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Editorial

Sedation for fibreoptic bronchoscopy

The fibreoptic bronchoscope has extended the range of examination of the bronchial tree and increased the ease with which the examination can be carried out. With this has come the realisation that the procedure has its risks. The various audits of bronchoscopic practice[1-6] have reported mortality rates of 0·01–0·5% and major complication rates of 0·08–5% (table 1). Most deaths and complications arise from the procedure itself, but at least five deaths and up to half of the major life threatening complications have been related to the sedative regimen used. Deaths associated with sedation for endoscopy but due to other causes (for example, tension pneumothorax) are reported separately.[7,8] This has led to an increased awareness of the need for a satisfactory sedative regimen for bronchoscopy.

Techniques available

Fibreoptic bronchoscopy may be performed without sedation[2,6,9] and in one study this technique was found to be very acceptable to patients.[9] In another study, however, 60% of patients reported their bronchoscopy without sedation as very unpleasant or intolerable.[10] Standard bronchoscopic practice in the United Kingdom includes some sedative regimen. Of 227 physicians routinely performing fibreoptic bronchoscopy, only 6% routinely used no sedative.[6] Drugs were given as parenteral premedication by 47% and as intravenous sedation during the procedure by 17%; 19% used both premedication and intraoperative sedation and 12% administered a general anaesthetic.

Table 1 *Reported mortality rates and incidences of major complications associated with fibreoptic bronchoscopy*

Reference	*Mortality rate (%)*	*Major complications (%)*	*No of procedures*
Credle 1974[1]	0·01	0·08	24521
Suratt 1976[2]	0·02	0·30	48000
Pereira 1978[3]	0·10	1·70	908
Dreison 1978[4]	0·50	5·00	205
Lukowsky 1981[5]	0·00	0·30	1146
Simpson 1986[6]	0·04	0·12	4000

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The sedative drugs preferred were an opioid and a benzodiazepine, alone or in combination, though some endoscopists use more complex regimens.

Drugs available

DIAZEPAM

Diazepam has an elimination half life of 24–57 hours in normal subjects. Its action is prolonged by its active metabolites, particularly desmethyldiazepam, which is eliminated more slowly than diazepam. Clearance of diazepam is slower in males than in females and is increased in cigarette smokers. The elimination half life of diazepam increases with age.[11] Diazepam causes respiratory depression, though the ventilatory response to carbon dioxide appears to be relatively well preserved.[12]

In patients with liver disease there is a decreased clearance, prolonged elimination half life, an increased volume of distribution, and decreased protein binding of diazepam.[13-18] The clearance of desmethyldiazepam is also reduced. These changes produce a greater degree of sedation and a significantly slower recovery after administration of diazepam,[19,20] the greatest sedation being in the most severely ill.[18,19] Renal disease does not alter the pharmacokinetics or pharmacodynamics of diazepam to any clinically important extent.[21]

MIDAZOLAM

Midazolam is a water soluble benzodiazepine with an elimination half life of about two hours[22] and a rapid onset and short duration of action in normal subjects.[23] Its primary metabolite is pharmacologically active but has a shorter half life than midazolam itself.

The dose requirements for midazolam differ between the sexes, males requiring about 1 mg more than females.[24] There is a strong association between dose requirement and age; elderly patients are particularly sensitive to midazolam,[7,8,25,26] and extreme caution is recommended with its use in the elderly.[24] Like other benzodiazepines, midazolam causes respiratory depression. With low doses the decreased tidal volume is compensated for by an increased respiratory rate[27]; with larger doses this compensation mechanism is lost and hypoxaemia or apnoea may occur.[28,29]

In about 6% of the population midazolam has a prolonged action, probably due to impaired metabolism and thus accumulation of the drug.[30] In patients

with liver disease the pharmacokinetic and pharmacodynamic alterations appear to be related to the degree of liver impairment and to a history of previous encephalopathy. Patients with compensated liver disease have a normal pharmacokinetic profile of midazolam,[31 32] but the effect of the drug is prolonged in patients with severe liver disease.[19 31 33 34] Patients with chronic renal failure have an increased volume of distribution and clearance of midazolam[35] but the clinical effects of these alterations are minimal.

