RISK FACTORS FOR OXYGEN DESATURATION DURING SLEEP, AFTER ABDOMINAL SURGERY


SUMMARY

The postoperative period after major abdominal surgery is known to be a period of increased episodic oxygen desaturation. In order to assess the risk factors for episodic desaturation, we have studied 29 surgical patients using pulse oximetry during the preoperative night (N\text{pre}) when they received benzodiazepine premedication and breathed air, and also during the first three nights after operation when they received nasal oxygen supplementation. Modal oxygen saturation (\text{SpO}_{2}) exceeded 95% during all nights studied. The time spent at less than 90% (\text{SpO}_{2}\text{ <90}) and 85% (\text{SpO}_{2}\text{ <85}) did not differ each night. Heart rate was greater (mean 90.1 (SD 16.6) vs 68.2 (12.0) beat min\textsuperscript{-1}, P < 0.001) during the second night after operation (N\text{post}) than during N\text{pre}. Before operation, the number of desaturations, \text{SpO}_{2}\text{ <90} and \text{SpO}_{2}\text{ <85} correlated with pharyngeal hypertrophy (P = 0.003, P = 0.002, P = 0.001, respectively). At the same time, \text{SpO}_{2}\text{ <90} and \text{SpO}_{2}\text{ <85} correlated with body mass index (P = 0.02 and P = 0.05, respectively). During N\text{post}, \text{SpO}_{2}\text{ <90} correlated with radiological lung consolidation (P = 0.05) and \text{SpO}_{2}\text{ <85} correlated with FEV\textsubscript{1} (P = 0.03). We conclude that there are several mechanisms responsible for oxygen desaturation and that these mechanisms differ before and after surgery.

KEY WORDS

Complications: oxygen desaturation. Sleep: postoperative

Pulse oximetry allows continuous monitoring of postoperative oxygen saturation and has revealed desaturation [1, 2]. Arterial desaturation is known to occur from the onset of anaesthesia [3] and is increased by surgery [4]. Hypoxaemia results mainly from reduction in residual functional capacity [5] which favours atelectasis and ventilation-perfusion mismatch [6]. After operation, other factors such as sleep apnoea in response to upper airway obstruction or nocturnal hypventilation resulting from central respiratory depression may induce hypoxaemia, especially when opioids are used [2]. These events may be favoured by factors such as age more than 50 yr [7], obesity [8] or heavy snoring associated with inspiratory oropharyngeal collapse [9]. Previous studies of postoperative oxygen saturation have been conducted in patients who did not receive hypnotics the night before surgery or oxygen supplementation in the postoperative course. However, both therapies are used routinely in order to minimize preoperative anxiety and insomnia, and postoperative severe oxygen desaturation, respectively [10]. This study was designed to assess the risk factors for oxygen desaturation during sleep in the perioperative period of major abdominal and vascular surgery, in an unselected population of patients who had received hypnotics before operation and nasal oxygen therapy after operation.

