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Alfentanil Infusion for Postoperative Pain: A Comparison of Epidural and Intravenous Routes

Frederic Camu, M.D., Filip Debucquoy, M.D.†*

The efficacy of intravenous (iv) and epidural infusions of alfentanil for postoperative pain relief was investigated in 24 patients (ASA physical status 1–2) who were scheduled for abdominal hysterectomy. The patients were allocated randomly to receive either epidural or iv alfentanil. In both groups, a loading dose of 15 $\mu g \cdot kg^{-1}$ was administered, followed by a constant rate infusion of 18 $\mu g \cdot kg^{-1} \cdot h^{-1}$ alfentanil for 20 h. Both routes provided similar degrees of analgesia; however, analgesia occurred earlier in the intravenously treated group ($P < 0.03$). Mean plasma alfentanil concentrations (C_Ps) varied between 42 and 82 $ng \cdot ml^{-1}$ in the iv group and 23 and 68 $ng \cdot ml^{-1}$ in the epidural group, with higher concentrations in the iv group for the first 60 min only ($P < 0.01$). C_Ps increased with infusion time, suggesting accumulation of alfentanil. After infusion ended, pain recurred at the same time in both groups, whereas the alfentanil C_Ps still were greater than 45 ng/ml. Postoperative epinephrine concentrations decreased after 60 min of infusion ($P < 0.02$), whereas, after 6 h, cortisol levels decreased to preoperative values. Norepinephrine concentrations decreased only slightly. The only clinically meaningful effect on vital signs that occurred was an abrupt reduction of respiratory rate after the iv loading dose. Pa_{CO_2} increased to the same extent in both groups during the first 15 min only. The incidence of opioid-related side effects was similar in both groups. These results suggest that the iv and epidural routes were equally effective for providing postoperative pain control and controlling the postoperative response to surgical stress. (Key words: Analgesia: postoperative. Analgesics, opioid: alfentanil. Anesthetic techniques: epidural; intravenous. Hormones, adrenal: cortisol. Pain: postoperative. Sympathetic nervous system, catecholamines: epinephrine; norepinephrine.)

EPIDURAL AND INTRAVENOUS (iv) infusions of opioids provide effective postoperative pain control.[1–7] It is postulated that the mechanism of analgesia is different for the two routes. Systemically administered opioids produce analgesia by acting predominantly on supraspinal locations, in particular the cerebral mu–opioid receptor sites. A gradual uptake in cerebrospinal fluid (CSF) has been demonstrated for morphine.[8] Lipophilic opioids such as alfentanil administered intravenously also may occupy spinal receptors with short-lived but intense and rapid suppression of neuronal activity, as shown in animals in which the spinal cord was transected.[9]

It is suggested that epidural administration of opioids primarily and selectively blocks nociceptive transmission at the spinal opiate receptors.[7] The analgesic effect of epidural opioids depends on migration of the drug across the dura, arachnoid, and pia mater to reach the spinal cord. Membrane permeability is different for hydrophilic and lipophilic opioids,[10] which may be reflected in the CSF pharmacokinetic profile. Spinal opioids also undergo supraspinal redistribution by CSF bulk flow, inducing side effects such as respiratory depression and itching.[11,12] Hydrophilic drugs probably are more prone to this redistribution. Also, a significant vascular uptake of epidurally injected hydrophilic and lipophilic opioids can result in plasma concentrations similar to those observed after intramuscular (im) administration.[13–15] The vascular uptake associated with epidural administration cannot be disregarded as a contributor to analgesia, especially with lipophilic opioids that are removed more rapidly from the epidural space. Thus, both supraspinal and spinal mechanisms are involved in the analgesia provided by systemic or epidurally administered opioids.

Shorter-acting lipophilic agents given by continuous infusion should ensure more stable postoperative analgesia compared with that after intermittent injections of longer-acting hydrophilic drugs such as morphine. The physicochemical characteristics of alfentanil are significant elements for its transfer across the meningeal membranes into the CSF. Indeed, although alfentanil's lipophilicity is intermediate between that of morphine and fentanyl (octanol–water partition coefficient at $pH = 7.4$: morphine 6, alfentanil 145, fentanyl 11,220),[16] the unbound unionized fraction of alfentanil (7.12%) is much greater than that of fentanyl (1.36%) but less than that of morphine (16%).[17] The greater unionized fraction coupled with the lower tissue–blood solubility explain the more rapid onset of alfentanil's opiate effect relative to fentanyl.[18,19] The relatively rapid elimination pharmacokinetics results in a duration of analgesia that also will be short. The analgesic efficacy of alfentanil can be sustained only through continuous infusion.

