Use of midazolam ('Dormicum') and flumazenil ('Anexate') in paediatric bronchology

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Summary

One hundred and seven bronchological examinations using midazolam narcosis in association with flumazenil were carried out in 100 children (mean age 3.5 years, range 4 months to 14 years) suffering from chronic non-specific lung disease. Rigid bronchoscopy was followed in 49 cases by bronchography. All patients were premedicated with atropine followed by midazolam (0.2 mg/kg intravenously). Ventilation was carried out with nitrous oxide and oxygen in 47 children and with oxygen only in 60 patients. After 3 mins, suxamethonium (2 mg/kg intravenously) was given for muscle relaxation and intubation carried out. Fifty-one of the children ventilated with oxygen only also received fentanyl (0.002 mg/kg intramuscularly), at the same time as atropine, to provide analgesia. After extubation, all patients were given flumazenil (0.1 to 0.2 mg intravenously) to reverse the effects of midazolam. The results showed that midazolam provided effective sedation and comfortable sleep (mean examination time 12 min 50 sec) and it was considered that the method using fentanyl rather than nitrous oxide for analgesia was the most satisfactory one. Patients awakened promptly (1 min) after flumazenil and quick and effective expectoration was noted, particularly important in those who had undergone bronchography. No complications were observed. Since this investigation, a further 500 bronchoscopics have been carried out using this method with the same results. Even though no narcosis equipment is required, it is recommended that, as with other procedures involving narcosis with muscle relaxation, bronchoscopy with these drugs should not be used in out-patients.

Key words: Midazolam — flumazenil — bronchology, paediatric

Introduction

The widespread use of bronchological examinations in the diagnosis of chronic non-specific lung diseases in children is mainly based on two techniques. These are the inhalation method using halothane-nitrous oxide-oxygen and the intravenous one using barbiturate-suxamethonium chloride.[11,21] Because inhalation narcosis equipment suitable for use with young children is not available everywhere, there is still a need to develop new, effective and safe techniques for the intravenous method.

The development of flumazenil ('Anexate'†), the first specific benzodiazepine antagonist, highlighted the feasibility of using short-acting imidazobenzodiazepines, particularly midazolam ('Dormicum'†). Flumazenil specifically blocks the central effects of midazolam via the benzodiazepine receptor.[7] The use of these two agents together, therefore, seems to offer promising possibilities for anaesthesia in paediatric bronchology.

This paper reports on our experience using midazolam-flumazenil narcosis in 100 children suffering from chronic non-specific lung disease.

Patients and methods

One hundred and seven bronchological examinations were carried out with the use of midazolam-flumazenil on 100 children suffering from chronic non-specific lung disease seen at the Department of Bronchology between October 1989 and February 1990. There were 66 males and 34 females with a mean age of 3.5 years. Table I gives details of distribution by age and weight and the diseases diagnosed.

Table I. Details of the patient population studied and the bronchoscopic findings: number of patients

Patients	No. patients
Total no. studied	100
Sex: Male	66
Female	34
Age (years):	
0 to 1	26
1 to 3	30
3 to 5	19
Over 5	25
Weight (kg):	
0 to 5	1
5 to 10	30
10 to 15	28
15 to 20	28
Over 20	13
Diagnosis	
Hypoplasia of the cricoid cartilage	4
Tracheal stenosis	9
Stenosis of left main bronchus	13
Other stenoses and divisional disorders	7
Chronic bronchitis	53
Bronchial deformation	14
Bronchiectasis	3
Plastic fibrinous bronchitis	2
Foreign body aspiration	1
Normal bronchi	9

Bronchoscopy was carried out using rigid Friedel and/or Storz bronchoscopes and this was followed by bronchography in 49 instances. Pulse and electrocardiograms were monitored using Hellige Servocard equipment.