PATIENTS AND METHODS

Patients, anaesthesia and monitoring

We studied 31 consecutive patients undergoing major abdominal or vascular surgery (21 aortic replacements, five colonic resections, five miscellaneous). Two patients were excluded because they could not be weaned from mechanical ventilation before the first night after operation and therefore 29 patients (23 male) were included in the study. All gave informed consent and the project was approved by the Ethics Committee of our institution. In the week before surgery, patients underwent routine chest radiography and lung function testing, including arterial blood-gas analysis. The day before surgery, we collected the following data: age, gender, size, weight, body mass index (kg m\textsuperscript{-2}) and smoking habits (packs yr\textsuperscript{-1}). The patients and their relatives were questioned concerning snoring which was graded from 0 to 3 (0 = never snore; 1 = light or intermittent snoring; 2 = daily and moderate snoring; 3 = daily heavy snoring, disturbing the bed partner). Careful examination of the oropharyngeal cavity was performed. Thickened mucosa, narrow velopharyngeal space, hypertrophy of the soft palate were assessed as 0 (normal) to 3 (marked hypertrophy).
During the night before operation (N<sub>pre</sub>) and the first three nights after operation (N<sub>i</sub> - N<sub>3</sub>), oxygen saturation was monitored continuously at the bedside (from 21:00 to 07:00) using a Nellcor N200 monitor and a disposable finger probe. The night before operation, patients received routine premedication comprising flunitrazepam 1 mg orally at 20:00 and also at 06:30 on the operative day. Before surgery and after an extradural catheter had been inserted at the T10 level and a radial artery catheter had been inserted for arterial pressure monitoring, anaesthesia was induced with pentobarbitone 7 mg kg<sup>-1</sup>, fentanyl 3 μg kg<sup>-1</sup> and vecuronium 0.1 mg kg<sup>-1</sup>. The trachea was intubated and the lungs ventilated mechanically with 60% nitrous oxide in oxygen. Anaesthesia was maintained with 0.8 MAC of isoflurane and extradural doses of a 50% mixture of 2% lignocaine and 0.5% bupivacaine. After surgery, patients were kept in the recovery room until complete rewarming occurred and the trachea had been extubated, which always occurred within 6 h after operation. Thereafter they were admitted to the surgical intensive ward where they stayed for at least three days after operation. Oxygen was administered continuously, in all cases via a nasal cannula at a rate of 4 litre min<sup>-1</sup> until the end of the third day after operation. Extradural analgesia was continued for the first 48 h after operation, with a continuous infusion of 0.125% bupivacaine at a rate of 7-10 ml h<sup>-1</sup> (with or without boluses of preservative-free morphine sulphate 3 mg in 9% saline 10 ml, every 12 h at the discretion of the anaesthetist in charge of the patient). All patients had been anaesthetized by the same six anaesthetists. Four routinely prescribed extradural opioids with bupivacaine whereas the other two preferred to give i.v. paracetamol, if needed, instead of extradural morphine. Chest x-ray was performed in a semi-recumbent position at the bedside on the morning of the second day after operation. This was scored 0 = normal or identical to the x-ray before operation; 1 = slight basal limited consolidations; 2 = one lobar consolidation; 3 = more than one lobe consolidated. On each study night, including the preoperative night, the patient’s care was unrestricted and standard nursing procedures were applied. These included postoperative hourly recording of invasive arterial pressure, heart rate, oxygen saturation (Sp<sub>O<sub>2</sub></sub>), urine output and other standard clinical variables. In all cases efforts were made to preserve the patient’s sleep: the room was dimly lit, and nursing care was limited at night to mandatory procedures.

**Data collection and processing**

The Nellcor N200 pulse oximeter is equipped with a memory capacity to store Sp<sub>O<sub>2</sub></sub> and heart rate (HR) in a compressed database. Each 5-s period is averaged by the oximeter and stored in the 12-h memory set. For offline analysis, the raw Sp<sub>O<sub>2</sub></sub> and HR data were transferred from the oximeter memory to an IBM compatible computer via the RS232 output of the monitor, using a specially designed program (courtesy of M. Gauté, CMC Foch, Suresnes, France). During this procedure, the computer rejected Sp<sub>O<sub>2</sub></sub> or HR artefacts. Artefacts were considered to be present if one of these two variables reached zero values, or if Sp<sub>O<sub>2</sub></sub> decreased by more than 25% from one 5-s average value to another. Artefactual data points were replaced by blank values so as not to change the time scale of the record. In addition, each record was reviewed on screen by the same investigator for cross validation.

We computed the modal Sp<sub>O<sub>2</sub></sub> (Sp<sub>O<sub>2</sub></sub>modal) for each night (i.e. the mode of the Sp<sub>O<sub>2</sub></sub> distribution)[11] (fig. 1) and the modal heart rate (HR<sub>modal</sub>) of both Sp<sub>O<sub>2</sub></sub> and HR during the night was expressed as the SD of the corresponding frequency distribution. In order to assess the oxygen desaturation phenomena, for each study night and each patient, we computed the percentage of total time in bed spent with Sp<sub>O<sub>2</sub></sub> values less than 90% and the number of episodes of desaturation corresponding to a decrease in Sp<sub>O<sub>2</sub></sub> to less than this value. This threshold was chosen arbitrarily to describe moderate hypoxaemia. Also, the smallest Sp<sub>O<sub>2</sub></sub> value recorded during each desaturation less than 90% was individualized and averaged throughout the night (Sp<sub>O<sub>2</sub></sub> nadir). The percentage of time spent at less than 85% Sp<sub>O<sub>2</sub></sub> was computed also as an index of severe hypoxaemia [12].