Experience with continuous analgesic infusion of alfentanil is limited; parenteral patient-controlled analgesia (PCA)[20] and constant rate infusion[1] provided effective

* Professor of Anesthesiology; and Chairman, Department of Anesthesiology.

† Resident in Anesthesiology.

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Address reprint requests to Dr. Camu: Department of Anesthesiology, Flemish Free University of Brussels Medical Center, Laarbeeklaan 101, B-1090 Brussels, Belgium.

analgesia. Continuous epidural infusions of alfentanil have been used in obstetric practice but provided unsatisfactory results.[21] At present, there is no conclusive evidence that alfentanil injected epidurally produces analgesia that is equally effective to that obtained by the iv route.

In this prospective randomized trial, we investigated the effect of a fixed alfentanil dose—given as a constant-rate iv or epidural infusion for 20 h—on analgesia, pharmacokinetics, vital signs, and hormonal responses during postsurgical pain treatment. This study evaluated the influence of route of opioid administration on clinical outcome.

Materials and Methods

The study protocol was approved by the university Committee on Human Research. Postrandomization informed consent was obtained from 24 female patients scheduled for abdominal hysterectomy (ASA physical status 1–2). The patients were allocated randomly to two groups receiving either an intravenous (iv group) or an epidural (epidural group) infusion of alfentanil for postoperative pain relief. No patients were taking analgesics or benzodiazepines on a regular basis or had a history of allergy to opiates. Other occasional medication was stopped 48 h before surgery. The patients received midazolam 5 mg and atropine 0.3 mg im 90 min before surgery. In the operating room, an iv catheter was inserted for fluid administration and a radial artery catheter for pressure monitoring and blood sampling. Before surgery, an epidural catheter was inserted at the L2–3 vertebral interspace in the patients in the epidural group. A dedicated iv catheter was used to infuse alfentanil.

All surgery was started at 8:30 A.M. Anesthesia was induced with thiopental 4 $mg \cdot kg^{-1}$ and maintained with halothane and a mixture of oxygen–nitrous oxide. Pancuronium bromide (0.08 $mg \cdot kg^{-1}$) was used to facilitate intubation and for muscle relaxation throughout surgery. No opioid analgesics were administered during anesthesia.

After surgery, the patients were admitted to the postanesthesia care unit. All patients received oxygen (3 l/min) by nasal cannula for 24 h. When they were sufficiently mentally alert and complaining of pain, they received analgesic treatment according to the randomized parallel-groups protocol. The alfentanil loading dose was 15 $\mu g \cdot kg^{-1}$—given in a volume of 10 ml saline over a 3-min period—and was followed immediately by a constant-rate infusion of 18 $\mu g \cdot kg^{-1} \cdot h^{-1}$ alfentanil for 20 h. If the patient judged the analgesia to be insufficient, incremental doses of 10 $\mu g \cdot kg^{-1}$ alfentanil could be given every hour.

Pain intensity was assessed by the patient, using a visual linear analog scale (VAS) ranging from 0 (pain free) to 10 (worst imaginable pain).[22] A nurse assessed sedation on a scale of 0 (no sedation) to 3 (heavy sedation). Heart rate (HR), mean arterial pressure (MAP), and respiratory rate (RR) were recorded automatically. Evaluations of these parameters, together with arterial blood sampling for Pa_{CO_2} and alfentanil C_P, were made before and at 5, 10, 15, 30, 45, and 60 min, then at 2, 4, 6, 10, 14, and 20 h after the start of the alfentanil loading dose. After the infusion was stopped at 20 h, the patients were observed every 15 min until they requested additional conventional analgesic medication (morphine 10 mg im) because severe pain had recurred. An additional blood sample was taken at this time to determine alfentanil concentrations.

