Respiratory effects of intraoperative alfentanil infusion in post-abdominal hysterectomy patients: A comparison of high versus low dose

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Summary
A number of reports have been published describing (recurrent) respiratory depression after the use of alfentanil intraoperatively. To evaluate the severity of respiratory depression after the administration of alfentanil, 49 patients undergoing general anaesthesia for abdominal hysterectomy were randomly allocated to one of three groups and studied in a double-blind manner. During surgery patients received no opioids (group 1), low dose (group 2) or high dose of alfentanil (group 3). Postoperatively patients were monitored with pulse oximetry and respiratory inductive plethysmography. Postoperative pain was managed with PCA morphine.

Thirty-nine patients completed the study. Respiratory depressant effects were found in all three groups. A higher number of apnoeas (at 60 minutes in group 1: 3.3 ± 1.6; group 2: 3.5 ± 1.8; group 3: 12.2 ± 2.8) and a higher morphine consumption was found in group 2 when compared with group 1 and 3. No differences were found among the groups in the other respiratory parameters or in terms of the number of patients with respiratory depression at any one time. No cases of clear-cut recurrent respiratory depression were identified.

Keywords: opioids; alfentanil, intraoperative infusion; complications; respiratory depression

Introduction
Alfentanil has become popular as an opioid suitable for continuous infusion perioperatively. It has a shorter terminal elimination half-time than fentanyl (t1/2β of 70 min) due to its smaller steady-state volume of distribution, although its hepatic clearance is also less than that of fentanyl. Its short blood-brain equilibration time results in rapid onset of analgesia. Alfentanil has been postulated to provide a better safety index with regard to postoperative respiratory depression than its analogues fentanyl and sufentanil when used perioperatively. Nonetheless there are several reports of respiratory depression in the early postoperative period after the use of alfentanil intraoperatively. In all of these cases severe respiratory depression occurred some time after the patients were obviously fully recovered from anaesthesia. In most cases naloxone had to be given, after which rapid resumption of spontaneous respiration occurred. This phenomenon has been called recurrent, biphasic or delayed respiratory depression.

This study was performed to assess the preemptive analgesic effect of a high dose alfentanil infusion maintained throughout the intraoperative course. The findings of that aspect of the study are reported elsewhere. It was also recognised that this study could provide valuable information as to the respiratory depressant effects of alfentanil in the postoperative period. Thus part of the study was designed to assess the severity of depression of ventilation in the first three postoperative hours.
Methods
Ethical approval was obtained from The Toronto Hospital Committees for Research on Human Subjects. All patients gave their written informed consent to participate before entering the study.

Patient selection
Patients scheduled for abdominal hysterectomy were included in the study. Inclusion criteria were age 18 to 60 years, ASA physical status 1 or 2, body weight between 50 to 100 kg, no significant central nervous system, respiratory, cardiac, hepatic or renal dysfunction, no previous allergies or adverse reactions with opioid analgesics, no history of opioid or substance abuse, and no history or symptoms of sleep apnoea syndrome.

Randomisation and blinding procedures
Before the start of the study, a computer generated randomisation schedule was used to specify the group (1 = no opioid, 2 = low dose alfentanil, 3 = high dose alfentanil) to which each prospective patient would be assigned upon entry into the trial. An opaque envelope containing the group assignment was prepared, sealed and numbered for each prospective patient. On the morning of surgery, the anaesthetist in charge of the case opened the patient's envelope, read its contents, and prepared the syringes of alfentanil for subsequent administration.

With the exception of the anaesthetist, who was responsible for the general anaesthesia, the patients and personnel who collected study data were blinded to the treatment.