**Data analysis and statistics**

Values are expressed as mean (sd). Characteristics of the patients who received extradural morphine and those who received bupivacaine alone were compared using Student's t test (table II). The variables from the postoperative nights were compared for differences per day, by two-way ANOVA, including Tukey multiple range tests (table III). The second night after operation was considered to be of particular interest and was compared with the preoperative night by Wilcoxon tests (table III). For the different oxygenation variables, correlations were performed between measurements made during N<sub>pre</sub> and N<sub>3</sub> by Pearson linear regressions.

Possible associations with desaturation (i.e. age,
body mass index, snoring, pharyngeal hypertrophy, FEV\textsubscript{1}, opioid therapy and radiological consolidations) were identified by multiple linear correlations (table IV) [13].

## RESULTS

The principal characteristics of the patients are presented in table I. Six patients were overweight (BMI > 27 kg m\textsuperscript{-2}), 23 patients smoked (79%) and three had obstructive lung disease (FEV\textsubscript{1}/FVC < 70% of predicted values). Eighteen patients (62%) did snore, and seven (24%) snored heavily (score = 3). The score for snoring was, on average 0.89 (0.86).

Pharyngeal hypertrophy was observed in nine patients (31%) with a mean score of 0.48 (0.87) for the study group. Those who received extradural morphine before operation (16/29), in addition to bupivacaine, did not differ from those who received only plain 0.125% bupivacaine (13/29) (table II). The duration of surgery was 3.3 (0.6) h and was uneventful in all patients. Thirteen patients (45%) had lung consolidations on the second day after operation (mean postoperative radiological score 0.79 (1.05)).

We found that the second night after operation differed from N\textsubscript{1} and N\textsubscript{2} in the size of HR\textsubscript{modal} (P < 0.05). The other variables describing oxygenation at N\textsubscript{1} were also slightly different from those recorded during N\textsubscript{2} and N\textsubscript{3}. However, these differences did not reach statistical significance. HR\textsubscript{modal} was greater than 95% on average, during all the nights studied (table III) and the average HR\textsubscript{modal} did not differ statistically each night.

HR\textsubscript{modal} was 32% greater (90.1 (16.6) vs 68.2 (12.0) beat min\textsuperscript{-1}, P < 0.001) during N\textsubscript{2} than during N\textsubscript{pre}. The patients with the smallest HR\textsubscript{modal} values before operation had the greatest number of desaturation episodes and the greatest time spent with Sp\textsubscript{O\textsubscript{2}} less than 90% and 85% before operation (r = 0.58, P = 0.001; r = 0.64, P = 0.0001 and r = 0.52, P = 0.005, respectively). A highly significant correlation was found at N\textsubscript{2} between Sp\textsubscript{O\textsubscript{2}}\textsubscript{modal} and the time spent with Sp\textsubscript{O\textsubscript{2}} less than 90% and 85% (r = -0.70, P = 0.00005 and r = -0.55, P = 0.009, respectively). However, the regression between Sp\textsubscript{O\textsubscript{2}}\textsubscript{modal} and the number of desaturations was not significant during N\textsubscript{2}. The degree of Sp\textsubscript{O\textsubscript{2}} abnormality after operation did not correlate with that measured before operation. Finally, there was no correlation between pharyngeal hypertrophy and postoperative lung consolidations.

We tested the role of several risk factors in nocturnal hypoxaemic events. Two dependent variables (pharyngeal hypertrophy and body mass index) were related to the incidence of desaturation

### Table I. Prooperative clinical characteristics of patients (n = 29) (mean (SD) [range]). BMI = Body mass index. FEV\textsubscript{1} = forced expiratory volume over 1 s, FRC = functional residual capacity, expressed as percentage of predicted values according to age, size and weight [34]. Hospital stay starts on the operative day