FLUMAZENIL

Flumazenil is a specific benzodiazepine antagonist with an elimination half life of about one hour in normal volunteers.[36] Flumazenil reverses the effects of both diazepam[37] and midazolam,[38] but its short elimination half life means that repeated bolus doses or continuous infusions are needed to avoid resedation in the case of substantial benzodiazepine accumulation.[39] Appropriate doses of midazolam may be reversed by flumazenil with little risk of resedation. Memory is regained from the time of administration of flumazenil with preservation of amnesia for the procedure. The usual dose required is 0·3–0·6 mg. Flumazenil may precipitate a withdrawal syndrome if given to patients taking benzodiazepines regularly.[40]

MORPHINE

Morphine is usually given as papaveretum to patients undergoing bronchoscopy. It has an elimination half life of 2·5 hours[41] and the elderly are especially sensitive to its effects. Like all opioids, morphine may produce profound respiratory depression.

Patients with compensated liver disease have a normal pharmacokinetic profile for morphine.[42] Patients with severely impaired liver function[43] or reduced liver blood flow due to septic shock,[44] however, have reduced clearance. In patients with renal failure morphine is metabolised normally but the metabolites are not eliminated. Morphine has several active metabolites, including morphine-6-glucuronide[45] and normorphine.[46 47] Morphine-6-glucoronide is particularly potent in animals[45] and its accumulation in patients with renal failure leads to clinical signs of opioid intoxication.[48 49]

PETHIDINE

Pethidine has an elimination half life of 3·2 hours in normal subjects. It also produces respiratory depression, and its cardiovascular depressant effect is thought to be greater than that of morphine.[50] Plasma concentrations of pethidine are increased in the elderly. The clearance of pethidine is also decreased in patients with impaired liver function.[51] Pethidine is metabolised to norpethidine and accumulation of this after repeated dosage or in patients with renal failure may lead to central excitatory effects, including convulsions.[52]

ALFENTANIL

Alfentanil has an elimination half life of 98 minutes in healthy subjects[53]; it is extensively redistributed and rapidly metabolised to inactive products. A reduced clearance of alfentanil is seen in the elderly[54] and a subset of the normal population,[55] possibly due to a reduced metabolic capacity of the liver. Alfentanil clearance is decreased in patients with impaired liver function.[56–58] There is no corresponding pharmacodynamic information but the results suggest an increased sensitivity to alfentanil and a prolonged effect in patients with liver disease. Clearance of alfentanil is unchanged in patients with renal failure.[59]

NALOXONE

Naloxone is a specific opioid antagonist; in the normal subject it has a high hepatic extraction and an elimination half life of about one hour.[60] Studies in patients with septic shock have shown profoundly decreased clearance, thought to be due to decreased liver perfusion.[61]

LIGNOCAINE

The elimination half life of lignocaine varies considerably, being two to three hours in normal subjects.[62–64] It is rapidly absorbed from mucosal surfaces and the gastrointestinal tract but undergoes extensive first pass metabolism. Hepatic metabolism produces active metabolites,[65] which are thought to contribute to its toxicity. The clearance of lignocaine is decreased in patients with chronic liver disease.[66 67] Lignocaine toxicity is generally due to overdose. Initial signs include circumoral paraesthesia and anxiety progressing to convulsions, cardiac arrhythmias, and cardiovascular collapse.

