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Pharmacokinetics of Alfentanil after Epidural Administration

Investigation of Systemic Absorption Kinetics with a Stable Isotope Method

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Background: **The effects of epidurally administered alfentanil may be due in part to its uptake into the systemic circulation. Therefore we examined the systemic absorption kinetics after epidural injection of alfentanil.**

Methods: **Pharmacokinetics were determined using a stable isotope method in ten patients, undergoing lower abdominal surgery under general anesthesia. After epidural injection of 0.68 mg deuterium-labeled alfentanil (alfentanil-d_5), 1 mg unlabeled alfentanil was administered over 1 h by an intravenous infusion. Blood samples were collected for 12 h. Concentrations of alfentanil and alfentanil-d_5 were measured by a combination of gas chromatography and mass fragmentography. The systemic absorption profiles of alfentanil-d_5 were determined by deconvolution of the plasma alfentanil-d_5 concentrations with the biexponential unit disposition functions, derived from the intravenous data. In addition, data were analyzed by moment analysis.**

Results: **The mean (± SD) steady-state volume of distribution, total plasma clearance, elimination half-life and mean residence time, derived from the unlabeled alfentanil concentration–time data, were 43.2 ± 19.5 l, 418 ± 129 ml/min, 119 ± 34 min, and 103 ± 26 min, respectively. The absorption of alfentanil-d_5 was monophasic in most patients. The mean systemic availability and mean absorption time derived from the deconvolution data were 100 ± 17% and 114 ± 24 min. The values determined by moment analysis were 107 ± 18% and 112 ± 36 min, respectively.**

Conclusions: **After epidural administration alfentanil is slowly absorbed into the general circulation. Resulting plasma concentrations are very low and do not contribute appreciably to the systemic opioid effect. (Key words: Analgesia, epidural: alfentanil. Anesthetics, intravenous: alfentanil. Pharmacokinetics: alfentanil; systemic absorption.)**

EPIDURAL administration of opioids provides effective postoperative analgesia.[1–8] In addition, epidural opioids may contribute to general anesthesia. For example, it has been shown that epidural administration of sufentanil reduces intraoperative sufentanil requirements in patients undergoing thoracotomy.[5,9] Also, epidural injection of alfentanil, followed by epidural infusion of alfentanil, has been shown to reduce intraoperative alfentanil dose requirements as well as the plasma concentrations of alfentanil that are required to suppress responses to intraoperative surgical stimulation.‡‡ These effects of epidurally administered opioids are most likely mediated by a direct action on spinal opioid receptors.[10,11] In addition, systemic effects of the opioids after uptake from the epidural space into the systemic circulation may contribute to the analgesic and intravenous opioid sparing effects.

Plasma concentrations of alfentanil measured after epidural administration vary markedly between studies.

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‡‡ Haak-van der Lely F: Regional opioid analgesia: Its contribution to general anaesthesia (Ph.D. thesis). Leiden, University of Leiden, 1993.

Chauvin *et al.*[2] reported mean peak alfentanil concentrations of 54 and 155 ng/ml after epidural injection of 15- and 30-μg/kg bolus doses, respectively, whereas Haak-van der Lely reported a mean peak concentration of 9.7 ng/ml after injection of a 1-mg bolus dose.‡‡ Also, whereas peak concentrations were attained in 16 min, on average, in the study by Chauvin *et al.*, the median peak time in the study of Haak-van der Lely was 90 min. Continuous epidural infusion of alfentanil has been shown to result in plasma concentrations that after some time approach the plasma concentrations that are obtained with intravenous infusion at the same dose rate as the epidural infusion.[8]

Quantitative data on the absorption of opioids cannot be derived from the plasma concentration–time profiles of epidurally administered drugs, because these profiles depend also on the systemic disposition. Also, although the short peak times observed after epidural injection of sufentanil[12] and in some studies of alfentanil[2] suggest a rapid absorption of these agents, the associated low peak concentrations can in all likelihood be accounted for by rapid absorption of only a small fraction of the administered dose, whereas the remaining fraction of the dose is absorbed at a much slower rate. Such a biphasic absorption pattern has been observed in several studies of the absorption profiles after epidural injection of local anesthetics.[13–15]

In this study we examined the pharmacokinetics of alfentanil after epidural administration using a stable isotope method, which enables simultaneous investigation of the absorption and disposition kinetics.