Arterial blood samples for epinephrine, norepinephrine, and cortisol assays were taken before surgery; postoperatively before the alfentanil loading dose; and at 60, 360, and 1,200 min after the loading dose. All blood samples were collected in heparin and centrifuged immediately, and the plasma samples were frozen at −27° C until assay. Plasma alfentanil concentrations were determined with the use of gas chromatography.[23] A radioimmunoassay was used to determine plasma cortisol levels (Gammacoat® ^{125}I cortisol RIA kit; Travenol-Genentech Diagnostics). For measurement of plasma epinephrine and norepinephrine levels, 50 μl sodium metabisulfite was added to the separated plasma before freezing. Catecholamines were assayed with the use of a high-performance liquid chromatography technique.[24] The limit of sensitivity of the assay was 0.015 $ng \cdot ml^{-1}$ for norepinephrine (coefficient of variation, 5%) and 0.02 $ng \cdot ml^{-1}$ for epinephrine (coefficient of variation, 15%).

To assess differences in disposition of alfentanil during iv infusion, the plasma alfentanil concentrations were averaged for the periods 1–10 h and 10–20 h to obtain steady-state concentrations (C_{SS}) for each infusion period. Steady-state clearance (Cl_{SS}) was estimated from the ratio R_o/C_{SS}, where R_o = infusion rate. The volumes of distribution during each infusion period were calculated with the use of the formula $Vd = (D_L/C_{SS}) \cdot \exp(-K \cdot t) + (R_o/[C_{SS} \cdot K]) \cdot \exp(-K \cdot t)$ for iv infusion in a two-compartmental model, where D_L = loading dose, K = elimination rate constant, and t = infusion period. K was estimated from the C_P decay after cessation of the infusion until the moment that rescue analgesic was administered.

The demographic data and baseline values for the different variables were examined by testing for equality of the variances and with the use of the Kruskal-Wallis one-way analysis of variance. Analysis of continuous variables included the Friedman two-way analysis of variance, Wilcoxon matched-pairs signed-ranks test for intragroup comparisons, and Mann-Whitney U-test for intergroup comparisons. Statistical significance for differences was accepted if P was less than 0.05 (two-tailed). All data are presented as mean values ± standard error of the mean.

Results

Both groups of patients were comparable with respect to patient age, weight, and height; duration of anesthesia;

TABLE 1. Patient Demographics and Characteristics

Parameters	IV Group	EP Group	*P*
Sample size	12	12	
Age (yr)	54 ± 3	46 ± 3	NS
Weight (kg)	62 ± 2	68 ± 4	NS
Height (cm)	164 ± 3	163 ± 2	NS
Duration of anesthesia (min)	198 ± 30	155 ± 45	NS
Interval end of anesthesia to start of infusion (min)	56 ± 9 (25–140)	77 ± 22 (38–165)	NS
Interval end of infusion to onset of pain (min)	79 ± 14 (25–180)	66 ± 19 (30–105)	NS
VAS at onset of pain postinfusion (min)	6.2 ± 0.4 (5–9)	6.4 ± 1.9 (5–8)	NS

Values are mean ± SEM (range in parentheses). NS = not significant.

and interval between end of anesthesia and start of infusion (table 1).

Pain intensity (VAS) decreased steadily during the initial phase of the epidural alfentanil infusion, reaching a minimum value of 1.2 ± 0.4 at 30 min. In the iv group, the decrease of pain intensity was maximal at 5 min (VAS 0.9 ± 0.7) (*i.e.*, soon after the end of the loading dose). Thus, the onset of analgesia was significantly quicker in the iv group *versus* the epidural group ($P < 0.004$). From 15 min until 20 h, the analgesia was virtually equivalent in both groups (fig. 1). During alfentanil infusion, no patients in either group requested incremental doses of alfentanil. In the iv group, seven patients had incomplete analgesia, with the VAS scores ranging from 1 to 5, whereas in the epidural group eight patients reported VAS scores from 1 to 4 during infusion. At the end of infusion, moderate to severe pain recurred in all patients in both groups at the same rate, and rescue analgesics were requested at similar pain intensities (table 1).

