Comparison of three techniques on time to awakening, time to orientation and incidence of nausea and vomiting using alfentanil in balanced anesthesia in an outpatient surgical setting

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Maximizing patient safety and comfort while minimizing adverse sequelae are continuing anesthetic challenges. The purpose of this study was to examine three anesthetic techniques utilizing alfentanil with regard to time to awakening, time to orientation and incidence of nausea and vomiting. Surgical procedures were limited to knee arthroscopy, laparoscopy and dental extractions. Unpremedicated ASA I/II outpatients (n = 74) between the ages of 18 and 59 were randomly assigned to one of three groups:

Group I: alfentanil + 67% N₂O + 33% O₂
Group II: alfentanil + 67% N₂O + 33% O₂ + droperidol 0.015 mg/kg
Group III: alfentanil + 100% O₂ + 0.7% isoflurane

Anesthesia was induced with alfentanil 40 μg/kg, atracurium 0.4 mg/kg, thiamylal 4 mg/kg and 100% O₂ and was maintained according to group assignment. The anesthetic was supplemented as clinically indicated with incremental boluses of alfentanil 10 μg/kg. Upon completion of surgery, muscle relaxation was reversed with edrophonium 0.75 mg/kg and atropine 0.015 mg/kg.

Analyses indicated that the three groups were comparable in terms of potentially confounding variables including gender, race, surgical procedure, age, percent of ideal body weight, case length and dose of alfentanil in μg/kg/hr. Time to awakening was significantly shorter in the two N₂O groups by approximately 1.5 minutes, as compared to the O₂ and isoflurane group (p = .0060). Time to orientation was significantly shorter in the N₂O groups by approximately 1.5 minutes also, as compared to the O₂ and isoflurane group (p = .0142). The two N₂O groups did not differ significantly in either measure. The incidence of vomiting in the postanesthesia recovery room (PARR) indicated a significant difference (p = .0317) among groups with vomiting occurring 45.8% of the time in Group I, 28.8% of the time in Group II and 8% of the time in Group III. Total emetic score (nausea and vomiting) in the PARR indicated a significant difference (p = .03) among groups with symptoms occurring 50% of the time in Group I, 28% of the time in Group II, and 16% of the time in Group III.

Introduction

The ability to provide high quality, cost-effective care has made outpatient surgery one of the fastest growing areas in the health care delivery system.
Wetchler suggests that more than 60% of all surgical procedures could be performed in the outpatient setting. The objective of this research was to evaluate postanesthesia time to awakening, time to orientation and the incidence of nausea and vomiting in three different techniques. The anesthetics included alfentanil with nitrous oxide and oxygen, or with nitrous oxide, oxygen and droperidol, or with oxygen and isoflurane.

Comprehensive summaries of inhalational versus intravenous anesthetics are suggested. Alfentanil is a short-acting opioid with an analgesic potency approximately one-fourth that of fentanyl. Two key pharmacologic properties make alfentanil particularly well suited to meet the demands of short surgical procedures. It has a rapid onset of action which affords prompt control of hemodynamic responses to surgical stimulation. Also, it has a short duration of action with a short elimination half-life, primarily due to a relatively small volume of distribution, which enables accurate titration to patient response. Due to this close overlap over serum drug levels, alfentanil facilitates rapid recovery, even after repeated injections. The high fraction of unionized drug available for diffusion contributes to prompt blood-brain equilibration, with extremely rapid binding to and dissociation from receptor sites. The net clinical result is a rapid onset and brief duration of analgesic effect.

Pollard found that time to awakening and time to orientation were both significantly shorter with alfentanil than with isoflurane anesthesia. The most recent iteration of potent inhalational agents, isoflurane, has been suggested as particularly desirable for outpatient anesthesia due to its relatively low degree of metabolism and low solubility. A multicenter study compared the clinical differences between an intravenous technique employing fentanyl and droperidol and an inhalational technique employing isoflurane. The conclusion was that the intravenous technique offered clinically useful advantages over isoflurane for outpatient procedures, providing stable intraoperative blood pressure and heart rate and more rapid recovery of motor responses, consciousness and orientation.