Preoperative assessment
On the night prior to surgery, patients were familiarised with the visual analogue pain scale (VAS) and introduced to the patient-controlled analgesia (PCA) pump (Abbott Life Care Infuser, Chicago, Illinois) and instructed in its use. Respiratory pattern was assessed continuously with respiratory inductive plethysmography (RIP - NIMS, Miami Beach, Florida) and haemoglobin oxygen saturation (SpO₂) was continuously measured using pulse oximetry (Nellcor N-100, Nellcor Inc, Hayward, California) in the postoperative period (see 'Postoperative monitoring'). Baseline measurements of RIP and SpO₂ were performed over a 30 minute period approximately 12 hours prior to surgery. Calibration and validation of the RIP - as well as its application in previous postoperative analgesic studies - have been described elsewhere. Respiratory rate (RR), episodes of apnoea (AP = tidal volume of less than 100 ml for more than 15 seconds) and episodes of slow respiratory rate (SRR = respiratory rate less than 8 breaths/min persisting for more than 5 min) were measured continuously and recorded in five minutes epochs and calculated for each 30 minute interval. Patients were attended continuously by trained personnel during the entire preoperative and postoperative data collection periods. Respiratory pattern abnormalities were confirmed by the analysis of real time respiratory inductive plethysmography output and direct observation of the patient. Episodes of desaturation (SpO₂ < 90 for 30 seconds) and the number of patients with respiratory depression (SpO₂ < 85% for 30 seconds and/or a respiratory rate of less than 10 for more than 15 minutes) were also measured and the average SpO₂ was calculated for each 30 minutes interval.

General anaesthesia
Patients were kept nil per os for six hours before surgery. All patients received diazepam per os (5-10 mg) two hours prior to surgery as premedication. Patients were assigned at random to one of three groups.

For patients in group 1, anaesthesia was induced with midazolam (0.05 mg kg⁻¹) and thiopentone (3-5 mg kg⁻¹). In all groups muscle relaxation and tracheal intubation was achieved with vecuronium (0.1-0.15 mg kg⁻¹). Anaesthesia was maintained with 70% N₂O in O₂ and isoflurane. Opioids were not administered at induction or intraoperatively.

For patients in group 2, anaesthesia was induced with alfentanil (30 μg kg⁻¹), midazolam (0.05 mg kg⁻¹), and thiopentone (3-5 mg kg⁻¹). Anaesthesia was maintained with 70% N₂O in O₂, isoflurane and bolus doses of alfentanil (10-20 μg kg⁻¹) every hour. For groups 1 and 2, isoflurane was titrated to maintain systolic blood pressure within 20% of baseline systolic blood pressure derived from preoperative ward measurements.

For patients in group 3, anaesthesia was induced with midazolam (0.05 mg kg⁻¹) and alfentanil (100 μg kg⁻¹). Anaesthesia was maintained with 70% N₂O in O₂ and a continuous infusion of alfentanil (1-2 μg kg⁻¹ min⁻¹). The alfentanil dose was adjusted to maintain haemodynamic variables within 20% of preoperative ward values by administering a bolus
To deliver a 1.5 mg intravenous bolus of morphine the procedure with a non-invasive blood pressure cuff, electrocardiogram, pulse oximetry, temperature probe, nerve stimulator and end-tidal carbon dioxide and anaesthetic agent analyser. For groups 1 and 2, the continuous background infusion. This regimen was calculated from hard copy records (Abbott TRW Printer Model TP 40).

Postoperative pain measurement
A 10 cm visual analogue scale (with endpoints labelled ‘no pain’ and ‘worst possible pain’) was used to assess pain intensity at rest (VAS-R) two and four hours after completion of surgery.

Postoperative respiratory monitoring
When the patient arrived in the PACU, pulse oximetry monitoring was reinstituted and the two transducer bands of the respiratory inductive plethysmography were attached around the rib cage and abdomen of the patient. Pulse oximetry and plethysmography were continued for three hours after surgery. Oxygen supplementation was routinely provided for the first 30 minutes in the PACU and then discontinued. If respiratory depression (SpO₂ <85% for 30 seconds or a respiratory rate of less than 10 for 15 minutes) occurred at any time an arterial blood gas sample was analysed. If the SpO₂ persisted at <90% after 30 seconds, supplementary oxygen was provided by face mask to provide an SpO₂ of >90%.

