

Epidural Versus Intravenous Fentanyl for Reducing Hormonal, Metabolic, and Physiologic Responses after Thoracotomy

Timo E. Salomäki, M.D.,* Juhani Leppäluoto, M.D., Ph.D.,† Jorma O. Laitinen, M.D., Ph.D.,‡
Olli Vuolteenaho, M.D., Ph.D.,§ Lauri S. Nuutinen, M.D., Ph.D.¶

Background: Previous attempts to prevent all the unwanted postoperative responses to major surgery with an epidural hydrophilic opioid, morphine, have not succeeded. The authors' hypothesis was that the lipophilic opioid fentanyl, infused epidurally close to the spinal-cord opioid receptors corresponding to the dermatome of the surgical incision, gives equal pain relief but attenuates postoperative hormonal and metabolic responses more effectively than does systemic fentanyl.

Methods: Forty patients were randomly assigned to receive either fentanyl epidurally and saline intravenously, or fentanyl intravenously and saline epidurally, in a double-blind fashion for the first 20 h after thoracotomy. For each patient, the fentanyl infusion was titrated to the rate required for pain relief (pain score < 3, maximum 10). Postoperative changes in blood pressure, heart rate, rectal temperature, and blood concentrations of adrenocorticotrophic hormone, β -endorphin immunoreactivity, cortisol, growth hormone, prolactin, glucose, and leukocytes were assessed.

Results: Patients reported similar median pain scores, but the epidural group required about 40% less fentanyl than the intravenous group. Four hours postoperatively, the β -endorphin immunoreactivity concentrations were less in the epidural than in the intravenous group. Plasma cortisol increased in a similar manner in both groups within 4 h of surgery, but the increase persisted to the next morning only in patients receiving intravenous fentanyl. Adrenocorticotropin, growth hormone, and prolactin responses were similar in both groups. The postoperative hyperglycemic response, leukocytosis, and

blood pressure were greater, and mean rectal temperature was lower, in the intravenous than in the epidural fentanyl group.

Conclusions: The authors' results indicate that some aspects of the hormonal response to surgery are blocked more completely with epidural than with intravenous fentanyl. Adequate pain relief with epidural fentanyl, with a smaller mean dose, led to a smaller increase of some hormonal, metabolic, and physiologic responses after thoracotomy than in association with the adequate pain relief provided by intravenous fentanyl. (Key words: Analgesia: postoperative. Analgesics, opioid: fentanyl. Anesthetic techniques: epidural; intravenous. Hormones: adrenocorticotrophic hormone; β -endorphin; cortisol; growth hormone; prolactin. Metabolic response: glucose; leukocytes.)

EFFORTS to prevent or attenuate endocrine, metabolic, and inflammatory responses to surgery have been made with various anesthetic techniques to reduce postoperative morbidity.¹⁻⁵ Epidural blockade, including all the afferent pathways from the site of the trauma, will prevent a large proportion of the endocrine and metabolic responses that follow lower abdominal operations and procedures on the lower extremities.^{6,7} However, epidural neural block has been less efficient in reducing these responses to upper abdominal and thoracic procedures.⁸⁻¹¹ The addition of morphine to an epidural infusion of local anesthetic has beneficial effects on postoperative pain relief, but only minor ones on other responses.⁸⁻¹⁰ Epidural morphine, rather than low-dose parenteral morphine, appears to be the treatment of choice for postoperative pain, but, in some trials, both parenteral and epidural morphine failed to prevent unwanted responses to surgery, and in others, responses have been less marked with epidural morphine in the late postoperative periods.^{8,12-14}

With diamorphine, which is considerably more lipophilic than morphine, the concentrations of glucose and cortisol have been less with epidural than with parenteral administration after major abdominal surgery.^{15,16}

* Clinical Instructor.

† Professor of Physiology.

‡ Senior Staff Anaesthesiologist.

§ Senior Lecturer of Physiology.