Gross and Alexander utilized a randomized double-blind design to determine how morphine or placebo affected recovery from oxygen and isoflurane anesthesia. Times from discontinuation of isoflurane until eye opening in response to verbal command were similar in the morphine and placebo groups. It was concluded that the awakening concentration (minimum alveolar concentration-awake) during recovery from isoflurane anesthesia is not affected by analgesic doses of morphine. This study has important implications since it was done without nitrous oxide and showed that a narcotic technique using 100% oxygen and isoflurane could be managed without sacrificing rapid awakening.

Stevens and associates described the concept of minimum alveolar concentration with isoflurane, with and without nitrous oxide. He stated that for every 10% decrease in nitrous oxide, isoflurane would have to be increased by 0.1% to maintain an equivalent level of anesthesia. On this basis, approximately equipotent (67% N₂O and 0.7% isoflurane) anesthetic levels were employed in this study.

Early recovery from anesthesia may be judged by many criteria. Several studies have utilized opening of eyes to command and giving correct name and age or current day as tests of early recovery and orientation. In this study, the ability to respond to a simple command was used as a measure of recovery. This ability implies the return of consciousness and, as such, is a reasonable test of immediate recovery from anesthesia. It is also an endpoint which is easy to define, repeatable and has the advantage of requiring no equipment. Inevitably, it does not reflect the speed or quality of return to full normality. Various psychomotor test batteries, driving simulators and paper-and-pencil tests have been employed to assess patients' psychomotor recovery or "street fitness." These tests are complex and obviously cannot be used routinely in clinical practice.

A common postoperative complication is vomiting. To the patient, this problem may be perceived as an unpleasant, possibly unavoidable outcome of anesthesia. To the anesthetist, postoperative nausea and vomiting is undesirable not only for altruistic reasons, but it also delays the time for total anesthesia recovery — perhaps even indicating an overnight stay following intended same-day surgery. Moreover, it carries with it the potentially lethal sequela of pulmonary aspiration of gastric contents. This risk is present in the immediate postanesthesia period when protective reflexes may be obtunded by residual effects of anesthetic and adjunctive drugs.

Several observations suggest that the addition of fentanyl to an inhaled anesthetic increases the incidence of nausea and vomiting. Gaskey and associates found that the use of fentanyl is associated with a higher incidence of nausea and vomiting in ambulatory surgical patients. They conclude that to avoid these symptoms, "it may be necessary to decrease or eliminate the use of narcotics." How-
ever, in a multicenter clinical evaluation of 6,800 patients, no correlation was found between either nausea or vomiting and narcotic administration. In a multicenter clinical evaluation of 6,800 patients, no correlation was found between either nausea or vomiting and narcotic administration. Epstein and associates reported 40.5% nausea and 32.4% emesis with fentanyl and nitrous oxide during elective termination of pregnancy. Williams et al. found a 54% incidence of nausea and 44% incidence of vomiting when using sufentanil with nitrous oxide in short-term anesthetics.

In 1960, Adriani and associates noted nitrous oxide probably causes emesis by central and peripheral effects but that it does not stimulate the vomiting center. Eger suggested that air swallowing occurs and gastric inflation by manual ventilation with translocation of nitrous oxide was a major contributing factor to postoperative vomiting. Perreault stated an effect of nitrous oxide is substantial pressure developed in the middle ear possibly causing nausea and vomiting by effects on the vestibular system. It can also interact centrally with the endogenous opioid receptor systems, thereby stimulating nausea and vomiting at this level.

Several conflicting studies have recently appeared concerning the role of nitrous oxide in causing postoperative nausea and vomiting. Alexander showed that laparoscopic patients who received nitrous oxide and fentanyl had a significantly greater incidence of nausea and emesis than patients who had received either the combination of isoflurane and fentanyl or just isoflurane alone. He concluded that nitrous oxide may play a significant role in the production of nausea and vomiting. Lonnie and Harper found that addition of nitrous oxide to an anesthetic of enflurane and fentanyl for laparotomy patients increased postoperative nausea and vomiting. Melnick and Johnson attempted to determine the effect of omitting nitrous oxide from a general anesthetic technique. Nausea and vomiting was much less when nitrous oxide was omitted (3.2%) than when it was used (25%). However, Kortilla and associates found that omission of nitrous oxide did not decrease emesis in patients undergoing abdominal hysterectomy. Muir and associates had similar findings in a group of pediatric patients undergoing various surgical procedures. Because of concerns about possible risks to operating room personnel, inhibition of methionine synthetase, expansion of gas containing spaces and increased nausea and vomiting, the continued use of nitrous oxide as a component of most general anesthetics has come under scrutiny. In a letter to the editor, Tyson and Cullen reported the use of nitrous oxide decreased from a high of 84% in 1982 to 43% in 1986 at their academic institution.