Materials and Methods

The study protocol was approved by the Committee on Medical Ethics of the University of Leiden. After giving informed consent, eight female and two male patients (age 26–51 yr, body weight 50–76 kg, ASA physical status 1 or 2), scheduled for lower abdominal gynecological or general surgery (hysterectomy, hemicolectomy or sigmoid resection), participated in the study. Patients with liver, kidney or heart disease and patients with bleeding disorders were excluded from the study, as were patients with a history of opioid abuse. Patients were allowed to take sleep medication (temazepam, 10–20 mg orally) on the evening before surgery if desired.

All patients received temazepam, 20 mg orally, approximately 1 h before the induction of anesthesia. Upon arrival in the induction room electrocardiograph electrodes were placed and cannulae were inserted into a radial artery and a peripheral vein. The former was used for measurement of blood pressure and arterial blood sampling, the latter for administration of fluids and intravenous drug administration. Subsequently, 500 ml saline (sodium chloride 0.9%) was infused. Thereafter a second intravenous cannula was inserted in the contralateral arm. This cannula was used for intravenous infusion of alfentanil. A Tuohy needle was then inserted at the second or third lumbar interspace using a midline approach, an epidural catheter introduced and advanced 2 cm cephalad into the epidural space. A test dose of 3 ml mepivacaine 2% with epinephrine (5 μg/ml) was administered to test for an inadvertent subarachnoid or intravascular location of the tip of the catheter.

After breathing 100% oxygen for 3 min, pancuronium, 0.02 mg/kg, was administered. Anesthesia was then induced with sufentanil, 1 μg/kg intravenously in 60 s, and thiopental, 2–5 mg/kg, until the patient had lost consciousness. After administration of pancuronium, 0.08 mg/kg, the trachea of the patient was intubated. Anesthesia was maintained with nitrous oxide in oxygen (60%/40%), halothane, 0.3%, and intravenous sufentanil, as required (see below). Ventilation was adjusted to maintain the end-tidal carbon dioxide concentration between 4 and 5 vol%. Muscle relaxation was maintained with intermittent doses of pancuronium, and registered every 5–15 min by transcutaneous stimulation of the ulnar nerve with the Neuromyotest using the train-of-four method.

After 10 min, if the blood pressure and heart rate were stable, a bolus dose of 0.68 mg (base equivalent) deuterium-labeled alfentanil hydrochloride (alfentanil-d_5, fig. 1), dissolved in a volume of 2 ml and diluted

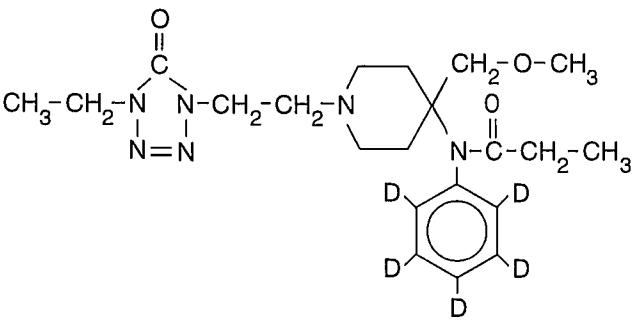

Fig. 1. Chemical structure of deuterium-labeled alfentanil, in which deuterium atoms replace each of five hydrogen atoms in the benzene ring.

to 14 ml with saline, was injected *via* the epidural catheter. At the same time an intravenous infusion of unlabeled alfentanil hydrochloride, dissolved in a volume of 2 ml, and diluted to 20 ml with saline was started. The duration of infusion was 60 min and the total dose (base equivalent) was 1 mg. The infusion regimen was chosen on the basis of a pilot study, which demonstrated that peak plasma concentrations after epidural administration of alfentanil are generally reached after 30–120 min. Therefore, administration of the intravenous dose over 1 h resulted in a relatively narrow range of alfentanil/alfentanil-d_5 concentration ratios (see "Blood Sampling and Analysis," below). The purity of the unlabeled alfentanil and alfentanil-d_5 solutions was checked by mass spectrometry and mass fragmentographic analysis (see below). These analyses showed that the amount of unlabeled alfentanil in the alfentanil-d_5 solutions, as well as the amount of alfentanil-d_5 in the unlabeled alfentanil solutions, was negligible (<0.01% of the dose). Any other impurities, such as alfentanil molecules containing one to four or more than five deuterium atoms, are accounted for in the reported doses and plasma concentrations, which refer to the pure alfentanil-d_5 and unlabeled alfentanil molecules.

