potassium concentrations were within normal limits, and there was no significant difference between the three groups.

ACTH

Preoperative ACTH levels were similar in all groups. Following the operation, there was a statistically significant increase of median levels from 7.3 (range 2–26) to 13.8 (range 2–32) pmol/l in the patients receiving etomidate ($P < 0.05$), and from 9.2 (range 3–25) to 15.6 (range 5–38) pmol/l in the patients receiving methohexital ($P < 0.05$), but not in those patients receiving midazolam (from 5.2 [range 2–10] to 7.6 [range 2–18] pmol/l).

Six hours postoperatively, the median ACTH level had increased further to 23.3 (2–74) pmol/l in patients receiving etomidate ($P < 0.01$ from baseline). At this time, the value for patients receiving methohexital was 12.4 (2–34) pmol/l and 3.8 (2–5) pmol/l for those receiving midazolam. The difference between the three groups was significant at this time ($P < 0.05$). At 20 h postoperatively, the medians were 10.1 (5–24) in the patients receiving methohexital, 13.4 (2–50) in the patients receiving etomidate, and 5.0 (2–9) in those receiving midazolam. These differences were not statistically significant. The medians are presented in figure 1.

β-ENDORPHIN

The time courses of β-endorphin levels were similar to those of ACTH. Baseline levels were the same in all three groups. The preoperative medians and ranges were 5.9

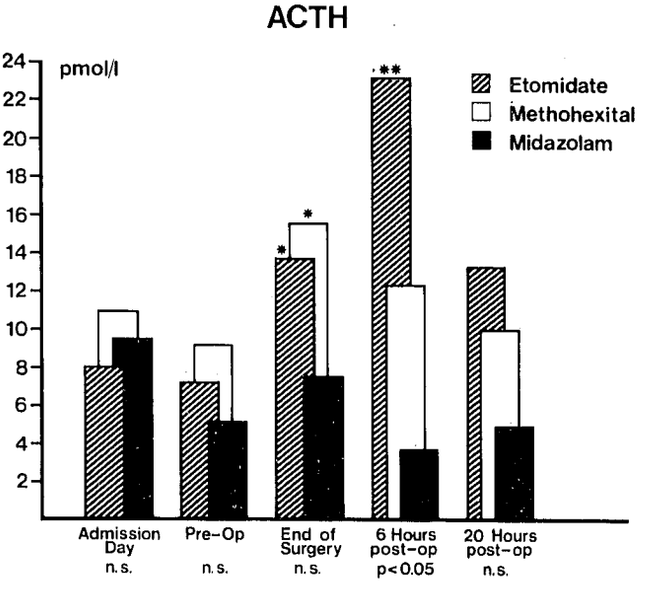

FIG. 1. Median plasma ACTH levels. Symbols beneath the abscissa refers to inter-group differences: (n.s. = not significant [$P > 0.1$], Kruskal-Wallis H-test). Asterisks above columns denote significance of change relative to preoperative levels: * < 0.05; ** < 0.01 by Mann-Whitney U-test.