†trade marks, Roche

Atropine premedication was used in every case. In 51 patients, fentanyl was given intramuscularly at the same time. Midazolam was administered intravenously 15 or 30 minutes after premedication. Three minutes afterwards the children were relaxed with intravenous suxamethonium chloride. Ventilation was carried out by a mixture of nitrous oxide and oxygen in 47 children and by oxygen alone in the 51 children premedicated with fentanyl and in a further 9 cases. Table II gives details of the schedule used previously with the halothane-nitrous oxide-oxygen method in about 1500 cases per year and with the newly introduced methods using midazolam. Table III lists the drugs used.

Table II. Schedule of narcosis using the 'routine' gas technique and with midazolam in association with flumazenil for bronchoscopy

'Routine' (∝ 1500 cases/year)

Atropine sulphate —15 min— Halothane/N_2O/O_2 (1:1, 2:1) —1 to 2 min— Suxamethonium chloride ↓—(S)—↑ End of relaxation spontaneous awakening

Group 1 (47 cases)

Atropine sulphate —15 min— Midazolam/N_2O/O_2 (1:1, 2:1) —3 min— Suxamethonium chloride ↓—(S)—↑ Flumazenil — Awake (specific reverse)

Group 2 (9 cases)

Atropine sulphate —15 min— Midazolam —3 min— Suxamethonium chloride ↓—(S)—↑ Flumazenil — Awake (specific reverse)

Group 3 (51 cases)

Atropine sulphate/fentanyl —30 min— Midazolam —3 min— Suxamethonium chloride ↓—(S)—↑ Flumazenil — Awake (specific reverse)

(S) = repeat doses of suxamethonium chloride, as necessary. ↓ = intubation, ↑ = extubation

Table III. Drugs used in the study for bronchoscopies

Compound	Concentration	Dose	Administration
Atropine sulphate (EGIS, Budapest)	1 mg/ml	0.01 mg/kg	Subcutaneous
Fentanylum ('Fentanyl', Köbányai, Budapest)	0.05 mg/ml	0.002 mg/kg	Intramuscular
Flumazenil ('Anexate', Roche, Basle)	0.1 mg/ml	0.1 to 0.2 mg	Intravenous
Halothanum ('Narcotan', SPOFA, Prague)	150 g/1 bottle	1.5 vol %	Inhalation
Midazolam ('Dormicum', Roche, Basle)	5 mg/ml	0.20 mg/kg	Intravenous
Suxamethonium chloride ('Sukolin', Orion, Helsinki)	50 mg/ml	1 to 2 mg/kg	Intravenous

Table IV shows the mean times for the duration of the bronchological examinations using the different methods. Overall, the mean time from the administration of midazolam until the end of bronchoscopy was 12 min 50 sec. The longest time was 35 minutes recorded for the foreign body extraction; the shortest time for bronchoscopy was 3 min 40 sec.

Table IV. Duration of bronchological examinations using the different methods: mean (±S.D.) times

Period	Group 1 (n=47)	Group 2 (n=9)	Group 3 (n=51)
From midazolam administration to intubation	4 min 50 sec (±59 sec)	4 min 20 sec (±18 sec)	4 min 58 sec (±52 sec)
From intubation to extubation	7 min 50 sec (±4 min 40 sec)	7 min 10 sec (±2 min 43 sec)	8 min 15 sec (±5 min 3 sec)
Total time	12 min 40 sec (±6 min 3 sec)	11 min 30 sec (±2 min 47 sec)	13 min 10 sec (±5 min 10 sec)

Results

Experience gained from using routine halothane-nitrous oxide-oxygen anaesthesia was taken into consideration when it was decided to investigate the use of midazolam and flumazenil. As a first step, halothane was omitted from the regimen. Three different methods were used in groups of children.

Group 1. Midazolam-nitrous oxide-oxygen-flumazenil anaesthesia: 47 cases

Fifteen minutes after premedication with atropine, midazolam (0.20 mg/kg) was given intravenously. Pulse rate and ECG were monitored continuously. Contact with the older children gradually decreased during the first minute; in infants, a change in behaviour was observed. Inhalation of the nitrous oxide-oxygen mixture was then started. It was found that children struggled against the face mask if it was applied tightly; if gently placed over their face, however, it was calmly accepted. Pulse rate decreased slightly but breathing was unchanged. The children had usually fallen asleep by the end of the third minute. Only the sensation of pain still remained. A short period of apnoea occurred in 1 patient but this was resolved with oxygen ventilation. Three minutes after midazolam administration, i.e. when the child was unconscious, muscle relaxation was induced by suxamethonium chloride and intubation carried out. When necessary, suxamethonium chloride was repeated at half the initial dose, but no additional doses of midazolam were given.