The Friedman test on sedation data showed significant differences for route effect ($P < 0.03$) and time of measurement ($P < 0.001$). In the epidural group, only "mild" sedation was observed after 15 min until 10 h (sedation score, 0.83 ± 0.11; $P < 0.01$ *vs.* baseline). In the iv group, sedation was "moderate" for the first 10 min after the loading dose (sedation score, 1.40 ± 0.44; $P < 0.002$ *vs.* the epidural group) and remained "mild" thereafter until 20 h (sedation score, 0.89 ± 0.14; $P < 0.02$ *vs.* baseline; P = not significant [NS] *vs.* the epidural group).

In the epidural group, alfentanil plasma concentrations (C_P) (fig. 2) increased progressively from 31.5 ± 2.4 ng · ml^{-1} after the loading dose to 67.6 ± 10.6 ng · ml^{-1} at 20 h of infusion. In the iv group, the loading dose yielded C_Ps almost twice those achieved by the epidural infusion for 60 min ($P < 0.007$). After 1 h, alfentanil C_Ps were similar in both groups. When the pain recurred after the infusions were stopped, alfentanil C_Ps were 55.5 ± 11.0 ng · ml^{-1} in the epidural group and 45.6 ± 8.2 ng · ml^{-1} in the iv group (P = NS). During iv administration of alfentanil, the averaged C_{SS} for the first and second

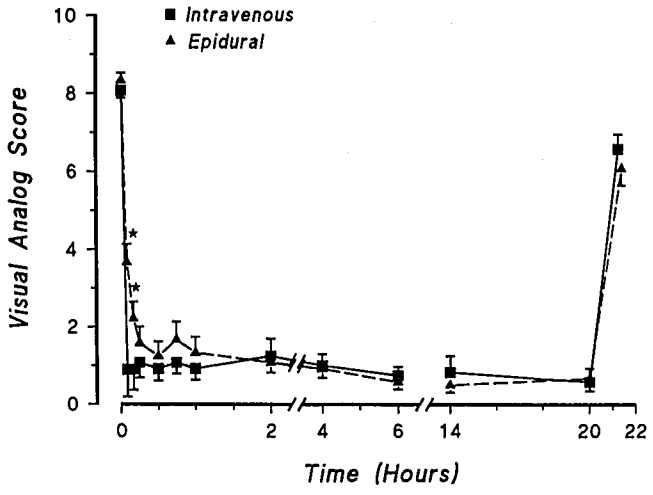

FIG. 1. Time course of analgesia during constant-rate intravenous and epidural infusions of alfentanil. *$P < 0.03$ for differences between groups.

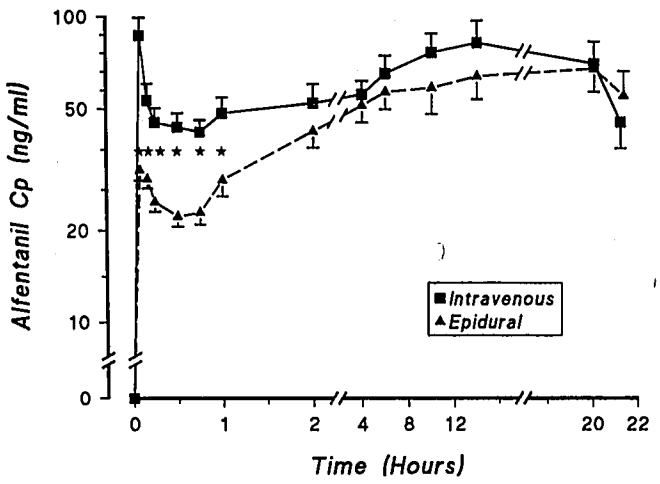

FIG. 2. Plasma alfentanil concentrations during intravenous and epidural constant-rate infusions of alfentanil. *$P < 0.01$ for differences between groups.

10-h infusion periods increased from 49.6 ± 1.5 to 71.7 ± 3.1 ng · ml^{-1} (P = NS). The mean coefficient of variation of C_{SS} was 16.7 ± 0.8% (first period) and 27.3 ± 2.0% (second period). Cl_{SS} of alfentanil decreased significantly from 444 ± 12 ml · min^{-1} to 325 ± 11 ml · min^{-1} ($P < 0.04$), whereas steady-state Vd remained unchanged (1.26 ± 0.24 l *vs.* 1.25 ± 0.16 l; P = NS). In the epidural group, the mean C_{SS} increased from 34.9 ± 3.3 to 61.4 ± 3.2 ng · ml^{-1} during the second 10-h infusion period ($P < 0.03$).