Choice of technique

The aim of sedation for bronchoscopy is to provide patients with comfort so that they will cooperate with the investigation and if necessary be willing to return for a repeat procedure. Drugs are therefore used to provide amnesia for the procedure, anxiolysis, and appropriate analgesia. Sedation is not necessary and may reduce the patient's cooperation. The properties desirable in such an agent are detailed in table 2. Since bronchoscopy is frequently performed as a day case procedure, an appropriate technique should allow a rapid throughput of patients with a short stay in the ward, efficient use of beds, and minimal nursing requirements.[68] No single agent provides amnesia, anxiolysis, and analgesia, so a combination of drugs is necessary. A benzodiazepine will provide amnesia and

Table 2 *Properties of an ideal agent to make the patient comfortable during fibreoptic bronchoscopy*

Has rapid onset of action
Has short duration of action and safe reversal
Allows rapid recovery
Safe:
Cardiovascular stability
No respiratory depression
No risk of hypoxaemia
No unwanted side effects
Produces amnesia
Produces anxiolysis
Cheap

anxiolysis, and analgesia is usually provided by local anaesthesia or an opioid. The regimen should be simple and the degree of sedation kept to the minimum compatible with the patient's comfort.[28 69-71]

The use of opioids has been questioned.[28 70 72 73] They have no intrinsic amnesic or anxiolytic properties and analgesia can be provided as effectively with local anaesthesia.[74] The advantage of the antitussive effect of opioids is unproved as temazepam[74] and diazepam[10] suppress cough to the same extent as papaveretum. The most important complication of opioids is profound respiratory depression. Opioid sedation is consistently associated with respiratory depression[74-76] and a greater degree of hypoxaemia than the benzodiazepines,[28 70 72-74 77] particularly when used in combination with another agent.[28 71] The risk of aspiration of gastric contents may be increased by opioids[75]; thus opioids may not be appropriate for short stay patients' endoscopy.[78]

Benzodiazepines produce amnesia and anxiolysis but no analgesia. The acceptability of the procedure to patients is correlated with amnesia.[76 79 80] The incidence and severity of respiratory depression is lower with benzodiazepines than with opioids.[74] Unless they are used carefully, however, patients may be less cooperative after administration of benzodiazepines than with opioids.[74]

Choices of agents

Midazolam has theoretical advantages over diazepam because of its shorter elimination half life and lack of metabolites with a prolonged action.[23] Paradoxically, a better recovery has been thought to occur with diazepam[19 81 82]; in some cases this is due to the use of a relatively high dose of midazolam. Midazolam has two to three times the potency of diazepam.[79 83]

Midazolam has a more rapid onset of action than diazepam,[83] produces a greater degree of amnesia,[77 79 80 83 84] and is more acceptable to patients.[77 79 80] The degree of respiratory depression and oxygen desaturation is similar with the two drugs.[85] The recommended dose of midazolam for conscious sedation is 0·07 mg/kg,[86] as little as 1–2 mg being required in the elderly.[87] Careful titration of the dose is recommended.

Local anaesthesia should provide the necessary analgesia for bronchoscopy when benzodiazepine is used for sedation. The safe dose of lignocaine for infiltration is 3 mg/kg, toxicity being associated with a plasma concentration of 5 μg/ml. A survey of British bronchoscopists showed that the average dose of lignocaine used was 342 (range 100–960) mg and the maximum dose 368 (range 100–1180) mg.[6] Some studies have suggested that doses higher than those recommended may be safe[62-64] as much of the administered lignocaine may be swallowed or aspirated by suction.In these three studies peak plasma concentrations of lignocaine occurred between five and 90 minutes after administration and plasma concentrations of lignocaine above the toxic limit were seen in patients with impaired liver function. The recommended dose of 3 mg/kg should not be exceeded in patients with liver disease, and any patient receiving more than this dose should be closely monitored for at least 90 minutes after the procedure.

Reversal of sedation

The availability of specific antagonists for both opioids and benzodiazepines has led to their use in reversing sedation after endoscopy. The advantages of this technique are that the patient is rapidly awake and self caring and has a better comprehension of any postoperative instruction. It also reduces the need for recovery time and facilities. Some dangers, however, are inherent in this technique. Both flumazenil and naloxone have short half lives. The half life of flumazenil is less than half that of midazolam in normal subjects and considerably less in individuals who are slow metabolisers. There is therefore a risk of resedation when the action of flumazenil ends. This risk is greater if flumazenil is used to reverse the action of diazepam[88] or if the reversal agent is given intravenously after intramuscular administration of the agonist. Resedation with opioids after reversal with naloxone is almost inevitable as most of the opioids used have an elimination half life two to three times that of naloxone. Another danger with the use of reversal agents is the temptation to use higher doses of agonist to achieve perfect conditions. This has already been suggested for midazolam[37] but is likely to result in an increased incidence and severity of side effects.[8]