¶ Professor of Anaesthesiology.

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Address reprint requests to Dr. Salomäki: Departments of Anaesthesiology, Oulu University Hospital, Kajaanintie 50, SF-90220 Oulu, Finland.

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Apart from the results of Bormann *et al.*, which indicate that the highly lipophilic opioid fentanyl administered epidurally inhibits the postoperative anti-diuretic hormone response,¹⁷ there are no other data available on the effects of epidural fentanyl on postoperative endocrine and metabolic responses.

We have shown earlier that it is possible to achieve equal relief from pain with a smaller dose and less respiratory depression, nausea, and sedation by administering fentanyl epidurally than by administering it intravenously, after thoracotomy.¹⁸ In a separate analysis of data obtained in these patients, our hypothesis was that the lipophilic opioid fentanyl, infused epidurally close to the spinal cord opioid receptors corresponding to the dermatome of the surgical incision, more effectively attenuates postoperative hormonal, metabolic, and physiologic responses than does systemic fentanyl when doses have been titrated for equal relief from pain in both groups. To demonstrate this difference in efficacy, we compared changes in hemodynamics, rectal temperature, and blood concentrations of adrenocorticotrophic hormone, β -endorphin immunoreactivity (ir β -E), cortisol, growth hormone, prolactin, blood glucose, and leukocytes in both groups.

Materials and Methods

Postoperative hormonal and metabolic responses were studied in the same 40 patients scheduled for elective thoracotomy as described earlier in the comparison of the analgesic effects of epidural and intravenous fentanyl infusions.¹⁸ The patients, ASA physical status 1–3, with no known endocrine disorder except for two cases of controlled diabetes mellitus in each group, were randomly allocated to one of two treatments, intravenous or epidural fentanyl. Those in the intravenous group received fentanyl intravenously and saline epidurally for 20 h postoperatively, and those in the epidural group received fentanyl epidurally and saline intravenously in a double-blind fashion.¹⁸ The tip of the epidural catheter was introduced into the fourth or fifth thoracic interspace. For each patient, the fentanyl infusion was titrated to a rate required for pain relief (pain score < 3, maximum 10).¹⁸

The visual pain score (VPS; 0 = no pain, 10 = worst pain imaginable), respiratory rate, blood pressure, heart rate, and rectal temperature were recorded every 20 min until the patients were comfortable (VPS < 3), and every hour after that up to 20 h postoperatively.

The patients assessed their incisional pain on tidal breathing.

Arterial blood-gas analyses, total leukocyte counts, and plasma glucose were measured preoperatively, 30 min and 4, 10, and 16 h after arrival in the intensive care unit and on the first morning postoperatively. Arterial blood samples for ir β -E, ACTH, cortisol, growth hormone, and prolactin analyses were taken on the afternoon and morning before surgery because of their known diurnal variation, and also 4 h after arrival in the intensive care unit and on the first postoperative morning. Arterial blood for plasma ACTH, cortisol, and ir β -E analyses was collected into 10-ml EDTA tubes and centrifuged immediately, and the plasma was stored at -20°C until assayed. Plasma ACTH (ACTH Double Antibody Kit, Diagnostic Products Corporation, Los Angeles, CA), cortisol (Cortisol 125I, Orion Diagnostica, Orion Corporation, Espoo, Finland), growth hormone (Pharmacia hGH Kit, Pharmacia Diagnostics, Upsala, Sweden), and prolactin concentrations (Prolactin Double Antibody Kit, Diagnostic Products Corporation) were measured by radioimmunoassay. Plasma samples for Ir β -E were extracted with SEP PAK C18 cartridges (Water Associates, Milford, MA). Our β -E antiserum cross reacted fully with β -lipoprotein and β -endorphin.¹⁹ β -Lipoprotein, which has no known biological activity, and β -endorphin are secreted from the pituitary gland concomitantly by comparable stimuli.²⁰ Hence, the term β -endorphin immunoreactivity (ir β -E) means, in this context, β -E/ β -LPH activity. The sensitivity of the radioimmunoassay was 4 pg/tube.¹⁹ The intraassay and interassay coefficients of variation were less than 10 and 15% for β -E, 4.9–10.0% and 6.4–11.7% for ACTH, 1.5–3.9% and 3.5–7.1% for cortisol, 2.5–5.1% and 3.5–5.6% for growth hormone, and 2.3–4.4% and 6.3–8.6% for prolactin. Arterial plasma concentrations of fentanyl were measured 4 and 18 h postoperatively. The plasma was anticoagulated with heparin, centrifuged, and stored at -20°C until analyzed by radioimmunoassay at the Bioanalytical Laboratory of Janssen Pharmaceutica. The lowest detection limit for the assay is 0.1 ng/ml.