The visual linear analog scale and C_P data were correlated significantly in the iv (r = −0.28; $P < 0.01$) and epidural groups (r = −0.35; $P < 0.01$), but these correlations were weak and probably of no practical significance, because only 8% and 12% of the total variance could be explained by the regression.

Variances of both patient groups were equal for MAP, RR, and Pa_{CO_2} assessments but not for HR. Friedman's test showed only significant differences in the time component of the analysis for HR, RR, and Pa_{CO_2}. No significant differences in MAP, RR, and Pa_{CO_2} were found between the overall averages of the route effects for both treatment groups. Table 2 indicates that only slight changes in these variables occurred. One major difference between both groups was the abrupt decrease of RR after the loading dose in the iv group (fig. 3).

Baseline mean values for plasma cortisol, norepinephrine, and epinephrine were similar in both groups before surgery. After surgery, significant increases in plasma epinephrine ($P < 0.01$) and cortisol levels ($P < 0.02$) were seen in both groups before analgesic treatment was started. Alfentanil infusions reduced epinephrine concentrations considerably after 60 min ($P < 0.02$ *vs.* 0 min postoperatively in both groups), but they remained significantly higher than the preoperative control values (fig. 4). No meaningful differences in plasma norepinephrine concentrations occurred before and during the alfentanil infusions in both groups. Cortisol concentrations decreased significantly at 6 and 20 h in both groups ($P < 0.03$), reaching preoperative control values. In the iv group, the reduction in plasma cortisol levels was more pronounced at 20 h ($P < 0.01$ *vs.* the epidural group).

TABLE 2. Changes in Hemodynamic Variables during Postoperative Alfentanil Treatment

Time	Heart Rate (beats per min)		MAP (mmHg)	
	EP Group	IV Group	EP Group	IV Group
0 min	95 ± 5	82 ± 4	102 ± 3	98 ± 4
5 min	88 ± 5	70 ± 3*	102 ± 3	87 ± 4*†
15 min	83 ± 4*	75 ± 3	95 ± 4	93 ± 4
60 min	84 ± 4*	75 ± 3	94 ± 4	93 ± 2
6 h	89 ± 4	77 ± 2	92 ± 3*	90 ± 3
10 h	88 ± 4	80 ± 4	93 ± 4	91 ± 4
20 h	90 ± 4	83 ± 3	94 ± 4	92 ± 3

* $P < 0.03$ *versus* baseline.
† $P < 0.01$ *versus* EP group.

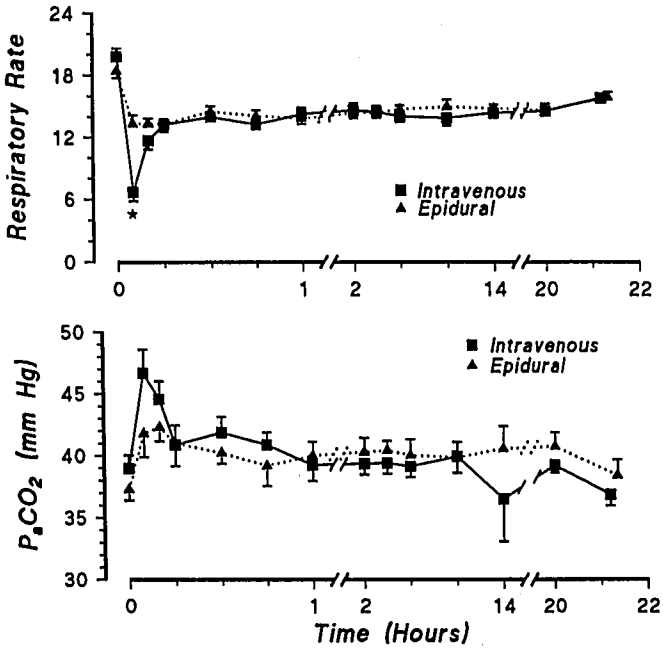

FIG. 3. Changes of mean respiratory rate and Pa_{CO_2}; during infusion of alfentanil. *$P < 0.001$ for differences between groups.