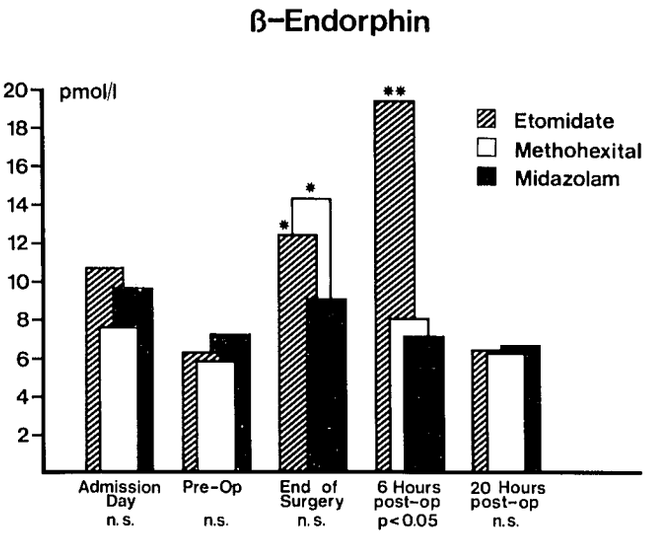

FIG. 2. Median plasma β-endorphin levels. Symbols beneath the abscissa refers to inter-group differences: (n.s. = not significant [$P > 0.1$], Kruskal-Wallis H-test). Asterisks above columns denote significance of change relative to preoperative levels: * < 0.05; ** < 0.01 by Mann-Whitney U-test.

(range 3–8.6) pmol/l in the group receiving methohexital, 6.3 (range 3–8.8) pmol/l in patients receiving etomidate, and 7.3 (range 3–18.9) pmol/l in those receiving midazolam. These levels increased at the end of operation to 14.3 (3–45) pmol/l ($P < 0.05$) in the group receiving methohexital, and 12.4 (3.7–41) pmol/l ($P < 0.05$) in patients receiving etomidate. The corresponding value for the group receiving midazolam was 9.1 (4.2–20.3) pmol/l ($0.05 < P < 0.1$). There was a further increase following etomidate to 19.4 (3–71) pmol/l 6 h postoperatively ($P < 0.01$). The results for methohexital and midazolam were 8.1 (3–28) and 7.2 (3–11.2) pmol/l, respectively. The difference between the three groups was significant at this time ($P < 0.05$).

At 20 h postoperatively, the values were 6.3 (3–16), 6.5 (3–15.5), and 6.7 (3–11.6) pmol/l for methohexital, etomidate, and midazolam, respectively. β-endorphin median values are illustrated in figure 2.

CATECHOLAMINES

Pre-induction epinephrine and norepinephrine levels were similar in all groups (table 4). At the end of operation, catecholamine levels had increased significantly in all three groups compared to preoperative values.

Immediately after the operation, there was a significantly greater increase of the epinephrine levels in patients receiving etomidate or methohexital as compared to those receiving midazolam ($P < 0.05$). Otherwise, there were no significant differences in catecholamine levels between the three groups.

Discussion

Increased plasma levels of hormones of the pituitary-adrenal axis are the typical endocrinologic response to trauma and stress. Although attenuation of inappropriate stress reactions may, on the one hand, be beneficial to the surgical patient, suppression of cortisol synthesis may, on the other hand, be associated with increased mortality.[15,20]

The suppression of the cortisol levels we observed in patients receiving etomidate is in agreement with the results of all previous studies, except that of Wagner and White,[10] who were unable to detect any temporal cortisol changes in a study of very short duration in patients with very minor surgical trauma. However, one must note that

TABLE 4. Serum Catecholamines (Means and Standard Errors)

	Group			Comparison of All Groups with One-way ANOVA
	Etomidate	Methohexital	Midazolam	
Epinephrine (pg/ml)				
Sample points				
Admission day	39 ± 4.1	33 ± 3.2	26 ± 2.6	$0.05 < P < 0.1$
Before induction	39 ± 6.2	39 ± 11.0	26 ± 3.5	$P > 0.25$
After operation	83 ± 15.6†	101 ± 23.0*	38 ± 5.6*	$P < 0.05$
6 h after operation	45 ± 4.6	49 ± 9.1	32 ± 3.8	$P > 0.1$
20 h after operation	52 ± 11.6	37 ± 4.7	27 ± 3.9	$P > 0.1$
Norepinephrine (pg/ml)				
Sample Points				
Admission day	249 ± 32.6	263 ± 28.5	232 ± 47.1	$P > 0.25$
Before induction	209 ± 50.3	268 ± 82.1	166 ± 14.6	$P > 0.25$
After operation	404 ± 83.9‡	770 ± 213*	506 ± 172*	$P > 0.1$
6 h after operation	207 ± 32.7	225 ± 38.3	150 ± 16.3	$P > 0.25$
20 h after operation	224 ± 17.5	240 ± 32.6	167 ± 22.3	$P > 0.1$