During bronchoscopy, physiological parameters such as pulse and ECG remained stable and sufficient sleep occurred. Relative bradycardia with suxamethonium was seen in 21 (44.7%) patients but this was not more frequent than using the 'routine' inhalation method.

Extubation was done when cough, the most important sign of the relieved breathing, occurred. Immediately after extubation, flumazenil (0.1 to 0.2 mg) was given intravenously. The children had completely woken up in 1 minute; the older ones could speak to the physician and the infants contacted with the doctor in a

way suitable for their age. The change in behaviour was also a positive sign. Productive cough was quickly observed. The intensity and characteristics of this cough are influenced by anatomical findings such as a narrow larynx, by the amount of bronchial discharge and, when bronchography has been carried out, by the contrast medium used.

After flumazenil administration, children were observed in the operating theatre over a 10-minute period. Pulse rate and ECG were monitored. No apnoea or sleep occurred in any of the children. Anterograde amnesia was investigated only in children aged over 5 years. Evaluating the answers obtained to the questions asked concerning the first part of the examination, it was considered that 9 (19.1%) of the 47 children had this. During this observation period, crying occurred in 17 patients and 4 were upset (Table V). This may have been because of the location but it is also possible that it may have been due to the fact that nitrous oxide has only a mild analgesic effect.

Table V. Symptoms and behaviour of the children during the 10-minute observation period after extubation and flumazenil administration: number (%) of patients

Symptoms and behaviour	Group 1 (n=47)	Group 2 (n=9)	Group 3 (n=51)
Apnoea	0	0	2 (3.9%)
Sleep	0	0	0
Anterograde amnesia*	9	0	8
Calm	26 (55.3%)	3 (33.3%)	40 (78.4%)
Crying	17 (36.2%)	3 (33.3%)	8 (15.7%)
Upset	4 (8.5%)	3 (33.3%)	3 (5.9%)

*Assessed in 25 children aged over 5 years

Patients were observed over a further 1-hour period after being returned to the ward. Almost two-thirds of them were fully or partially awake whilst the others were asleep (Table VI). Nevertheless, all of them were awakable and could drink, etc. No complications occurred in any of the children.

Table VI. Behaviour of children during the 1-hour observation period in the ward: number (%) of patients

Behaviour	Group 1 (n=47)	Group 2 (n=9)	Group 3 (n=51)
Asleep	20 (42.6%)	1 (11.1%)	23 (45.0%)
Alert	8 (17.0%)	2 (22.2%)	14 (27.5%)
Partly asleep and partly awake	19 (40.4%)	6 (66.7%)	14 (27.5%)

Group 2. Midazolam-oxygen-flumazenil anaesthesia: 9 cases

In urgent cases, bronchoscopy can be done with minimal medication. Based on the experience of Kortilla and other workers,[10,21] it was decided to carry out bronchoscopy in a small number of patients using midazolam alone with only oxygen ventilation after suxamethonium relaxation (Table II).

There were no differences between the physiological parameters of patients in Groups 1 and 2 during the time preceding bronchoscopy and during broncho-

scopy. During the 10-minute observation period after extubation, 3 of the 9 patients were crying and another 3 were upset. It was considered that these symptoms were probably caused by the lack of analgesic effect of the anaesthesia. There was no pathological change in pulse rate, ECG or breathing. None of the children had apnoea or were asleep (Table V). During the 1-hour observation period in the ward, these children were more awake than those in Group 1 (Table VI).

As a result of the findings in 51 children it was decided to add a narcotic analgesic, fentanyl, to the regimen.