Plasma alfentanil concentration analysis
Blood samples (10 ml) were drawn in all patients from a radial artery at 30 minutes and 120 minutes after arrival in the PACU. Samples were collected in heparinised glass vials, centrifuged immediately, and the separated plasma stored at -27°C until analysis at the end of the study. Assays were performed by a blinded technician on samples obtained from patients in groups 2 and 3 only. Concentrations of alfentanil were measured in duplicate using a specific radioimmunoassay kit (Janssen Biotech NV Research Products). The sensitivity of the assay is 0.1 ng ml⁻¹ and the intra- and inter-assay coefficients of variation covering the therapeutic range of concentrations were <10%.

Adverse effects
Nausea and vomiting were treated as needed with dimenhydrinate 25-50 mg.

Statistical analysis
Demographic, clinical, and intraoperative treatment variables were analysed by \( \chi^2 \) test (frequency data) or one-way, between-groups ANOVA (parametric data). VAS R, morphine, plasma alfentanil concentrations, MRR, number of apnoeas, saturations, episodes of desaturation and number of patients with respiratory depression were analysed by two-way repeated measurements ANOVA using group and
the independent samples factor and time after surgery as the repeated measures factor. Significant effects were followed up with Fisher's protected LSD test to determine the pattern of differences between pairs of means. Cumulative morphine consumption was analysed by one way ANOVA.

Results

Patient withdrawals
Forty-nine patients were recruited into the study. Three were removed for protocol violations, four for technical problems with the respiratory inductive plethysmograph monitoring equipment and three for lack of arterial blood sampling (no arterial catheter). Thirty-nine patients completed the study.

Demographic, clinical and intra-operative variables
The three groups did not differ significantly on demographic variables (Table 1) or in frequency of diagnosis, incision type or surgical procedure (Table 2). Group 3 received significantly more alfentanil than group 2 (\(p = 0.0001\)). Mean isoflurane requirements were significantly greater in group 1 than group 2 (\(p = 0.0006\)). Nine patients in group 1 received propranolol (\(p = 0.001\)).
Time after surgery | Group 1 | Group 2 | Group 3
---|---|---|---
30 minutes | VAS-R | VAS-R | ALF | VAS-R | ALF
2 hours | 6.2 (1.9) | 5.9 (1.4) | 4.0 (1.9)* | 3.9 (2.0)* | Nm
4 hours | 6.8 (1.6) | 5.6 (2.5) | Nm |

Nm = Not measured
* p ≤0.006 versus Group 1 and 2
† p = 0.0001 versus Group 2

Table 3: Mean (standard deviation) VAS in rest (VAS-R) and mean (standard deviation) plasma alfentanil (ALF) concentrations after surgery

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of patients with respiratory depression</th>
<th>pH</th>
<th>PO₂ (mmHg)</th>
<th>PCO₂ (mmHg)</th>
<th>Plasma concentrations of alfentanil (ng ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>One episode</td>
<td>Two episodes</td>
<td>30 min</td>
<td>60 min</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>1</td>
<td>7.39 (0.11)</td>
<td>89 (28.9)</td>
<td>41 (10.6)</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>1</td>
<td>7.34 (0.03)</td>
<td>83 (11.0)</td>
<td>54 (18.9)</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>3</td>
<td>7.29 (0.05)</td>
<td>108 (71.0)*</td>
<td>49 (5.5)</td>
</tr>
</tbody>
</table>

* Two patients in group 3 with respiratory depression received supplemental oxygen before the blood gas was drawn.

Table 4: Number of patients with respiratory depression and the mean (standard deviation) results of their blood gas and plasma alfentanil analysis

Pain and morphine consumption
Over the four hour period, VAS-R pain scores (Table 3) were significantly lower in group 3 than in the other two groups (p ≤0.006). Cumulative morphine consumption (mg) at 180 minutes (Figure 1) was significantly lower in group 3 than in group 2 (p=0.02).