During anesthesia supplemental doses of sufentanil, 25 μg intravenously, were given if signs of inadequate anesthesia occurred. Signs of inadequate anesthesia were:

1. An increase in systolic blood pressure to more than 15 mmHg above the normal blood pressure. The normal blood pressure was determined from measurements, made in the evening on the day of admission, just before premedication and upon arrival in the anesthesia induction room, and defined as the mean of these three measurements.
2. A heart rate exceeding 90 beats/min in the absence of hypovolemia.
3. Other autonomic responses such as lacrimation, sweating or flushing.
4. Body movements, such as movements of a leg or arm, swallowing, coughing or opening of the eyes.

If the systolic blood pressure decreased more than 15 mmHg below normal, this was corrected by administration of intravenous fluids or, if necessary, ephedrine, 2.5–5 mg intravenously. Crystalloid solutions, Haemaccel, or blood were administered on the basis of urine production and blood loss. Blood pressures (invasive and noninvasive), nasopharyngeal temperature, respiratory pressures, tidal volume, respiratory minute volume, fraction of inspired oxygen, hemoglobin oxygen saturation and inspiratory and expiratory halothane concentrations were monitored throughout the anesthetic period.

After termination of anesthesia residual neuromuscular block was antagonized with neostigmine, 1–2 mg intravenously, after administration of atropine, 0.5–1 mg intravenously. When patients were breathing spontaneously with a frequency of at least 10 breaths/min and a tidal volume of at least 7 ml/kg, nitrous oxide was discontinued and 100% oxygen administered. When patients were awake and protecting reflexes established, the trachea was extubated. If respiratory depression occurred in the absence of neuromuscular block, naloxone, 0.04 mg, was administered intravenously every 2 min until adequate respiration was established. The total dose of naloxone was not to exceed 0.4 mg. After extubation the patients were transported to the recovery room, where they remained for at least 2 h before returning to the ward.

Blood Sampling and Analysis

An arterial blood sample was obtained before the administration of alfentanil and alfentanil-d_5. Further samples (6 ml) were collected 5, 10, 15, 20, 30, 45 and 60 min after the epidural injection of alfentanil-d_5 and start of the alfentanil infusion, 5, 10, 15, 20, 30 and 60 min after stopping the infusion, then at 1-h intervals until 7 h and finally at 2-h intervals until 11 h after stopping the infusion. Total alfentanil + alfentanil-d_5 concentrations were determined with a capillary gas chromatographic method, as described elsewhere.[16] Calibration lines were constructed by analyzing plasma samples spiked with known amounts of alfentanil, and were linear ($r > 0.999$) in the concentration range encountered in this study (0.3–100 ng/ml). The coefficient of variation of this method was <7% in the concentration range encountered in this study, and the detection limit was approximately 0.3 ng/ml. The ratios of the alfentanil to alfentanil-d_5 concentrations were determined with a mass fragmentographic (GC-MS) method. The mass spectrometer (Fison Instruments Trio-2) was operated in the electron impact and selected ion monitoring mode. The temperature of the ion source was 180°C. The electron energy was 65 eV, and the electron current 150 μA. Gas chromatographic settings were similar to those described elsewhere.[16] Alfentanil and alfentanil-d_5 were detected at 289 (mass/charge ratio) and 294, respec-

tively. The retention time was 3.6 min. Calibration lines were constructed by analyzing plasma samples with known amounts of alfentanil-d_5 and unlabeled alfentanil and were linear ($r > 0.999$) in the concentration ratio range encountered in this study (measured alfentanil/alfentanil-d_5 concentration ratios ranged from 0.25 to 8). Within this range the coefficient of variation was ≤7%. Detection limits were <0.1 ng/ml for both unlabeled alfentanil and alfentanil-d_5.