Group 3. Midazolam-fentanyl-oxygen-flumazenil anaesthesia: 51 cases

As premedication, children in this group received fentanyl (0.002 mg/kg) intramuscularly as well as atropine. Hypotension due to fentanyl occurred in 4 (7.8%) older children. Midazolam (0.2 mg/kg) was administered intravenously 30 minutes after premedication and oxygen started 1 minute afterwards. The face mask was applied gently and was well accepted by the children. None of them showed signs of apnoea or excitation and pulse rate and breathing were stable. The patients were relaxed with suxamethonium chloride (2 mg/kg intravenously) 3 minutes after midazolam administration and ventilation continued with oxygen. Relative bradycardia after suxamethonium chloride occurred with a similar frequency (26 patients, 51%) as in the patients in Group 1. Midazolam was not repeated.

Flumazenil (0.1 to 0.2 mg) was injected intravenously when the effect of the muscle relaxant had disappeared, just after extubation. All the patients were awake in 30 seconds. Overstimulation had not occurred. Contact with the older children was good and change in behaviour in the infants showed the end of sleep.

During the 10-minute observation period in the operating theatre, more than three-quarters of the children were calm and only 8 were crying and 3 were upset. As in Group 1 patients, 8 children of those aged over 5 years showed anterograde amnesia. Two children had a short apnoea which was resolved by oxygen ventilation (Table V). During the 1-hour observation period in the ward, there were no significant differences in behaviour and the proportion of children asleep or alert was similar to that in the other two groups (Table VI).

Discussion

Improvement in intravenous anaesthesia was made possible by the introduction of new, non-barbiturate compounds such as the hypnotic tranquillizers,[2,6] e.g. the benzodiazepine, midazolam. Midazolam has been widely used in anaesthesia for short-term surgical interventions and endoscopic examinations.[12-14] Its advantage is quick action and a short elimination time of about 2 hours.[8] For bronchoscopy in adults, midazolam has been used in combination with local anaesthetics and different analgesics, and a number of studies[8,20,23] have underlined its anterograde amnesic effect and good tolerability. For narcosis induction in children, some investigators[3-5] have found a dose of 0.15 to 0.3 mg midazolam/kg to be sufficient; others,[17,18] however, have advised giving even 0.6 mg/kg combined with other hypnotics. Doses of 0.1 to 0.8 mg/kg have been reported for intramuscular premedication.[5,15,19,22,24] From the data in the literature, it was assumed that

midazolam would provide sufficient sleep for paediatric bronchoscopy. In the present study it was decided to use midazolam intravenously to achieve a quick effect and a dose of 0.20 mg/kg was chosen.

Midazolam was tried in three combinations for bronchoscopy: with gas (nitrous oxide) narcosis, in combination with a narcotic analgesic, and without any other medication. In our experience, whilst all three methods proved effective the best was the one using midazolam with fentanyl, patients being calmer and presenting less symptoms of excitation. This combination of a narcotic analgesic and a hypnotic tranquillizer is a variation of neuroleptanalgesia[6] and very close to the ataranalgesia described by de Castro.[2] One important advantage of this method is that there is no need for any narcosis equipment. The special benefit of midazolam is the anterograde amnesia it produces. This we showed occurred in 68% of our patients aged over 5 years.

The specific benzodiazepine antagonist flumazenil provides the possibility of being able to discontinue the effect of midazolam immediately. After its administration patients normally awaken in about 1 minute and in adults they can be assessed by specific tests.[1,16] In our experience in children, a dose of 0.1 to 0.2 mg flumazenil is sufficient to produce awakening. No specific tests were used but the establishment of contact and change in behaviour were employed to assess this had happened. An important sign that the child is alert and that flumazenil has produced its effect is a productive cough. In cases where bronchography has been carried out cough is important for the expectoration of retained contrast medium.

In conclusion, midazolam and flumazenil used in association provide a new, promising method of anaesthesia for paediatric bronchology. Since 1990, this method has become the primary one used in our practice and between May 1990 and February 1991 we have carried out 500 examinations using the technique described for Group 3 patients with the same results. It must be underlined, however, that the use of this method in ambulant patients is not recommended because, as with any narcosis requiring relaxation, there is always the risk of complications developing after 24 hours which may require special ward facilities.

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