Symbols denote statistical significance of changes relative to pre-induction levels determined by Student's t test for paired samples. * = $P < 0.05$; † = $P < 0.01$; ‡ = $P < 0.005$.

the patients in their study had pathological preoperative cortisol levels. The cortisol suppression was of shorter duration in those studies in which the patients only received an induction dose of etomidate,[5,8,9] although this might also be due to the fact that the surgical trauma was greater in two of these studies.[8,9] In the study of Wanscher *et al.*,[11] in which a much larger etomidate dose was administered, the cortisol suppression was prolonged. Lacoumenta *et al.*,[13] who employed an etomidate dose similar to that given in the present study, found significant differences between the cortisol levels of patients receiving etomidate and those receiving thiopental at later times than we could detect.

The ACTH increases which were observed in patients receiving either etomidate or methohexital are similar to those described in the majority of those studies in which this hormone was measured.[3,8,9,12] But Duthie *et al.*[5] detected ACTH increases in patients receiving thiopental, but not in those given etomidate. This is most unusual, since they did demonstrate increased levels of the indirect aldosterone precursor, 11-deoxycorticosterone, which reflects ACTH stimulation in the face of inhibited 11β-hydroxylase. Fragen *et al.*[9] found no change in the ACTH levels of patients receiving thiopental.

The β-endorphin levels changed in parallel with those of ACTH, which is what one would expect, since ACTH and β-endorphin are derived from a common precursor[21] and are released simultaneously.[22,23] Increased ACTH and β-endorphin levels reflect augmented hypothalamic corticotropin-releasing factor (CRF) secretion. CRF itself may lead to sympathetic activation and increased catabolism,[24] and β-endorphin may exert cardiodepressive effects.[25]

Cortisol levels in patients receiving midazolam were also suppressed, but, in contrast to patients receiving etomidate, their ACTH levels were not increased. This suggests that spontaneous cortisol levels alone are insufficient to judge the degree of adrenocortical impairment. Inhibition of corticosteroid synthesis is not an all-or-nothing phenomenon, but takes place in a dose-dependent,[2,6,7] and reversible (M. Obermaier, personal communication), manner. Therefore, the response of the adrenal cortex to exogenous ACTH is a more important parameter in evaluating the inhibition of corticosteroid synthesis than spontaneous cortisol levels.[26] The capability of the adrenal cortex to synthesize and secrete cortisol was suppressed by etomidate as shown by the flat response to exogenous ACTH stimulation immediately after the operation. The response had returned to normal at 6 h postoperatively.[26] Neither methohexital nor midazolam affected the cortisol increase following Synacthen®. There are only two previous studies in which serial ACTH stimulations were performed over a period of 24 h.[3,11] Both suffer from the very limited number of patients investigated, but they still show that the adrenal cortex regains its responsiveness to ACTH sometime between 4 and 48 h after etomidate administration, depending on the etomidate dose. As mentioned above, Synacthen® was not given immediately after operation to patients receiving methohexital. Although this omission precludes the direct comparison of the adrenocortical suppression of all three drugs at this particular time, the effects of etomidate and midazolam are still obvious.

Aldosterone levels in the patients receiving etomidate were suppressed almost completely for at least 20 h, and did not respond to Synacthen® stimulation. Since plasma levels are determined by plasma half-life, as well as synthesis rate, lower levels might be partially due to the shorter half-life of aldosterone, and not solely to a more complete inhibition of synthesis. It would have been desirable to follow up the patients receiving etomidate for longer than 20 h to determine when the aldosterone response to ACTH stimulation returned to normal, but most were discharged on the first postoperative day. Since fluid replacement was identical in all patients, we take the absence of changes in serum electrolytes as evidence that the suppressed aldosterone levels are not clinically relevant. It has been demonstrated *in vitro*[2,3] and *in vivo*[5,8] that the levels of the cortisol and aldosterone precursors 11-deoxycortisol and 11-deoxycorticosterone, which themselves have mineralocorticoid properties, increase following the administration of etomidate, and probably compensate the aldosterone deficiency.