The Mann–Whitney U test was used to analyze differences between groups (area under the curve for total leukocyte counts and plasma glucose concentration; changes from preoperative to postoperative concentrations of prolactin, ACTH, growth hormone, cortisol, and ir β -E; pain scores, mean fentanyl infusion rates, fentanyl plasma concentrations, and mean blood pressure), and the Wilcoxon signed rank test was used to

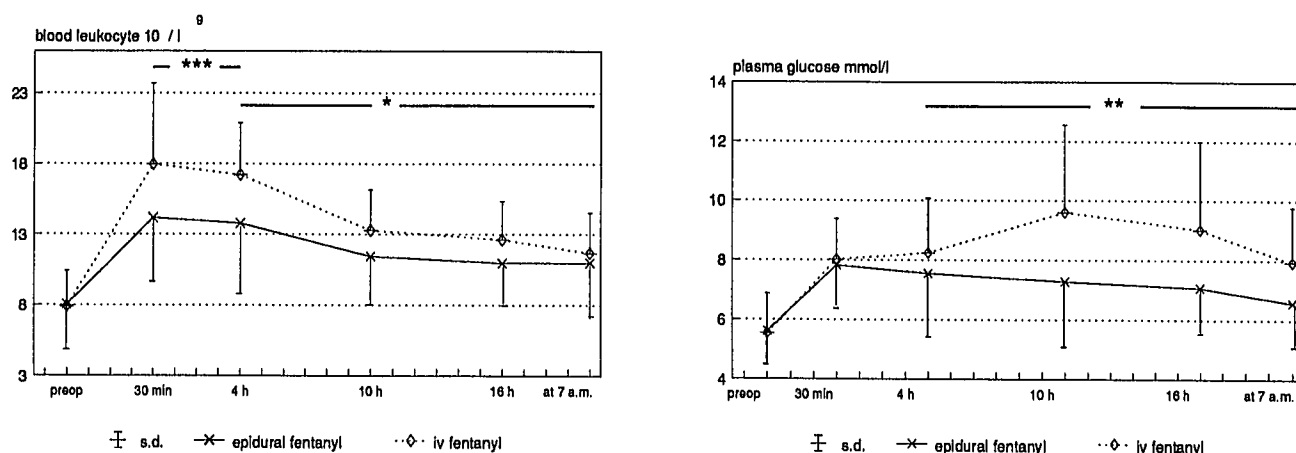


Fig. 1. Pre- and postoperative blood leukocyte count and plasma glucose (30 min and 4, 10, and 16 h after surgery, and the next morning). The difference between groups at 30 min–4 h was statistically significant for leukocyte count and at 4–20 h for leukocyte count and plasma glucose (* $P < 0.05$; ** $P < 0.03$; *** $P < 0.01$).