Side effects such as nausea, vomiting, and pruritus appeared with the same incidence in both groups. However, in the iv group the occurrence of bradypnea was much more common (table 3). No naloxone was given to these patients, but four patients needed verbal stimulation to breathe for at least 5 min after the iv alfentanil loading dose. Because all patients received nasal oxygen, no hypoxic episodes were observed (lowest hemoglobin oxygen saturation = 93% in a single patient). In both groups, no relationship was found between alfentanil C_P and RR, nor between RR and Pa_{CO_2}.

Discussion

This study compared two analgesic regimens for alfentanil, the iv route, which should act predominantly at the supraspinal site of action, and the epidural route, which is thought to act primarily by interruption of spinal nociceptive transmission. The most remarkable finding of this study was the similar efficacy of both routes of alfentanil administration with regard to analgesia. In addition, the plasma alfentanil concentrations observed with both techniques also were similar. At the dosage used, no patients required additional analgesics during the infusion.

One may criticize this study on two grounds: the study design was not double-blinded and the dosages of alfen-

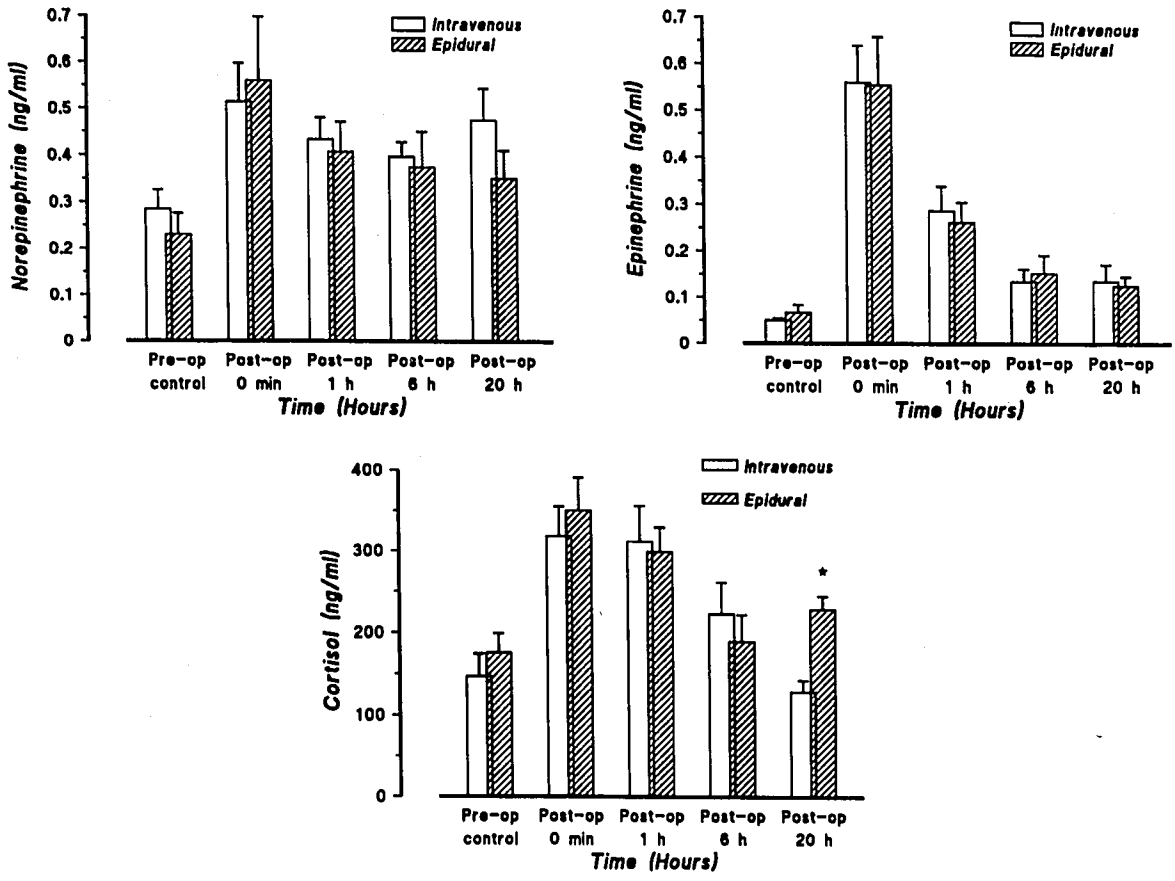

FIG. 4. Plasma norepinephrine, epinephrine, and cortisol concentrations before and during infusions of alfentanil. *$P < 0.02$ for differences between groups.