<table>
<thead>
<tr>
<th>Variables</th>
<th>Preoperative clinical characteristics of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>61.7 (3.9)</td>
</tr>
<tr>
<td>BMI (kg m\textsuperscript{-2})</td>
<td>24.6 (15.7)</td>
</tr>
<tr>
<td>Smoking habit (packs yr\textsuperscript{-1})</td>
<td>5.1 (3.1)</td>
</tr>
<tr>
<td>P\textsubscript{aCO\textsubscript{2}} (kPa)</td>
<td>11.5 (1.7)</td>
</tr>
<tr>
<td>P\textsubscript{aO\textsubscript{2}} (kPa)</td>
<td>4.8 (0.7)</td>
</tr>
<tr>
<td>FEV\textsubscript{1} (% of predicted)</td>
<td>80.4 (18.1)</td>
</tr>
<tr>
<td>FRC (% of predicted)</td>
<td>92.7 (24.5)</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>14.9 (7.4)</td>
</tr>
</tbody>
</table>

### Table II. Characteristics of patients according to analgesia regimen (mean (SD) [range]). There were no significant differences between the two groups (Student’s t test)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Extradural morphine</th>
<th>No extradural morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>59.2 (6.8)</td>
<td>64.8 (49.8-69.8)</td>
</tr>
<tr>
<td>BMI (kg m\textsuperscript{-2})</td>
<td>24.1 (4.4)</td>
<td>25.3 (3.5)</td>
</tr>
<tr>
<td>Snoring index (0-3)</td>
<td>0.87 (0.95)</td>
<td>0.92 (0.75)</td>
</tr>
<tr>
<td>Pharyngeal hypertrophy (0-3)</td>
<td>0.44 (0.80)</td>
<td>0.53 (0.89)</td>
</tr>
<tr>
<td>FEV\textsubscript{1} (% of predicted)</td>
<td>81.4 (16.7)</td>
<td>79.2 (20.9)</td>
</tr>
<tr>
<td>FRC (% of predicted)</td>
<td>93.2 (28.3)</td>
<td>92.0 (20.1)</td>
</tr>
<tr>
<td>X-ray changes (% of predicted)</td>
<td>0.68 (0.87)</td>
<td>0.69 (0.85)</td>
</tr>
<tr>
<td>Smoking habit (packs yr\textsuperscript{-1})</td>
<td>23.0 (17.6)</td>
<td>30.7 (27.2)</td>
</tr>
<tr>
<td>Duration of surgery (h)</td>
<td>3.2 (0.5)</td>
<td>3.6 (0.6)</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>16.7 (6.6)</td>
<td>12.7 (5.5)</td>
</tr>
</tbody>
</table>

### Table III. Saturation profile for the night before operation (N\textsubscript{pre}) and the first three nights after operation (N\textsubscript{1}-N\textsubscript{3}). Values are mean (SD) [range]. * P < 0.05 N\textsubscript{pre} compared with N\textsubscript{p} (Tukey’s multiple range test); *** P < 0.001 N\textsubscript{pre} compared with N\textsubscript{p} (Wilcoxon test)