analyze changes from preoperative to postoperative levels within the groups (prolactin, ACTH, growth hormone, cortisol, ir β -E, total leukocyte counts, and plasma glucose). The associated nonparametric 95% confidence intervals for median changes within groups and differences in medians between groups were calculated based on the statistics introduced by Gardner and Altman.²¹ The t test for two independent samples was used to compare the changes in mean rectal temperature and in mean heart rate between the groups. The P_{aCO_2} and P_{aO_2} were compared between the groups using a repeated-measures multivariate analysis of variance. A P value < 0.05 was considered significant. The data are presented as means \pm SD, as medians and 95% confidence intervals, and as 95% confidence intervals of group median differences.²¹ To estimate the relationship of possible differences between the groups, the Spearman correlation coefficient was calculated between VPS pain and glucose, blood pressure, leukocyte count, and the difference between postoperative and preoperative concentrations of ir β -E. The Pearson correlation coefficient was calculated between P_{aCO_2} and responses in glucose, blood pressure, leukocyte count, and the difference between postoperative and preoperative concentrations of ir β -E. The same calculations were performed for statistics between fentanyl doses and these responses.

Results

The demographic data, the visual pain scores, and the pain relief questionnaire scores were similar in both

groups.¹⁸ The mean fentanyl requirements per hour (micrograms per kilogram per hour) were larger in the intravenous group during hours 0–4 postoperatively (2.41 [0.99] vs. 1.27 [0.31], $P = 0.0001$) and hours 4–20 (1.50 [0.41] vs. 0.85 [0.26], $P = 0.0001$), while the mean plasma concentrations of fentanyl (nanograms per milliliter) were less in the epidural group at 4 h (0.81 [0.27] vs. 1.38 [0.36], $P = 0.0001$) and 18 h (0.94 [0.32] vs. 1.54 [0.65], $P = 0.0007$).¹⁸

The mean postoperative P_{aCO_2} was greater in the intravenous group ($P < 0.002$), in which 50% of patients had a $P_{aCO_2} > 53$ at least once, as compared with 10% in the epidural group.¹⁸ The postoperative P_{aO_2} was comparable in both groups (range: 64–90 mmHg).

Blood Pressure, Heart Rate, Blood Leukocyte, Plasma Glucose, and Rectal Temperature

The mean blood pressure was similar during the first 4 postoperative hours (intravenous group, 96 (15) mmHg; epidural group, 93 (16) mmHg), but higher in the intravenous group during the following 16 h (92 [11] mmHg vs. 84 [12] mmHg, $P < 0.05$). Mean heart rate was similar in both groups (intravenous vs. epidural: 0–4 h, 81 [13] vs. 84 [16], $P = 0.9$; 4–20 h, 87 [14] vs. 86 [10], $P = 0.8$). Postoperative leukocytosis was observed in both groups, but the leukocyte count was greater in the intravenous group during the first 4 h ($P < 0.01$) and the following 16 h ($P < 0.05$) (fig. 1). Plasma glucose also increased postoperatively in both groups (omitting the cases of diabetes mellitus), but to a higher level in the intravenous group during the last 16 h ($P < 0.03$) (fig. 1).

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Rectal temperature was comparable between the groups after arrival in the intensive care unit (difference between the sample means, epidural *vs.* intravenous: -0.2°C , 95% confidence interval -0.4 – 0.4°C), but increased more markedly in the epidural group (fig. 2). The difference in mean rectal temperature in the period of 4–20 h was 0.4°C (95% confidence interval 0.1 – 0.7°C) ($P < 0.01$).

Plasma β -Endorphin Immunoreactivity, ACTH, Cortisol, Growth Hormone, and Prolactin

The plasma ir β -E concentration in the intravenous group was significantly greater 4 h after thoracotomy than on the preoperative afternoon, and less on the first postoperative morning than on the preoperative morning (fig. 3; table 1), while, in the epidural group, it was approximately the same 4 h after surgery as on the preoperative afternoon, but, again, less on the first postoperative morning than on the preoperative morning (fig. 3; table 1). The median increase in plasma ir β -E was 14.3 pmol/l greater in the intravenous group ($P < 0.05$) 4 h after thoracotomy (table 1), but the median decrease on the first postoperative morning relative to the preoperative control value was similar ($P = 0.87$) in both groups (table 1). There were no significant increases in the plasma ACTH concentrations in either groups 4 h after thoracotomy (table 1), while the plasma ACTH on the first postoperative morning relative to the preoperative control value was less in both groups (table 1).

