The modifying influence of anaesthesia on postoperative protein catabolism

K. GIESECKE, C. KLINGSTEDT, O. LJUNGQVIST and L. HAGENFELDT

SUMMARY
We studied two groups of six patients scheduled for gastrointestinal surgery; they were allocated randomly to receive high- or low-dose fentanyl anaesthesia. The confounding effect of protein balance, before the trauma of surgery, on postoperative nitrogen excretion was controlled by standardized protein intake before operation, supplemented by adequate calories. The high-dose group had significantly lower stress levels during surgery, assessed by arterial blood concentrations of cortisone, adrenaline and glucose. After operation, protein catabolism was measured for 7 days. The high-dose group had significantly lower postoperative excretion of ammonia and slightly lower excretion of urea and 3-methylhistidine. Low-stress anaesthesia may thus diminish postoperative catabolism, which could be important in frail patients by reducing mortality, ICU resources, or both. (Br. J. Anaesth. 1994; 72: 697-699)

KEY WORDS
Metabolism: protein.

In acute trauma, such as surgery, hormonal and metabolic changes counteract disturbed homeostasis [1, 2]. Previous studies [3, 4] have shown that postoperative nitrogen retention occurs when this perioperative stress response is attenuated. The purpose of the present study was to determine if stress levels during two different anaesthetic techniques correlated with postoperative protein degradation.

METHODS AND RESULTS
After obtaining local Ethics Committee approval and informed consent, we studied 12 patients scheduled for gastrointestinal surgery; they were allocated randomly to receive either high- or low-dose fentanyl anaesthesia. ("High-dose" = loading dose of fentanyl 100 μg kg⁻¹ over 1-2 min and a continuous infusion of 5 μg kg⁻¹ h⁻¹ after 1 h of surgery. "Low dose" = fentanyl 5 μg kg⁻¹ initially and an infusion of 3 μg kg⁻¹ h⁻¹.) Premedication and neuromuscular block were the same in both groups. There was no significant difference in mean duration of anaesthesia between the groups. However, respiratory depression caused by the high-dose regimen required that these patients continued to receive artificial ventilation for 6 h after operation. There were no significant differences between the two groups in age, weight or sex. Arterial blood samples were obtained for measurements of glucose, cortisol and adrenaline concentrations before operation, 15, 30 and 90 min during operation and 1 h after operation.

Protein catabolism was assessed for 3 days before and for 7 days during and after operation. Three days before operation, patients were admitted and given a diet containing myofibrillar-free protein 0.5 g/kg body weight, with a total energy content of 35 kcal/kg body weight (fat:carbohydrate ratio, 50:50). On the day of surgery and for the next 4 days, patients were given an i.v. regimen with the same amino acid and calorie content and then they returned to the original oral diet for 2 days.

Urine was collected in 24-h periods for the entire 10-day period and analysed for urea, 3-methylhistidine, creatinine, ammonia and 1-methylhistidine concentrations. Blood concentrations of glucose and serum concentrations of urea were measured daily. Daily urea production was calculated as the amount excreted in urine plus the change in the urea pool from the previous day. Total body urea pool (mmol) was calculated as serum concentration of urea times total body water (57 % of body weight).

Differences between groups were tested for statistical significance by two-way ANOVA.

As in our previous study of patients undergoing cholecystectomy [5], the high-dose group had significantly smaller blood concentrations of adrenaline (P < 0.01), cortisone (P < 0.05) and glucose (P < 0.04) during surgery compared with the low-dose group.

Daily excretion of urea, 3-methylhistidine, ammonia and 1-methylhistidine during the entire study is shown in figure 1 and the postoperative mean values in table I. Excretion of the three former substances increased significantly (P < 0.05) from the preoperative to the postoperative period. Mean daily excretion of urea and 3-methylhistidine was consistently greater in the low-dose group for each of the 7 days after operation, but there were no significant differences between groups in the cumulative 1-week period.

KAJSA GIESECKE, M.D., PH.D., Department of Anaesthesiology, Huddinge Hospital, S-141 86 Huddinge, Sweden. CHRISTIAN KLINGSTEDT, M.D., PH.D., Department of Anaesthesiology, South Hospital, S-118 83, Stockholm, Sweden. OLLE LJUNGQVIST, M.D., PH.D., Department of Surgery, Karolinska Hospital, Box 60 500, S-104 01 Stockholm, Sweden. LARS HAGENFELDT, Department of Clinical Chemistry, Huddinge Hospital, S-141 86 Huddinge, Sweden. Accepted for Publication: December 3, 1993.
excretion of these two metabolites. However, the cumulative postoperative excretion of ammonia was twice as great in the low-dose group \((P < 0.002)\).

Daily creatinine output was similar for both groups and it remained virtually constant over the entire 10-day period (an indication of normal renal function).

Excretion of 1-methylhistidine is thought to result entirely from ingested animal protein, with no endogenous pool. However, we found a significant increase \((P < 0.05)\) in urine concentration of 1-methylhistidine from preoperative values to the first day after operation in both groups, followed by a return to preoperative values. This pattern implies that 1-methylhistidine may be a metabolite of endogenous protein catabolism also.

**COMMENT**

In response to trauma, such as surgery, the body mobilizes glucose to maintain blood concentration of glucose. As glycogen stores are small, protein stores are soon used for gluconeogenesis, reflected as increased excretion of urea in urine.

In our study, the total amount of urea produced in the postoperative period did not differ significantly between groups, but production in the first days after operation was greater in the low-dose fentanyl group. This indicates, as found by Brandt and colleagues [3] and Anand, Sippell and Aysnley-Green [4], that the degree of stress during surgery influences the rate of production of urea after trauma.

In all patients, urea production peaked on the first day after operation and the subsequent decline was followed by a more sustained increase. The absence of this initial peak for 3-methylhistidine, a degradation product of striated muscle, could indicate that initial excretion of urea does not originate from muscle protein catabolism, but rather from a free pool of amino acids, mainly glutamine, which has been reported to decrease after elective surgery and fasting [6]. Thus a reduction in the stress response during surgery may affect immediate demands in the amino acid pool, but not the long-term catabolic response, reflected by excretion of 3-methylhistidine.

In our study, excretion of 3-methylhistidine increased after operation, indicating increased muscle degradation in both groups. The level was greatest on days 2 to 4 after operation, coinciding with the second peak in excretion of urea and this did not differ significantly between groups.

After trauma, production of ketoacids from increased lipolysis necessitates an increase in renal production of ammonia to offset this acid load. Glutamine, which is released during injury, is the primary renal substrate in the production of ammonia. Catecholamines are extremely potent in mobilizing fat via activation of hormone-sensitive triglyceride lipase. Greater concentrations of adrenaline in the low-dose fentanyl group on the day of surgery and on the subsequent day might thus explain the greater excretion of ammonia in this group.

We conclude that our study does not provide support for the use of high-dose fentanyl anaesthesia to suppress postoperative metabolism in patients in good general health undergoing routine abdominal surgery.
surgery, as the overall differences between the two groups were small. The significant difference in excretion of ammonia and the slight differences in excretion of 3-methylhistidine and urea indicate, however, that low-stress anaesthesia may be beneficial during surgery in patients who have cardiac compromise and also after surgery in patients whose preoperative nutritional state makes them vulnerable to moderate postoperative protein catabolism.

REFERENCES
1. Roizen MF. Should we all have a sympathectomy at birth? Or at least preoperatively? *Anesthesiology* 1988; 68: 482-484.