<table>
<thead>
<tr>
<th>Night</th>
<th>Sp\textsubscript{O\textsubscript{2}}\textsubscript{modal} (%)</th>
<th>Sp\textsubscript{O\textsubscript{2}} &lt; 90% (%)</th>
<th>Sp\textsubscript{O\textsubscript{2}} &lt; 85% (%)</th>
<th>Number of desaturations (%)</th>
<th>Sp\textsubscript{O\textsubscript{2}}\textsubscript{median} (%)</th>
<th>HR\textsubscript{modal} (beat min\textsuperscript{-1})</th>
<th>Standard deviation of Sp\textsubscript{O\textsubscript{2}} distribution (%)</th>
<th>Standard deviation of HR distribution (beat min\textsuperscript{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>N\textsubscript{pre}</td>
<td>95.0 (2.3)</td>
<td>5.1 (11.0)</td>
<td>0.5 (1.4)</td>
<td>38.0 (57.2)</td>
<td>81.2 (5.0)</td>
<td>68.2 (12.0)**</td>
<td>1.8 (0.5)</td>
<td>6.6 (3.8)</td>
</tr>
<tr>
<td>N\textsubscript{1}</td>
<td>97.4 (2.4)</td>
<td>1.9 (3.2)</td>
<td>0.7 (1.9)</td>
<td>27.8 (30.7)</td>
<td>83.8 (5.4)</td>
<td>83.9 (15.1)</td>
<td>1.9 (1.5)</td>
<td>6.7 (5.3)</td>
</tr>
<tr>
<td>N\textsubscript{2}</td>
<td>95.9 (3.5)</td>
<td>8.1 (16.5)</td>
<td>2.4 (6.0)</td>
<td>55.3 (48.0)</td>
<td>82.2 (6.0)</td>
<td>90.1 (16.6)**</td>
<td>2.4 (1.4)</td>
<td>7.3 (4.8)</td>
</tr>
<tr>
<td>N\textsubscript{3}</td>
<td>96.2 (2.8)</td>
<td>6.2 (14.2)</td>
<td>1.9 (4.5)</td>
<td>26.4 (24.1)</td>
<td>81.6 (6.7)</td>
<td>83.7 (11.0)</td>
<td>2.5 (1.7)</td>
<td>6.8 (3.8)</td>
</tr>
</tbody>
</table>
during the night before operation (table IV). Indeed, the clinically assessed level of pharyngeal hypertrophy was the major variable, which accounted for about 30% of the variability in the number of desaturations and the time spent with SpO₂ less than 90% and 85% \( (r^² = 0.31, 0.32, 0.34, \text{ respectively}) \). Body mass index also correlated but was highly correlated with pharyngeal hypertrophy (table IV). When N₄ was analysed, the score for radiological lung consolidations was significantly different from zero \( (0.79 (1.04) \, P < 0.001) \) and the amount of consolidations correlated with SpO₂ modal \( (r^² = 0.13) \), and with the time spent with SpO₂ less than 90% \( (r = -0.13) \). FEV₁ was found to be an independent predictor of SpO₂ nocturne \( (P = 0.03, r^² = 0.15) \).

The number of artefacts recognized during the analysis and checked visually on every night record did not vary significantly during the study \( (\text{range 2.9-4.8% of the records}) \).

**DISCUSSION**

We have found that pharyngeal hypertrophy appeared to be a major risk factor for preoperative desaturation, whereas lung consolidations accounted only partly for postoperative hypoxic events.

We used pulse oximetry in order to monitor oxygen saturation continuously. This is the only technique available to assess sleep desaturation in the postoperative period \([1, 10, 14]\). Artefacts may occur and therefore records must be validated carefully. This was done in all recordings using a double approach. First we performed an automated rejection of the periods of signal loss. This method did not identify all these episodes and therefore each record was checked visually twice and again validated. The percentage of each study night corresponding to true artefacts which were rejected was small and was not significantly different between nights. Therefore, we believe that the SpO₂ measurements reported here are reliable.

The need for multiple reference nights has also been considered in the design of this study. Nevertheless, a "first night effect" (i.e. the occurrence of a lighter sleep on the first night in polysomnographic studies) has been documented for sleep variables but not for respiratory ones \([15]\). Accordingly, for simplicity, we chose to restrict the study of the preoperative period to the night immediately before operation. This night was of specific interest because patients were premedicated with flunitrazepam. In our experience, this reduces patient anxiety and increases preoperative comfort. However, such premedication was likely to increase the incidence of desaturation during sleep. Thus, it would have been of great interest to record another night before operation, without premedication, in order to provide a true in-hospital control night. Unfortunately, we could not consider such a procedure because patients were admitted to hospital on the day before surgery.

The population we studied was unselected and should be a representative sample of patients undergoing major abdominal and vascular surgery. Sixty-five percent of patients studied had vascular disease. The group included a majority of males aged approximately 61 yr and most of them were smokers. Consequently, the risks for sleep-related breathing disorders should have been larger in our group than in the general population \([16, 17]\). Indeed, six patients \( (21\%) \) spent more than 5% of the total time in bed with an SpO₂ value less than 90% and 11 \( (38\%) \) had more than 30 episodes of desaturation per night during the preoperative night. Although we did not measure ventilation or sleep pattern during this study, we suspect sleep apnoea syndrome plays a major role in the genesis of the hypoxaemic events we observed at night, both before and after operation.