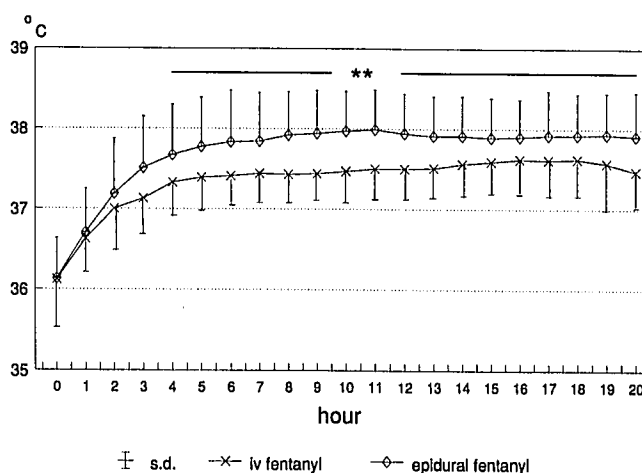


Fig. 2. Postoperative mean rectal temperature at each postoperative hour in both groups. The difference between groups at 4–20 h was statistically significant (** $P < 0.01$).

Plasma cortisol concentrations were significantly greater 4 h after thoracotomy ($P < 0.01$) than on the preoperative afternoon in both groups, and greater on the first postoperative morning ($P < 0.01$) than on the preoperative morning in the intravenous group, but not in the epidural group ($P = 0.13$) (table 1). The median changes between the preoperative and postoperative plasma cortisol concentrations were similar in both groups (table 1).

Plasma growth hormone and prolactin were similarly increased above the corresponding preoperative values 4 h after thoracotomy and on the first postoperative morning in both groups (table 1).

In the epidural group, the Spearman correlation coefficient was 0.62 ($P < 0.05$) at 16 h between VPS pain and leukocyte count, while the Pearson correlation coefficient at the same time was 0.71 ($P < 0.001$) between PaCO_2 and glucose. At all other observation points (30 min, 4 h, 10 h, and 20 h), however, VPS pain, PaCO_2 , and fentanyl dose were not related to leukocyte count, glucose, or blood pressure.

The difference between postoperative (at 4 h) and preoperative concentrations of ir β -E was related to high pain scores in the epidural group ($r = 0.77$, $P < 0.001$), but not in the intravenous group ($r = 0.11$, $P = 0.67$).

Discussion

Previously, surgical procedure has been found to be associated with a prolonged increase in plasma β -endorphin,^{22–25} and severe physical trauma causes an up to fivefold increase soon after trauma and for at least the following 4 days.²⁶ The intraoperative β -endorphin response has been prevented by medium or high doses of intravenous fentanyl,^{22,24,27,28} but there is little information available on the effect of opioids on this response during the later postoperative period. In our study, plasma ir β -E concentrations, 4 h after operation, were greater with intravenous than with epidural fentanyl infusion.

Although surgical procedure does mobilize plasma β -endorphin from the pituitary, the function of this release is, apparently, not to produce inhibition of pain transmission or to modulate the hormonal or metabolic response to surgery.^{29–30} Cohen *et al.* suggested that plasma β -endorphin may be used as an index of human arousal.³¹ The hypothalamic pericycarya, which contains β -endorphin course into many regions of the central nervous system involved in nociceptive processing³² and plasma endorphin levels, seem to reflect the activity