Data Analysis

Biexponential functions were fitted to the unlabeled alfentanil concentration–time data using iteratively reweighted ($1/\hat{y}^2$) nonlinear regression, where $\hat{y}$ is the predicted concentration, with the Software package Siphar (Simed, Créteil, France). Values of the pharmacokinetic parameters were then derived using standard equations.[17]

The systemic absorption profile of alfentanil-d_5 was determined using point-area deconvolution[18] of the alfentanil-d_5 concentrations with the unit disposition function, derived from the intravenous data. The deconvolution was constrained to be nonnegative. Subsequently, the areas under the absorption rate *versus* time curves (AUC) and the first moment of the absorption rate *versus* time curves (AUMC) were determined with the linear trapezoidal rule. The areas from the last sampling point to infinity were estimated after log-linear regression of the terminal part of the absorption rate-time curves, where appropriate (if the absorption rate had not decreased to 0 at that time), and added to the AUC and AUMC calculated by the trapezoidal rule.[19] Mean absorption times were then calculated as AUMC/AUC. Systemic availabilities were derived from the percentage absorbed *versus* time curves with addition of the percentage absorbed from the last sampling point to infinity, which was calculated by integration of the absorption rate *versus* time curve over that period.

For alfentanil and alfentanil-d_5, AUC and AUMC were determined using the linear trapezoidal rule when concentrations were increasing and the logarithmic trapezoidal rule when concentrations were decreasing, and with addition of the areas from the last sampling point to infinity which were calculated after log-linear regression of the terminal part of the plasma concentration *versus* time curve.[19] Steady-state volumes of distribution, total plasma clearances, and mean residence times were calculated from the AUCs and AUMCs of unlabeled alfentanil.[20] Mean absorption times were derived by subtracting the mean residence times derived from the AUCs and AUMCs of unlabelled alfentanil from the mean residence times derived from the AUCs and AUMCs of alfentanil-d_5.[19]

Results

The duration of anesthesia varied from 125 to 175 min. Five patients required supplemental sufentanil (25–50 μg) during surgery. Plasma alfentanil concentrations were detectable until at least 8 h after the epidural injection and start of the infusion. Figure 2 shows the measured plasma concentrations of unlabeled alfentanil of all individual patients. In all subjects the fitted biexponential function adequately characterized the measured unlabeled alfentanil concentration *versus* time data. Mean (± SD) distribution and elimination half-lives were 6.1 ± 3.4 min and 122 ± 40 min, mean

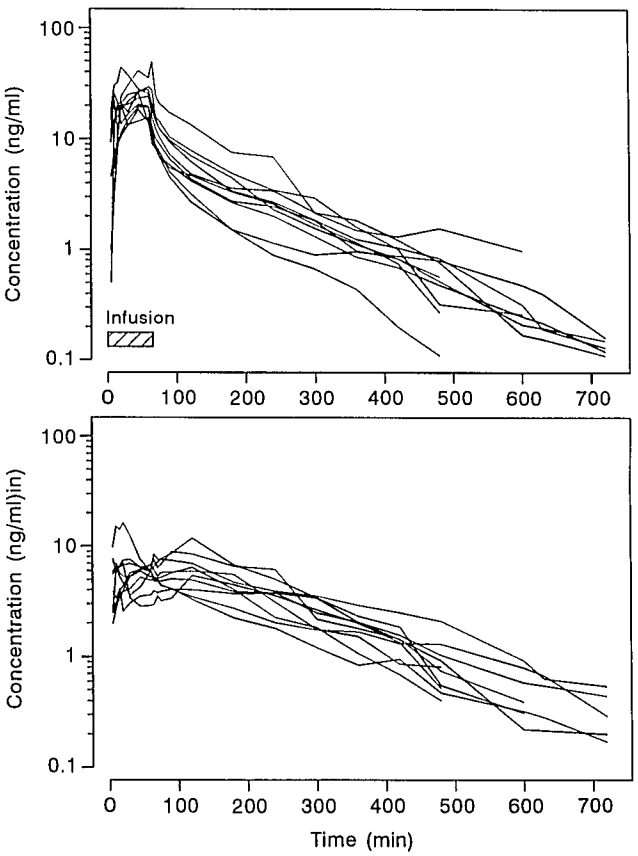

Fig. 2. (*Top*) Plasma concentrations of unlabeled alfentanil (resulting from intravenous administration) in all individual patients. (*Bottom*) Plasma concentrations of deuterium-labeled alfentanil (alfentanil-d_5) (resulting from epidural injection) in all individuals.

initial and steady-state volumes of distribution 8.0 ± 5.3 and 43.2 ± 23.7 l, and mean total-body clearance and distribution clearance 401 ± 137 ml/min and 457 ± 192 ml/min respectively. The mean residence time was 106 ± 31 min. Pharmacokinetic data, derived by moment analysis (table 1) corresponded with those derived from the exponential functions.