Flunitrazepam is likely to increase the incidence of preoperative desaturation in sensitive subjects \([18, 19]\). Indeed, benzodiazepines are known both to depress central control of ventilation \([20]\) and to augment airway collapse \([21]\). However, a study by Midgren and colleagues \([22]\) conflicts with these findings. They reported that a single dose of nitrazepam or flunitrazepam did not alter the sleep profile or the number and severity of oxygen desaturations in stable hypoxaemic, non-hypercapnic patients with chronic lung disease.

All our patients received routine oxygen supplementation, according to our usual practice. This
is probably the reason why $S_{\text{PO}_2\text{ modal}}$ was maintained after operation at the value before operation. From our data, we conclude that the $S_{\text{PO}_2}$ profile did not change significantly from $N_1$ to $N_2$ and despite postoperative oxygen therapy, some patients experienced marked desaturation. These results are in accord with the recent study by Reeder and co-workers [23], who reported much smaller $S_{\text{PO}_2}$ values in patients who did not receive postoperative oxygen therapy. Moreover, several patients breathing air experienced severe desaturation during the night. Thus, routine oxygen therapy in our population of smokers with mild lung disease undergoing major vascular surgery appears a simple protective measure.

Oxygen is known to interfere with saturation profile during sleep in several ways. Hudgel, Hendricks and Dadley [24] demonstrated in patients with pharyngeal hypertrophy and obvious snoring that breathing 50% oxygen induced a 25% increase in sleep apneic time, whereas mean $S_{\text{PO}_2\text{ nadir}}$ increased from 87% to 96%. Accordingly, Jones and colleagues [10] showed that oxygen increased $S_{\text{PO}_2\text{ modal}}$ during the first 12 h after operation but did not change the rate of central and obstructive apnoea. Hence, the administration of oxygen decreases the gain in the ventilatory control system and thereby increases the duration of apnoea or hypventilation periods. However, oxygen improves gas exchange and enables $S_{\text{PO}_2\text{ modal}}$ to increase. Then $P_{\text{AO}}$ remains on the flat portion of the oxygen dissociation curve of haemoglobin. Therefore, oxygen saturation at the end of an apnoea or an episode of hypventilation might be smaller if no oxygen had been administered [25, 26]. As expected, $S_{\text{PO}_2\text{ modal}}$ correlated with the severity of desaturation. The patients who had the most hypoxic basal value (smallest $S_{\text{PO}_2\text{ modal}}$) experienced the greatest desaturation episodes before and after operation.

When we analysed the aetiological factors for perioperative desaturation we found that they differed before and after operation. Hypertrophy of the upper airway, which was linked with excess weight, was related to the genesis of sleep-related breathing disorders, confirming what is well established [27]. Upper airways may be narrowed globally by obesity or locally by tonsillar or palatal hypertrophy [28]. The upper airway may also be more compliant than normal, leading to inspiratory collapse. Clinically, assessing pharyngeal hypertrophy detected only patients with oropharyngeal restriction and not those with functional inspiratory narrowing or with airway narrowing located elsewhere [9]. More sophisticated techniques such as CT scan or acoustic reflection techniques [29] would have been needed to quantify extrapharyngeal abnormalities. However, despite possible limited sensitivity in our scoring method, simple clinical examination was still predictive of preoperative desaturation in premedicated patients.

After operation, radiological abnormalities and extent of reduction in FEV1 correlated best with desaturation. These factors overwhelmed the effect of pharyngeal hypertrophy but accounted for only 11% of total variability in the model. In contrast with recent studies, we did not find any relationship between the severity of preoperative hypoxaemia and that in the postoperative period [14, 22]. However, the patients studied by these authors breathed air after operation in most cases.

The administration of morphine 3 mg extradurally every 12 h, with 0.125% bupivacaine was not associated with an increased risk of postoperative desaturation which is consistent with the literature, although the risk of ventilatory depression with opioids is low [30]. In a study of postoperative patients, Rosenberg and colleagues [31] showed that parenteral opioid analgesia did not increase the rate or severity of desaturation, in contrast with other studies [2, 32]. Oral administration of opioids has also been shown not to induce sleep disordered breathing in healthy adults [33]. However, induction of respiratory depression by opioids is dose dependent. In our study, the doses of both bupivacaine and morphine used were minimal and probably not sufficient to induce complete pain relief. Thus, residual pain may have been sufficient to antagonize respiratory depressant effects of the opioids.

REFERENCES