In the only previous study in which the effect of etomidate on catecholamine levels was investigated, Wagner and White[10] could detect no significant perioperative norepinephrine changes. However, one must again note that the preoperative hormone levels lay outside the normal range. Our results differed in that we found significant catecholamine increases in all three groups. The increases of the epinephrine levels immediately postoperatively were greater in the patients receiving etomidate and methohexital than in those receiving midazolam.

As shown by our data, cortisol levels in patients receiving midazolam are in the same range as in those receiving etomidate, and are lower than in those given methohexital. This is in contrast to the report of Dawson and Sear,[27] who observed identical cortisol increases in patients receiving either midazolam or thiopental. They administered midazolam as a single induction bolus, whereas our patients received a bolus followed by a continuous infusion. Calculations based on pharmacokinetic data show that, 30 min after the initial dose, the midazolam plasma concentrations would be higher in the patients of our study. The patients of their study were also subjected to a more severe surgical stress (abdominal surgery *vs.* minor body surface operations), which might also be the reason for the differing results. However, we have

previously found that flunitrazepam prevents the increase of cortisol levels in patients undergoing major abdominal surgery.[28] The cortisol response to exogenous ACTH was normal in our patients, and ACTH and β-endorphin levels were not increased. This finding is supported by a recently published report by Shapiro *et al.*[29] showing that midazolam does not affect the adrenocortical response to ACTH. We take this as evidence that adrenocortical steroidogenesis is unimpaired, and that midazolam presumably exerts its effect partly *via* hypothalamic GABA receptors,[30] and, possibly, also by reducing nociceptive input to the hypothalamus.[31,32] It does not appear to interrupt the normal feedback regulation of plasma cortisol levels.

Midazolam also attenuated the perioperative epinephrine increase which is unaffected by etomidate. This was demonstrated previously by Glisson *et al.* in dogs.[33] The effect of midazolam on epinephrine might be mediated through the GABA-benzodiazepine receptor complex demonstrated in the adrenal medulla,[34] in addition to the antinociceptive effects mentioned above.

Although cortisol levels following etomidate were never lower than the normal range for our laboratory and the response to $ACTH_{1-24}$ was markedly suppressed for only approximately 6 h, it is conceivable that situations such as sepsis or massive hemorrhage could arise in which an adequate cortisol response might be necessary for survival, in which case patients receiving etomidate might be at a disadvantage. Although the results of a previous study suggested that etomidate does not impair the normal increase of cortisol levels in patients undergoing aorto-coronary bypass surgery,[14] this question requires further research.

One can conclude from the data presented that etomidate, at a dose three to four times as large as that required for induction of anesthesia, impairs the cortisol response to minor surgical trauma or to exogenous ACTH stimulation for approximately 6 h, with a compensatory increase of ACTH levels and simultaneous release of β-endorphin. The normal increase of aldosterone levels following ACTH stimulation is impaired for at least 20 h, but this does not appear to be clinically relevant, since no changes of serum electrolytes are detectable. Etomidate does not appear to differ from methohexital in its influence on perioperative changes of circulating catecholamines. Midazolam attenuates cortisol as well as ACTH and β-endorphin increases suggesting a central site of action on the hypothalamo-pituitary-adrenal cortex axis, and, possibly, also an antinociceptive effect. It blunts the postoperative epinephrine increase seen in patients receiving etomidate or methohexital. Thus, whereas the effects of etomidate on adrenocortical function appear to be of shorter duration than previously assumed, our data show that midazolam can be regarded as a possible alternative drug which reduces stress-related hormone increases without inhibiting corticosteroid synthesis.

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