Measured plasma alfentanil-d_5 concentrations *versus* time data from all patients are also presented in figure 2. The mean (± SD) peak plasma concentration was 8.3 ± 3.5 ng/ml; the median peak time was 40 min.

Individual absorption rate *versus* time profiles and percentage absorbed *versus* time profiles (cumulative absorption profiles) are shown in figure 3. Mean absorption rate *versus* time and percentage absorbed *versus* time data are shown in figure 4. The overall absorption profile was monophasic in most patients, but initial absorption rates often tended to be zero-order. In a few patients a distinct biphasic absorption pattern was observed. The mean systemic availability and mean absorption time, derived from the deconvolution data were 100 ± 17% and 114 ± 24 min, respectively (table 2). Systemic availabilities and mean absorption times, as determined by moment analysis, were 107 ± 18%, and 112 ± 36 min, respectively (table 2).

Discussion

The main objective of this study was to determine the rate of the systemic absorption of alfentanil after epidural administration. However, to determine the absorption rate data on the disposition of alfentanil must also be obtained, in particular when the absorption and elimination rates are very similar, as in this study. Therefore we have used a stable isotope method enabling simultaneous investigation of the absorption and disposition kinetics. A prerequisite for using this method is that the pharmacokinetics of alfentanil-d_5 are similar to those of unlabeled alfentanil. This has been demonstrated by Bovill *et al.* (unpublished data).

The systemic disposition kinetics observed in this study are similar to those reported in several other studies that examined the systemic disposition after intravenous administration of a bolus dose or intravenous infusion of alfentanil.[16,21–27] The mean elimination half-lives reported in those studies varied from 70–118 min, steady-state volumes of distribution from 22–45 l, and total plasma clearances from 195–457 ml/min. Corresponding values observed in this study were 119 min, 43 l, and 418 ml/min, respectively.

Table 1. Systemic Disposition of Alfentanil: Pharmacokinetic Data Obtained by Noncompartmental (moment) Analysis

Patient	$t_{½z}$ (min)	V_{ss} (L)	Cl (ml/min)	MRT (min)
1	128	25.2	209	120
2	104	32.9	356	92
3	83	27.7	548	52
4	89	30.2	315	96
5	88	25.0	301	83
6	183	75.9	591	129
7	121	66.1	574	115
8	111	35.7	362	98
9	170	67.2	465	144
10	115	46.8	453	103
Mean	119	43.2	418	103
SD	34	19.5	129	26

$t_{½z}$ = terminal half-life; V_{ss} = steady state volume of distribution; Cl = total body clearance; MRT = mean residence time.