Historically, incidences of nausea and vomiting as high as 82% with diethyl-ether and as low as 8% with isoflurane have been reported. Many studies report various levels of symptoms depending on the drug milieu and the operational definition of nausea and vomiting. Zuurmond and van Leeuwen compared 67% nitrous oxide and 33% oxygen with either alfentanil (1 ug/kg/min) or isoflurane (0.9%) and found a more rapid awakening time with alfentanil. However, the alfentanil group showed a higher incidence of nausea and vomiting: 45% compared to 14% in the isoflurane group. Fragen and associates described a similar incidence with alfentanil (44%). Rising and associates described an incidence of 16% nausea and 12% vomiting after isoflurane anesthesia for outpatient laparoscopy compared to 60% nausea and 28% vomiting for fentanyl. These studies suggest that isoflurane has a more desirable nausea-vomiting profile when compared to a narcotic. However, nitrous oxide was a common agent and perhaps made a substantial contribution to the nausea/vomiting profiles when combined with the narcotic.

Palazzo and Strunin, in their comprehensive review article, suggested their prophylactic antiemetic of choice to be droperidol. Wetchler reported that droperidol has proven to be effective in reducing incidence and severity of emesis when low intravenous dosages (0.625-1.25 mg) were used and found no increase in recovery time. O'Donovan and Shaw found that ultra-low dose droperidol (0.25 mg) produced a significant decrease in nausea without delaying recovery or discharge from the hospital. Melnick and associates found that nausea and vomiting occurred in 36% of patients despite the intravenous injection of 0.625 mg of droperidol at induction.

Materials and methods

Study approval was secured from the Research and Human Subjects Review Committee and informed consent was obtained. A sample of 74 male or female outpatient surgical candidates were randomly assigned to one of three groups using a table of random numbers. Surgical procedures were limited to knee arthroscopy, laparoscopy and dental extractions. The randomization was carried out within each surgical procedure to avoid overrepresentation of any single procedure. No premedication was used.

Monitors utilized included electrocardioscope, precordial stethoscope, peripheral nerve stimulator, oxygen analyzer, pulse oximeter, capnometer and noninvasive electronic blood pressure monitor. After baseline vital signs were obtained, patients were preoxygenated by instructing them to take three maximal inspirations of 100% oxygen delivered through a tight-fitting face mask. Alfentanil

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40 μg/kg, atracurium 0.4 mg/kg and thiamylal 4 mg/kg were administered intravenously in that order within one minute. Respirations were assisted, then controlled by mask ventilation with 100% oxygen. The trachea was intubated under direct vision and respiration was controlled by mechanical ventilation to an end-tidal carbon dioxide of approximately 35 mmHg. Nitrous oxide 67% or isoflurane 0.7% was then administered according to group assignment. Droperidol 0.015 mg/kg was given intravenously to the Group II patients immediately after intubation.

Supplemental analgesia was administered with alfentanil 10 μg/kg when blood pressure or heart rate rose 20% above baseline. Atracurium 0.1 mg/kg was administered if neuromuscular blockade was assessed to be less than 75% suppression of 1st twitch (only 4th twitch eliminated), avoiding additional relaxant within 20 minutes of the estimated end of the surgical procedure.

Upon completion of surgery, muscle relaxation was reversed with edrophonium 0.75 mg/kg and atropine 0.015 mg/kg. Inhalational agents were also discontinued at this time, documented as “end of anesthesia.” Times to awakening and orientation were measured with a stopwatch from this time. Every 20 seconds, without physical contact, the patient was asked to open his/her eyes. Upon eye opening, the patient was considered “awake” and this elapsed time documented as “time to awakening.” Once the patient was awake, able to headlift and breathing adequately, the trachea was extubated.