tanil administered may have been too large. For ethical reasons, an epidural catheter was not inserted in patients in the iv group, because surgical anesthesia did not require such placement. The patients were randomized prospectively, and those allocated to receive epidural opioid treatment were informed fully about the risks of epidural analgesia. Also, the patients were taught to use the pain scale the day before surgery. The randomization was assumed to guarantee bias reduction during the clinical trial and validity for statistical analysis. Neither the patients nor the observers were blinded to the treatment. Under these conditions, pain intensity was evaluated exclusively by the patient, using the VAS. The nurses monitoring these patients only were allowed to comply with the patient's request for rescue analgesics, to observe and note the degree of sedation, and to draw blood samples at specified times. We checked the validity of the assessments independently. Although there may be bias in evaluation, the purpose of the trial was not to establish which route of administration of the opioid was best, but to compare the advantages and shortcomings of both techniques.

TABLE 3. Incidence of Side Effects

	IV Group	EP Group
Nausea	7	5
Vomiting	2	1
Pruritis	0	1
Respiratory rate < 8 breaths per min	7	1

In both groups and for all side effects listed, n = 12.

Using a single fixed dosage of alfentanil, we aimed to quantitate the analgesic, respiratory, hormonal, and concentration profiles under identical conditions in both groups. Subtherapeutic doses of alfentanil with incremental doses based on an analgesic end point are not appropriate for this purpose, because the C_{PS} of alfentanil would vary widely in all patients. Such a protocol addresses questions of a more qualitative nature, such as differences in efficacy and selectivity of analgesia. Furthermore, a dose-effect curve also should be established for both routes of administration of the opioid to determine the therapeutic window of C_{PS} for both techniques.

The rapid onset of analgesia by both routes can be explained by the physicochemical characteristics of alfen-

tanil, the potency of the drug, and the small hysteresis effect in the brain demonstrated by the EEG.[25] Although the kinetics for EEG effects may not apply to the kinetics of analgesia, it remains that the alfentanil C_P and alfentanil concentration in the brain (C_B) is related to the respective partition coefficients (blood–plasma λ_P = 0.63, brain–blood λ_B= 0.18) such that $C_P/\lambda_P = C_B/\lambda_B$. Björkman *et al.* demonstrated experimentally that the capacity of the brain for uptake of alfentanil was very small in relation to the rate of transfer of drug to the compartment.[19] At least during iv infusion when steady state is reached, C_P becomes constant, and thus brain concentration becomes proportional to C_P. Thus, one could expect an analgesic effect proportional to the C_P of the drug. This relationship is the mean effective analgesic concentration (MEAC). Data on MEAC for alfentanil are scarce. Patient-controlled analgesia studies indicated the MEAC could range between 10 and 58 $ng \cdot ml^{-1}$, with a large interindividual variability.[20,26,27] Therefore, we used an infusion rate of 300 $ng \cdot kg^{-1} \cdot min^{-1}$ alfentanil, based on an MEAC value of 50 $ng \cdot ml^{-1}$ and a clearance of 356 $ml \cdot min^{-1}$, to design the dosing schedule used in this study.[28] During iv infusion, the mean alfentanil C_{SS} approached this MEAC, providing satisfactory pain relief for the first 10 h. With prolongation of infusion, however, it increased to 71.7 $ng \cdot ml^{-1}$, clearly in excess of this target value. A similar increase of C_{SS} with infusion time also was observed in the epidural group.