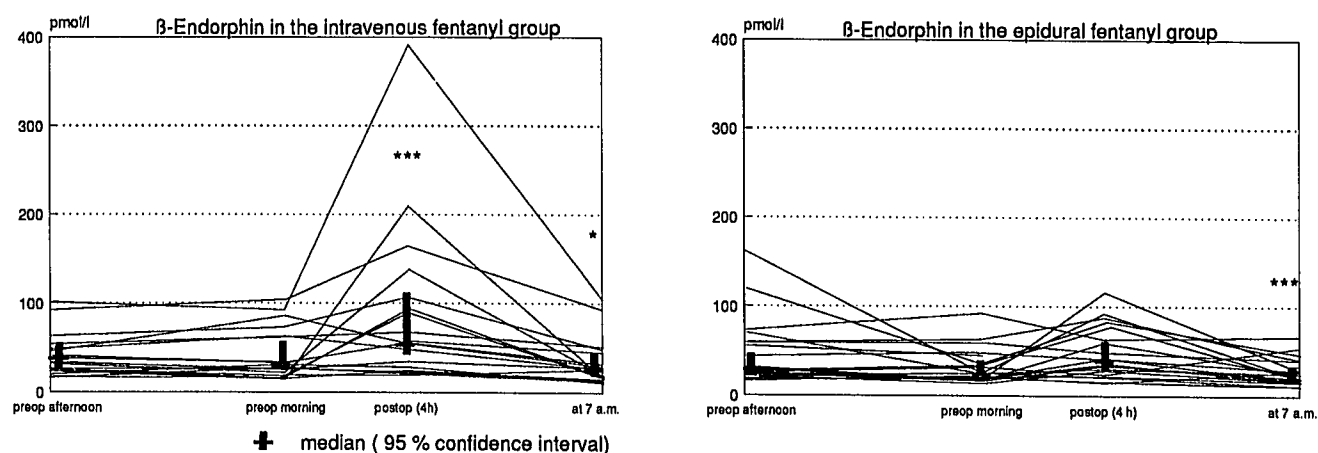


Fig. 3. Individual plasma β -endorphin levels in both groups on the preoperative afternoon, on the preoperative morning, 4 h postoperatively, and on the first postoperative morning. Differences within groups: * $P < 0.05$; *** $P < 0.01$. The difference between groups 4 h postoperatively was statistically significant ($P < 0.05$).

of these central opioid pathways.^{22,33-36} Our results indicate that the central opioid pathways were more active when pain was relieved with intravenous fentanyl than with epidural fentanyl. This occurred 4 h after major surgery, *i.e.*, at the time that is known to represent the period of the most vigorous metabolic and hormonal responses.³⁷

No statistically significant elevation of ACTH was found in either group 4 h postoperatively, but it should

be noted that, although β -endorphin and ACTH are secreted concomitantly by the pituitary gland,³⁸ the rapid elimination of ACTH, as compared to β -E/ β -LPH, may explain why their results were not of the same significance. Plasma cortisol increased in a similar manner in both groups within 4 h of surgery, but the increase persisted to the next morning only in patients receiving intravenous fentanyl. Nevertheless, there was no significant difference in changes in cortisol concentrations