If these dangers are appreciated, reversal of sedation may be appropriate after bronchoscopy but it should not be used to compensate for inadequate recovery facilities. The patient should still be observed closely in a recovery area, criteria for discharge should not be relaxed, and antagonists should not be given to patients already taking benzodiazepines or opioids in case a withdrawal reaction is precipitated.[88]

Safety

The safety of sedation for bronchoscopy depends not only on the agents used but also on the way their effects are monitored and on the facilities and personnel available. Dental practitioners have strict criteria for the level of staffing and the equipment necessary before drugs producing conscious sedation are administered. Bronchoscopy is usually performed within hospitals with resuscitation teams available and criteria are less formalised; similar standards should nevertheless apply.

PREOPERATIVE ASSESSMENT

Some preoperative assessment and investigation of the patient is required to detect risk factors,[1 2] correct anaemia or cardiac failure,[72] and assess the need for sedation. As aspiration of gastric contents may occur during or after bronchoscopy, patients should be starved for at least four hours before the procedure—though 15% of British bronchoscopists did not routinely starve patients.[6] In this study[6] only 27% routinely established intravenous access before the procedure.

EQUIPMENT

A full range of resuscitation equipment should be immediately available. This equipment should be checked frequently and should allow for head down tilt and pharyngeal suction, for additional oxygen to be administered, for the patient's airway to be controlled, for the patient to have assisted ventilation, and for cardiac arrythmias to be appropriately treated. Equipment for emergency endotracheal intubation was not available to 13% of bronchoscopists and a defibrillator was not available to 32%.[6]

PERSONNEL AND TRAINING

Both the quantity and the quality of staff for a bronchoscopy session are important. A separate individual, preferably a second doctor, should be responsible solely for the administration and assessment of sedation.[8 78] All staff should be trained in the use of the available resuscitation equipment and in resuscitation technique[8]; this training should be assessed and updated frequently.

OXYGEN

Fibreoptic bronchoscopy produces transient hypoxaemia in patients with chronic obstructive airways disease. Cardiac arrhythmias occur during bronchoscopy,[89] usually as the bronchoscope passes through the vocal cords or at the time of maximal hypoxaemia. The hypoxaemia has been attributed to lignocaine spray,[90] sedation,[69 87] partial airway obstruction,[90 91] abnormal distribution of ventilation,[90] previous hypoxaemia,[91] a reflex response to bronchoscopy or lavage,[91 92] and fear of carbon dioxide retention if oxygen is given.[91] It can be reduced by the administration of oxygen during bronchoscopy[69 73 77 92–95] and by avoiding oversedation.[77] Only 18% of bronchoscopists in Britain, however, used oxygen routinely and 9·5% never did.[6]

MONITORING

Physiological variables should be monitored during invasive procedures. This should include some continuous monitoring of ventilation and circulation, either clinical observations or electronic monitoring.[96] Circulation may be monitored by palpation of a pulse, though electrocardiographic monitoring may be valuable in some patients. Continuous monitoring of ventilation is more difficult in a patient whose airway is partially obstructed by a bronchoscope and a pulse oximeter may be valuable.[70]

RECOVERY

After bronchoscopy patients should recover under supervision until ready to go back to the ward or home. Day case patients should fulfil street fitness criteria before discharge. They should be accompanied by a responsible adult and warned not to drink alcohol and not to drive or operate heavy machinery for 24 hours.

Conclusion

The number of patients requiring fibreoptic bronchoscopy has increased rapidly and a sedative regimen for the procedure must be safe in a wide range of circumstances. Although anaesthetists have limited experience of sedation for fibreoptic bronchoscopy, they have extensive experience of sedation for other procedures as well as an in depth practical and theoretical knowledge of the drugs concerned. We hope that some of this knowledge may be useful to doctors carrying out bronchoscopy.

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