The progressive increase in alfentanil C_P seen in all but one patient would indicate a tendency for accumulation of the drug. During continuous iv infusions, the C_{SS} is dependent on the Vd and the rate of hepatic metabolism (clearance). Because infusion rate was kept constant, the increase in alfentanil C_{SS} could result from a decrease in the Vd or from a reduction in metabolic clearance. Vd remained unchanged during each 10-h infusion period. A dose-related reduction in clearance has been reported for prolonged infusions of thiopental.[29] For short-term alfentanil infusions, clearance was unaffected by infusion time,[30–32] except in one study.[33] A decreased clearance recently has been documented after prolonged infusions of alfentanil at a rate of 700 $ng \cdot kg^{-1} \cdot min^{-1}$.[34] In our study, the steady-state clearance decreased by 27% with infusion time. Although the amount infused in our study is unlikely to influence hepatic metabolism of the drug, this finding warrants additional investigation. The clearance from a continuous infusion of alfentanil appears to be less than the population value estimated by Maitre *et al.*[28] after an iv bolus injection.

This study does not disprove that epidural infusions of alfentanil provide "selective" spinal blockade of pain conduction.[7] Indeed, such selectivity may disappear if the alfentanil dose administered epidurally exceeds the amount of drug required to block spinal mu and delta receptors. Because the drug also is highly lipophilic, part of the dose is subject to systemic absorption, whereas the amount of alfentanil in excess of the amount fixed to the spinal opioid receptors may diffuse into the CSF or be absorbed into the circulation, where it behaves just as the systemically administered drug. If significant absorption of alfentanil in the CSF occurred, one would expect respiratory depressant effects resulting from cephalad migration of the drug, as has been observed for hydrophilic agents. The patients in the epidural group experienced neither delayed bradypnea nor hypercapnia. More detailed investigations of the respiratory drive and CO_2 chemosensitivity are required, however, to formally exclude a delayed respiratory depression resulting from rostral migration of alfentanil. One also would expect a more prolonged duration of effect of epidural alfentanil as shown in animal preparations.[9] Again, the fast receptor dissociation kinetics[35] may explain the lack of this property of selective spinal blockade under the current conditions of treatment. Epidural infusions of alfentanil may produce analgesic effects by different means than when given by a single epidural bolus.

The efficacy of both routes for pain control also is reflected in the hormonal response. Pelvic surgery increases plasma epinephrine levels[36] and, to a lesser extent, plasma norepinephrine levels. The greatest change in epinephrine values occurred after anesthesia was terminated. Inhalational anesthetic agents partly inhibit this sympathetic response to surgical stress.[37] Plasma cortisol concentrations increase rapidly after surgical stimulation and remain increased for at least 24 h after hysterectomy with halothane anesthesia.[38,39] Kehlet and others pointed out the lack of consistent influence on the surgical stress response, after upper abdominal surgery, of single-dose, PCA, or epidural injections of various opioids and local anesthetics.[40–42] In our study, both the iv and epidural routes significantly reduced the postoperative epinephrine and cortisol C_Ps, whereas the norepinephrine response to stress was not affected. The type of surgery our patients underwent might explain the difference between our data and those reported previously, but our results are consistent with the inhibition of the cortisol response to stress seen after the epidural administration of lipophilic agents.[43] The similarity of effect seen by iv and epidural routes also would indicate that this stress-inhibitory response is not mediated specifically by spinal cord receptors occupancy decreasing nociceptive traffic. A direct, centrally mediated effect appears more likely.

From the clinical point of view, the iv route induced some respiratory depression immediately after the loading dose; this probably was related to the rate of administration of alfentanil as evidenced by the peak alfentanil C_P. Therefore, we recommend that the loading dose be infused over a longer period of time (*i.e.*, 10 min) to avoid

excessive bradypnea. Both routes of alfentanil infusion could provide equivalent analgesia. Because the iv route is more readily accessible and less invasive than the epidural route, one should consider the potential morbidity associated with epidural catheters and continuous epidural infusions, when selecting the route of administration of lipophilic agents, except in clinical situations that favor the use of one *versus* the other. Indeed, several controlled studies have shown similar analgesic efficacies for iv and epidural routes for sufentanil[44] and fentanyl.[3,6]

In conclusion, continuous infusions of identical doses of alfentanil by the iv or the epidural route achieved similar C_{PS} of the drug and provided equivalent analgesia with only mild sedation. No clinically significant deleterious effects on vital signs were observed, except an abrupt bradypnea after the iv loading dose. To circumvent this problem, the loading dose should be administered as a loading infusion of brief duration. Both techniques effectively suppressed the cortisol and epinephrine response to surgical stress.

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