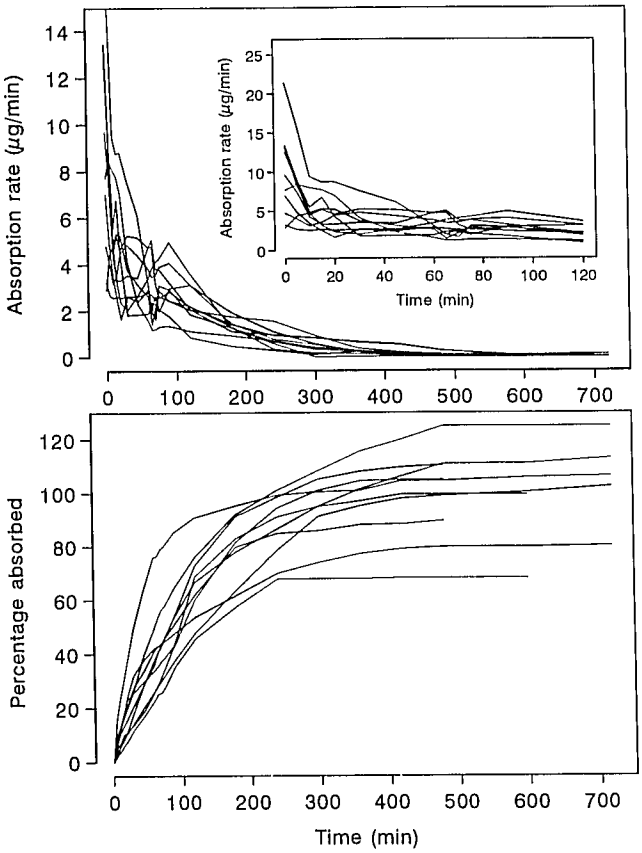

Fig. 3. (*Top*) Absorption rates of alfentanil-d_5 in all individuals. (*Bottom*) Percentages absorbed (cumulative absorption) of all individuals.

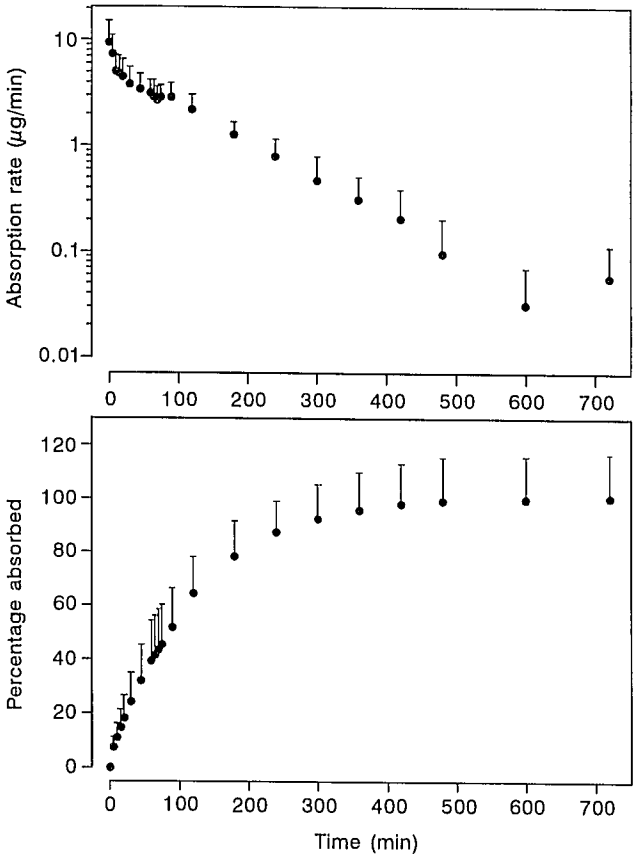

Fig. 4. (*Top*) Mean absorption rates of alfentanil-d_5. (*Bottom*) Mean percentages absorbed (cumulative absorption). Vertical bars indicate the standard deviations. Mean data were calculated from all individuals that had measurable plasma concentrations at the observation times: n = 10 for all observation times except 600 min (n = 7) and 720 min (n = 5).

The present study demonstrated that the overall systemic absorption profile of alfentanil-d_5 was monophasic in most patients, although initial absorption rates tended to be zero-order in some of the patients. This possibly reflects nonstationary absorption kinetics of alfentanil during anesthesia in these patients; *i.e.*, the absorption characteristics change with time. Such nonstationarity may be caused by, for example, changes in hemodynamics, changes in the partitioning of drug between the injected solution, tissue structures in the epidural space and blood perfusing the epidural space, secondary to changes in *p*H, or other factors. Furthermore, the study demonstrated that the uptake of alfentanil from the epidural space into the general circulation is a slow process. A rapid initial absorption phase was found in only two patients. This contrasts with earlier findings on the systemic absorption kinetics of the local anesthetic agents lidocaine, bupivacaine and etidocaine.[13–15] In all of these studies the absorption of local anesthetics followed a distinct biphasic pattern with a rapid initial absorption phase being followed by a much slower secondary absorption phase. In one study approximately 40% of the administered lidocaine dose was absorbed at a fast rate, characterized by an absorption half-life of 9 min, on average, whereas the remainder of the dose was absorbed at a much slow rate, characterized by an absorption half-life of 82 min.[14] The difference in the absorption pattern of alfentanil and the local anesthetics may be due in part to differences in vasoactivity. Epidural doses of plain solutions of lidocaine, bupivacaine and etidocaine are likely to produce local vasodilation, which should promote their absorption. Another factor, that may play a role is the difference in the *p*Ka values of these drugs. The *p*Ka of alfentanil is 6.5[28] and the *p*H of the administered solution was 6.4. Consequently, alfentanil was highly unionized in the administered solution. Furthermore, the degree of ionization is likely to increase further after epidural injection as a result of the buffering effect of local tissue bicarbonate stores. The high unionized fraction of alfentanil might then promote its uptake into local tissues (in particular epidural fat). In contrast, the *p*Ka values of local anesthetics are about 1–1.5 units higher than that of alfentanil and therefore