Plasma concentration of alfentanil
Plasma concentrations of alfentanil were available at 30 minutes and 120 minutes after surgery for 10 patients in group 2 and 10 patients in group 3 (Table 3). Mean alfentanil plasma concentrations in group 3 was significantly greater than that of group 2 at 30 and 120 minutes (p=0.0001).

Postoperative respiratory monitoring
The mean number of apnoeas (per 30 minutes) (Figure 2) in group 1 was significantly lower than in group 2 at 30 (1.7 ± 0.9 versus 11.9 ± 3.2 for group 1 and 2, respectively) and at 60 (3.3 ± 1.6 versus 12.2 ± 2.8 for groups 1 and 2, respectively) minutes after surgery (all p ≤0.007). Moreover, at 60 minutes the mean apnoea rate in group 3 (3.5 ± 1.8) was significantly lower than in group 2 (p=0.007). From 90 minutes onward, there were no significant differences among the three groups. The mean respiratory rate (MMR) was significantly lower in group 3 (14.7 ± 1.0) than in group 1 (20.9 ± 1.2) at 30 minutes after surgery (p=0.0002) (Figure 3). Thereafter MRR did not differ significantly among the groups. There was no significant difference among the groups in the mean number of slow respiratory rate episodes (SRR) or episodes of desaturation. Also no significant differences were found in terms of the number of patients with a respiratory depression at any one time (Table 4). It was noted in these patients that the respiratory depression occurred when the patients were asleep and that they were easily aroused by verbal stimuli.

Plasma concentrations of alfentanil did not differ significantly for patients with or without respiratory depression. There was no significant difference in average saturation although values for all three groups decreased significantly over time from 30 to 180 minutes after surgery (p=0.0001) (Figure 4).

Adverse effects
No adverse effects (in terms of nausea and vomiting) were seen for the duration of the study.
**Discussion**

The present study demonstrates that respiratory depression occurred in at least one patient in all three groups. One patient in group 1, three patients in group 2 and three patients in group 3 experienced one or two episodes of respiratory depression as defined by a respiratory rate lower than 10/min for 15 minutes and/or saturation lower than 85% for 30 seconds (see Table 4). It was noted in these patients that the respiratory depression occurred when the patients were asleep and that they were easily aroused by verbal stimuli.

Differences were found among the groups in the mean respiratory rate, the number of apnoeas, consumption of morphine and VAS-R.

The mean respiratory rate was lower in the high dose alfentanil group (group 3) than in the non-opioid group (group 1) at 30 minutes. Since at that time point, the mean respiratory rate was 14.7 for group 3 and 20.8 for group 1, this was not considered to be of clinical significance.

The number of apnoeas was found to be higher in group 2 than in group 1 at 30 minutes and in group 1 and 3 at 60 minutes after surgery. Furthermore, the patients in group 2 had higher morphine consumption than the patients in group 3 in the first 90 minutes after surgery and a higher mean VAS score during the first four hours after surgery. The finding of a higher number of apnoeas in group 2 is remarkable, especially since no differences were found among the groups in the other respiratory parameters or in SpO₂. Group 2 was the only group...
in which the patients received isoflurane and alfentanil during their general anaesthesia. Isoflurane is known to produce dose-dependent respiratory depression, although this effect is short-lived. It can be speculated that the finding of the higher number of apnoeas in group 2 is mainly caused by the higher morphine consumption combined with possible lingering effects of alfentanil.