When the patient was responding verbally to requests from the investigator, the patient was asked his/her name, where he/she was, and what day of the week it was. When three correct answers were received, the elapsed time from the end of anesthesia was documented as “time to orientation.” If no answer or an incorrect answer was received, the patient was requestioned in 20 seconds until a time to orientation was established. Transfer to the post-anesthesia recovery room (PARR) was then accomplished, and patients were monitored continuously for postoperative nausea and vomiting until time of discharge from recovery room, a minimum of one hour after admission to that unit. The next day, the investigator telephoned the patients and questioned them about nausea and vomiting within 24 hours of their discharge from the hospital.

Patton and associates developed the following scale that has been frequently utilized to measure nausea and vomiting symptoms postoperatively: 0—Patient without nausea, retching or vomiting during the preceding hour. 1—Nausea during the preceding hour. 2—Retching or gagging during the preceding hour. 3—One or more vomiting episodes during the preceding hour.

A modification to eliminate the retching parameter allowed a 0-1-2 scale that has also been used to measure nausea and vomiting.

One-way analysis of variance (ANOVA) was used to test the significance of variance between the three groups in terms of the two continuous dependent variables: time to awakening and time to orientation, which were treated as ratio data. If a significant difference was demonstrated by ANOVA with respect to either of the two variables, the Scheffe procedure was used to specify the significant difference between group means. Chi-square was used to test the difference between groups and emetic scores, which were treated as ordinal data. A significance level of p < .05 was used.

Results
In addition to the randomization process, statistical procedures were applied to potentially confounding variables to test the assumption of group homogeneity. Chi-square was applied by cross tabulating treatment groups by surgical procedure, with no significant relationship identified. ANOVA was used to compare group means for the continuous variables of age, percent ideal body weight, length of anesthesia and alfentanil dose in μg/kg/hr. No significant differences were found among groups for these variables. These data are presented in Table I.

ANOVA indicated a significant difference among groups on time to awakening in seconds (p = .0060). The Scheffe procedure denoted Group III to be significantly different from Group II, and Group III to be significantly different from Group I. Group I showed no statistical difference from Group II. ANOVA indicated a significant difference among groups when examining for differences in time to orientation in seconds (p = .0142). The Scheffe procedure denoted Group III to be significantly different from Group II, and Group III to be significantly different from Group I. Group I showed no significant difference from Group II. The mean times to awakening and orientation are presented in Figure 1.

Emetic scores were compiled for two time periods: for each patient in the PARR and as a 24-hour emetic score by tabulating emetic score for any time until the 24-hour follow-up telephone call. The
Table I
Group homogeneity: Continuous variables

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<th>II</th>
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<th>Sample</th>
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<td>Mean SD</td>
<td>Mean SD</td>
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<td>% Ideal body weight</td>
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<td>Case length (minutes)</td>
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<td>μg/kg/hr alfentanil</td>
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<td>63.2 19.1</td>
<td>.70 NS</td>
</tr>
</tbody>
</table>

SD-standard deviation
NS—not significant p < .05

Group I: alfentanil + 67% N₂O + 33% O₂
Group II: alfentanil + 67% N₂O + 33% O₂ + droperidol 0.015 mg/kg
Group III: alfentanil + 100% O₂ + 0.7% isoflurane

Figure 1
Time to awakening and time to orientation

Figure 2
Vomiting symptoms among groups in postanesthesia recovery room (PARR) and within 24 hours postoperatively

Vomiting symptoms alone in the PARR indicated a significant difference (p = .0317) among groups with vomiting occurring 45.8% of the time in Group I compared to 28.8% in Group II and only 8.0% in Group III. Although the 24-hour vomiting scores did not reach statistical significance among groups (p = .17), the results were in the same direction. These results are presented in Figure 2.

Examining total emetic symptoms (nausea and vomiting) among groups in the PARR and in a 24-hour score again showed significant differences (p = .03) in the PARR comparison with nausea and vomiting occurring 50% of the time in Group I compared to 28% in Group II but only 16% in Group III. The 24-hour total emetic symptoms showed substantial but not statistically significant (p = .15) differences in the 24-hour comparison. These results appear in Figure 3.

A chi-square analysis comparing percent ideal body weight with either emetic score in the PARR or emetic score in 24 hours, showed no significant findings. This, therefore, does not support findings of other investigators that increased body weight increases incidence of nausea and vomiting. Similarly, comparing sex with emetic score in PARR and in 24 hours showed no significant difference. Some authors have found that females are at higher emetic risk, a finding not replicated in this study.