Table 2. Systemic Availabilities and Mean Absorption Times Derived by Deconvolution Followed by Moment Analysis of the Absorption Rate *Versus* Time Curves and by Noncompartmental (moment) Analysis of the Plasma Concentration Curves

	Deconvolution + Moment Analysis		Noncompartmental Analysis	
Patient	F (%)	MAT (min)	F (%)	MAT (min)
1	68	99	69	81
2	91	98	96	98
3	112	117	116	119
4	99	113	111	100
5	80	101	90	99
6	125	130	126	141
7	107	73	107	77
8	113	140	131	161
9	105	116	110	72
10	103	157	113	174
Mean	100	114	107	112
SD	17	24	18	36

F = systemic availability; MAT = mean absorption time.

these agents are highly ionized both in the administered acid solutions and at physiological *p*H. This might prevent rapid uptake into local tissues so that a greater fraction will be available for absorption.

Based on the higher *p*Ka values of fentanyl (*p*Ka = 8.4) and sufentanil (*p*Ka = 8.0)[28] and the explanation given above one would predict a biphasic absorption pattern after epidural administration of these agents. This is to some extent supported by other studies, showing a very rapid increase in the plasma concentrations of sufentanil after epidural administration with very short peak times.[12,29] However, the systemic absorption rates of both fentanyl and sufentanil after epidural administration of these agents remain to be determined.

The mean systemic availability of alfentanil, observed in the present study (100 ± 17%) accounted for the administered dose. This suggests that no metabolism of alfentanil occurs in the epidural space and is in keeping with previous studies on the systemic absorption of local anesthetics.[13–15] The large variability in the systemic availability most likely represents cumulating experimental errors related to the complex study design.

The plasma concentration–time profiles of the epidurally administered alfentanil-d_5 observed in this study are broadly comparable to the plasma alfentanil concentration–time profiles after preoperative epidural administration of unlabeled alfentanil observed in a previous study from our group but contrast with the plasma concentration–time profiles after postoperative epidural administration of alfentanil, reported by other investigators.[2,8] This suggests that the postoperative systemic absorption or disposition of alfentanil may differ from the absorption or disposition after pre- or intraoperative administration, because of differences in hemodynamic status and perfusion of the epidural space, for example. Another factor that may contribute to the observed differences in the plasma concentration–time profiles is the use of an epidural test dose. In the present study a test dose of mepivacaine with epinephrine was administered before the epidural injection of alfentanil. This test dose may potentially cause local vasoconstriction. However, the total doses of mepivacaine (6 mg) and adrenaline (15 μg) were very low and the small volume administered should not undergo extensive spread within the epidural space to cause a generalized vasoconstriction within this space. Therefore we do not believe that the administration of the test dose may have slowed the systemic absorption of alfentanil to a great extent.

The slow absorption of alfentanil may make this drug superior to its congeners fentanyl and sufentanil for epidural administration, when systemic side effects are to be avoided, such as when it is used for postoperative pain relief. This holds in particular during the first period after injection of a loading bolus dose. Therefore, further studies on the role of epidural alfentanil in postoperative pain relief are warranted.

In conclusion, the present study demonstrated that the uptake of alfentanil from the epidural space into the general circulation is slow. This explains the very low (<10 ng/ml) plasma concentrations of alfentanil observed by us in this as well as in a previous study.‡‡ These observations support the conclusion from an earlier study that the reduced intravenous alfentanil requirements in patients who received an epidural bolus dose before induction of general anesthesia are due not to an increase in the plasma concentrations of alfentanil but to a direct action of the drug on spinal opiate receptors.‡‡

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