Table 1. Hormonal Changes

Hormone	Intravenous Fentanyl		Epidural Fentanyl		Δ Intravenous Fentanyl – Δ Epidural Fentanyl	
		<i>P</i>		<i>P</i>		<i>P</i>
β -Endorphin (pm)						
$\Delta 1$	13.4 (5.1–64.0)	<0.01	2.1 (–4.0–20.2)	>0.1	14.3 (1.8–53.2)	<0.05
$\Delta 2$	–6.9 (–16.2––2.6)	<0.05	–6.2 (–12.7––1.9)	<0.01	0.5 (–8.3–6.1)	0.87
ACTH (ng · l ^{–1})						
$\Delta 1$	0 (–3.0–36)	>0.1	0 (–4–2)	>0.1	3.3 (–1–13.7)	0.19
$\Delta 2$	–3.3 (–7.0–0)	<0.01	–1.3 (–7–0)	>0.1	0 (–5–2.5)	0.81
Cortisol (nm)						
$\Delta 1$	381 (171–750)	<0.001	328 (163–499)	<0.005	86 (–105–360)	0.40
$\Delta 2$	269 (76–422)	<0.005	58 (–50–447)	0.13	142 (–138–350)	0.52
Growth hormone (μ g · l ^{–1})						
$\Delta 1$	0.47 (0–1.10)	<0.05	0.46 (0–1.30)	<0.01	0 (–0.78–0.60)	0.87
$\Delta 2$	0.50 (0–1.20)	<0.1	0.65 (0–2.30)	<0.01	0.4 (–1.86–0.60)	0.7
Prolactin (μ g · l ^{–1})						
$\Delta 1$	6.9 (2.1–13.9)	<0.01	3.1 (1.9–7.1)	<0.01	2.6 (–1.7–6.6)	0.26
$\Delta 2$	7.5 (1.5–11.1)	<0.01	4.3 (0–5.5)	<0.02	2.7 (–2.7–7.0)	0.13

Values are median (95% confidence interval).

Δ Intravenous fentanyl – Δ epidural fentanyl = change in intravenous fentanyl group compared to the change in the epidural fentanyl group; $\Delta 1$ = change between preoperative (afternoon) and postoperative (4 h) concentrations; $\Delta 2$ = change between preoperative (morning) and postoperative (20 h) concentrations; ACTH = adrenocorticotrophic hormone.

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between the groups. Neither epidural nor intravenous fentanyl infusion could entirely prevent the postoperative growth hormone and prolactin responses to surgery. These results indicate that some functions of the pituitary–adrenal cortex axis were stimulated to a lesser degree when epidural, rather than intravenous, fentanyl infusion was used for pain relief.

The hyperglycemic response was more marked in the intravenous group than in the epidural group during the interval 4–20 h postoperatively. The postoperative hyperglycemic response has earlier been shown to be attenuated by epidural morphine and diamorphine.^{13,15} It has been shown that counterregulatory hormones, such as glucagon, catecholamines, and cortisol, accentuate postoperative hyperglycemia,³⁹ and this is consistent with our current finding of elevated plasma cortisol levels on the first postoperative morning in the intravenous group. It can also be assumed that catecholamine levels were more elevated in the intravenous group at the same time as the mean blood pressure was higher in that group in the period 4–20 h. Epidural morphine has been shown to decrease postoperative hypertension by attenuating sympathetic nervous system hyperactivity.⁴⁰ In the study of Gauman *et al.*, adrenal vein catecholamine levels did not increase above prestimulation values after painful stimulation when morphine had been administered intrathecally.⁴¹ Intrathecal morphine evidently depresses the reflex increase in the adrenal nerve induced by noxious stimuli.⁴² Differences in the degree of activation of spinal sympathetic reflexes because of a higher opioid concentration in the cerebral spinal fluid after epidural *versus* intravenous fentanyl could be one reason for the differences in plasma glucose in our study.

Postoperative leukocytosis was more pronounced in the intravenous fentanyl group. Leukocytosis has been shown to follow general anesthesia, but not regional anesthesia,^{43,44} and epidural morphine has not been shown to be superior to parenteral morphine in preventing this.¹² Neutrophil and lymphocyte activities are modulated by counterregulatory hormones,⁴⁵ but whether or not the increase of circulating neutrophils is related to the increased neutrophil release from bone marrow or blood vessel demargination mediated by catecholamine has not been documented.⁴⁶ A lower degree of activation of spinal sympathetic reflexes in the epidural group could be the reason for the less marked leukocytosis in our epidural group.