The idea that certain surgical procedures contribute to postoperative nausea and vomiting prompted a chi-square comparison of surgical type by emetic score in the PARR while controlling for sex. There were no statistically significant findings.
This is in agreement with a similarly designed study by Williams and associates in which sufentanil was used with no significant difference in nausea/vomiting found among arthroscopy, laparoscopy or dental extraction patients.  

Discussion and conclusions

Time to awakening was significantly shorter in the two nitrous oxide groups by 81 and 94 seconds respectively, compared to the 100% oxygen and 0.7% isoflurane group. (Group I - 94 sec, Group II - 81 sec, Group III - 175 sec). The nitrous oxide and the nitrous oxide and droperidol groups did not exhibit significantly different results between each other in the time to awakening comparison. Time to orientation was significantly shorter in the nitrous oxide and the nitrous oxide and droperidol groups by 98 and 103 seconds respectively, compared to the 100% oxygen and 0.7% isoflurane group (Group I - 199 sec, Group II - 193 sec, Group III - 296 sec). Again, the two nitrous oxide groups did not differ significantly in this comparison of time to orientation.

This is consistent with the generally held expectation that the less soluble nitrous oxide would be more rapidly eliminated compared to the potent inhalational agents, even the least soluble of these, isoflurane. The reticence of practitioners to relinquish use of nitrous oxide in a balanced general anesthetic often relates to this aspect of rapid elimination and, therefore, rapid awakening. These results showed that the addition of the butyrophenone tranquilizer droperidol as an antiemetic (0.015 mg/kg) did not result in significantly longer awakening times versus the nitrous oxide alone group. The time to awakening “penalty” was longer in the 100% oxygen and 0.7% isoflurane group versus the nitrous oxide groups by approximately 1.5 minutes. The time to orientation penalty for incorporating 100% oxygen and 0.7% isoflurane was also about 1.5 minutes greater than the nitrous oxide groups. Time to awakening is a concept that reflects controllability of an anesthetic. Therefore, the fact that the two techniques with nitrous oxide allowed for a statistically significant (more rapid) time to awakening would appear to favor nitrous oxide as opposed to 0.7% isoflurane as “background” agent to a narcotic-based technique. However, “clinical” significance is an important perspective, and whether the difference between about 1.5 minutes awakening time for Groups I and II and about 3 minutes awakening time for Group III is clinically important is doubtful.

Time to orientation, as defined in this study, addresses the rapidity of return to a state of wakefulness and awareness that begins the approach to the “street fitness” criteria for discharge of an ambulatory surgical patient. If a short time to orientation is considered a desirable characteristic, it appears that the nitrous oxide groups have a statistically significant advantage. Comparing about 3.5 minutes to orientation for Groups I and II to approximately 5 minutes for Group III again may be of questionable clinical significance. Individual anesthetists may have different views.

The incidence of vomiting alone, as well as nausea and vomiting, in the PARR was substantially lower in the 100% oxygen and 0.7% isoflurane group compared to the nitrous oxide techniques. Since these symptoms were not significantly different in the emetic scores at 24 hours, the group difference appears to be less evident as time increases beyond the end of anesthesia. The literature contains many articles addressing the virtues of droperidol as a prophylactic antiemetic when used as an adjunct to a general anesthetic. This study also showed a more attractive emetic profile in the PARR for the droperidol group.

Clinical research attempts to advance from anecdote to epidemiology. This study requires the anesthetist to ask if the forfeiture of approximately 1.5 minutes shorter time to awakening and 1.5 minutes shorter time to orientation profile for a significantly better emetic profile in the recovery room provides a clinically desirable cost-benefit ratio. A practitioner could possibly manipulate the defined
end of anesthesia time by discontinuing the 0.7% isoflurane approximately 1.5 minutes earlier than if a nitrous technique was being used. This would achieve the same proximity to end of surgery for awakening and orientation as a nitrous oxide technique, but with a substantially better emetic profile. This specific manipulation deserves clinical testing.

Perhaps future research could correlate time to awakening, time to orientation, and nausea and vomiting with delay in discharge. Repeating the study with a larger sample size and including a group including 100% oxygen, 0.7% isoflurane and 0.015 mg/kg droperidol may offer useful information for anesthesia care plans that facilitate higher quality care.

REFERENCES


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