Other studies also have tried to assess the problem of respiratory depression after the use of alfentanil. CO₂ response curve measurements are a sensitive way to demonstrate respiratory depression. Two open studies used this method to demonstrate that continuous infusion of alfentanil in patients resulted in depression of the CO₂ response curve, but with a lesser effect on tidal volume, breathing frequency and PCO₂ levels. Goldberg et al. found that the CO₂ response slopes were depressed for 120 minutes with a right shift of the slope in patients after an alfentanil-based anaesthetic. Mean plasma alfentanil concentrations ranged from 124.5 ng ml⁻¹ at 30 minutes to 58.9 ng ml⁻¹ at 150 minutes. Secondary increases in plasma alfentanil concentrations in five out of 21 patients were found and eight patients experienced desaturation (SpO₂ < 90%), but no relationship could be demonstrated between alfentanil plasma concentration and the CO₂ response curve or arterial O₂ desaturation. Also in Goldberg's study the episodes of desaturation most often occurred when the patients were asleep but arousable to verbal stimuli. Only one dose of alfentanil was used and no control group was included.

The disadvantage of using CO₂ response curve measurements is that it requires active patient collaboration. Since each test must be performed with a large mouthpiece and nose clips, it creates some disturbance on awakening the subject and will counteract any respiratory depressant effects by arousing the patient. By using non-invasive and non-interfering monitors such as inductive plethysmography and oximetry we tried to create a more realistic clinical PACU environment.

In the present study the highest mean plasma concentration of alfentanil measured was 217 ng ml⁻¹ (in group 3 at 30 minutes after surgery). This value is in the range of the threshold for resumption of spontaneous breathing (100-240 ng ml⁻¹). Plasma concentration of alfentanil did not differ between patients with or without respiratory depression. Cases of recurrent respiratory depression are described which have occurred at a plasma concentration of 87 ng ml⁻¹ and 95 ng ml⁻¹. Sternio et al. recently reviewed the published case reports of recurrent respiratory depression and found a very wide range in the alfentanil doses administrated (72-688 µg kg⁻¹) and in the duration of the infusions (45-465 minutes).

The cause of recurrent respiratory depression after the use of alfentanil remains unknown. The different theories include:

- Secondary peaks in plasma concentrations of alfentanil have been demonstrated to occur. This can be caused by 'pH trapping', which involves the sequestration of the ionised drug in the acidic environment of the stomach with re-absorption in the non-ionised form in the (less acid) intestine. Also the postoperative release of alfentanil from the muscular compartment (becoming more active after surgery) may contribute to a secondary peak in the plasma concentration of alfentanil. Both mechanisms have been described in the case of fentanyl. However, no studies have been published that specifically look at these mechanisms in the case of alfentanil.

- Alfentanil is known to have a large degree of interindividual variability in its pharmacokinetics. In the present study mean plasma concentrations of alfentanil were found to have large standard deviations (see Table 4). Obesity, age, variability in the level of α-glycoprotein, decreased hepatic blood flow, changes in acid-base status and differences in the cytochrome P450 isozymes activity are possible factors responsible for the large interindividual differences in the pharmacokinetic profile of alfentanil. Furthermore it is known that drugs like propofol, dexametomidine, erythromycin, cimetidine and fluconazole can influence the clearance of alfentanil by interference in its metabolism.

- Patients that are alert and awake on arrival in the recovery room are usually 'left alone' because they seem to be doing well. This means that after extubation, transport to the PACU and the initial assessments on arrival in the PACU these patients may not receive any further stimulation. The decreased stimulation in these patients, combined with a lingering opioid effect, can be a factor in some cases of recurrent respiratory depression.
This theory is supported by the fact that most cases of recurrent respiration depression occurred 15 minutes or more after extubation. Also the finding of very low pH values at the time of recurrent respiratory depression suggests that the respiratory depression evolved over some time. In the present study and in the study of Goldberg et al., patients who had an episode of desaturation appeared to be asleep but could be easily aroused when stimulated.

In this controlled, randomised, double-blind study respiratory depressant effects were found in post abdominal hysterectomy patients who received no opioids, low or high doses of alfentanil during general anaesthesia. No cases of clear-cut recurrent respiratory depression were identified.

Supported by a grant from Janssen Research Foundation and grant #MT-12052 from the Medical Research Council of Canada (JK). Presented in part at the Annual Meeting of the Canadian Anaesthetists Society, Ottawa, Ontario, 1995.

References