The postoperative increase in rectal temperature was more pronounced in the epidural than in the intrave-

nous fentanyl group. Postoperative fever has been considered to be an index of physiologic response to surgery, although the parenteral administration of fentanyl has been found to induce hypothermia in animals.⁴⁷ In this case, simply the fact of being physically restrained probably intensifies the hypothermic action of the opioid.⁴⁸ During epidural blockade, sympathectomy contributes to the redistribution of body heat from central to peripheral tissues, and skin-surface temperatures in the lower body increase.⁴⁹ Epidural opioids may alter the distribution of heat in the body as subarachnoid morphine intensifies the decrease in sublingual temperature after spinal anesthesia.⁵⁰ Recent evidence indicates that epidural fentanyl may affect thermoregulation during anesthesia.⁵¹ The increased blood flow in the pelvic area, which is presumably caused by attenuated adrenergic activity during epidural analgesia,^{40,52} may cause an elevation in rectal temperature. Thus, a decrease in core temperature may be underestimated by rectal measurement.⁵²

Our results are consistent with other studies that show a less hormonal response to surgery after epidural than parenteral administration of opioids.^{15–17} Epidural administration of morphine has been shown to decrease cortisol, norepinephrine, vasopressin responses,^{14,53,54} diamorphine glucose, cortisol responses,^{15,16} and the fentanyl vasopressin response¹⁷ to surgery more than does parenteral administration. In these studies, epidural administration has also been associated with a marked improvement in pain relief. However, in the recent study of Camu and Debucquoy,⁵⁵ cortisol and epinephrine responses and postoperative pain after abdominal hysterectomy were controlled equally well by intravenous and epidural alfentanil, the lipophilicity of which is intermediate as compared with morphine and fentanyl. Recent investigations have demonstrated that responses to surgery are mediated *via* complex interactions between the nervous, endocrine, immune, and hematopoietic systems.⁴ It has been suggested that stimulation of cytokine production is responsible for the development of some of the stimulation of the hypothalamo–pituitary–adrenal axis after upper abdominal surgery, in spite of adequate epidural blockade.⁵⁶ Thus, unattenuated cytokine production may be one cause of the only partial inhibition of responses to surgery in our study.

The explanation for the fact that some physiologic, metabolic, and hormonal responses were more pronounced in the intravenous than in the epidural group is not a difference in analgesia, because pain relief was

equal and adequate (VSP < 3) in both groups, and because pain was poorly related to these responses. The main differences between the groups were in the doses, in the route of fentanyl administration, and in the incidence of respiratory depression. Arterial carbon dioxide tension or fentanyl doses were unrelated, however, to the hormonal and metabolic responses after surgery.

It has been shown that the analgesic potency of supraspinal morphine can be greatly potentiated by the concurrent administration of spinal morphine.⁵⁷ In both groups, our patients rated similar pain scores and similar satisfaction to the overall pain relief according to the pain relief questionnaire. The analgesic effect was probably more spinal and less supraspinal in the epidural than in the intravenous group because the mean fentanyl blood concentrations after epidural fentanyl infusion were about 60% of those after intravenous infusion. The presumably greater opioid receptor occupancy of fentanyl in the spinal cord in the epidural group than in the intravenous group appears to be related to a diminished afferent drive and less pronounced hormonal, metabolic, and physiologic responses to the surgery. Intravenous fentanyl, on the other hand, penetrates mainly supraspinal structures and, therefore, would appear to cause a modified supraspinal response to afferent stimuli.

In summary, our results showed that the use of epidural fentanyl, as compared with intravenous fentanyl, with a smaller mean dose led to a similar relief from pain, but a significantly lower leukocyte count, during the first 20 postoperative hours; a lower plasma ir β -E concentration at 4 h postoperatively; and lower plasma cortisol, blood glucose, and arterial blood pressure levels during the following 16 h. Thus, the use of epidural fentanyl, which primarily blocks spinal opioid receptors, offers an advantage over intravenous fentanyl in inhibiting some postoperative hormonal, metabolic, and physiologic responses.

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