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Intensive care sedation: a review of current British practice

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Abstract *Objective*: Sedation is central to the management of intensive care patients. Many different techniques have been tried, all have potential side effects, and some have been associated with serious adverse effects. The aim of this work is to establish current sedation practice in British ICUs; the use of neuromuscular blocking drugs and the indications for their use, the use of sedation policies and scoring systems, the influence of cost on drug choice, and the use of propofol for sedation in paediatric patients. *Design*: A postal survey sent to all units identified in the Directory of Emergency Services. *Results*: Two hundred and fifty-five replies were received from 323 questionnaires (79 % response rate). The replies show that alfentanil, morphine, midazolam, and propofol are the most widely used drugs for sedation, and that changes occur in sedation policy with the time a patient spends in intensive care. Atracurium is the most widely used neuromuscular blocking drug, but the number of patients who receive therapeutic paralysis is relatively small and the indications for its use in different units is consistent. Propofol is used by many ICUs for the sedation of children despite reports linking its use to mortality in children and the advice of the regulatory authorities. *Conclusions*: Drugs used for the sedation of patients in intensive care have changed since previous surveys. The sedation policy of most units relies on the combination of small numbers of drugs. Sedation policies now seem to concentrate on achieving a lightly sedated co-operative patient.

Key words Sedation · Intensive care · Propofol · Benzodiazepines · Opiates · Neuro-muscular block

Introduction

Sedation in the (ICU) is used to provide patient comfort and safety. An ideal regimen is designed to achieve sleep, relaxation, analgesia, amnesia, and the ability to tolerate ventilation. These effects are produced by a combination of drugs, no single drug being able to achieve all the desired effects. Neuromuscular blocking agents may be used in the critically ill patient but they provide neither analgesia nor sedation so must always be used in combination with other drugs. It is generally considered that neuromuscular blocking drugs are required in only a small number of patients with special needs, such as patients with neurological conditions and to enable ventilation in severe ARDS.

Problems with sedative techniques include accumulation of the drug, prolonged effect, depression of the cardiovascular and respiratory systems, and depression of the immune system. The nature of sedation used in any patient can vary widely from producing complete unconsciousness to being nursed awake but comfortable.

Sedation in paediatric practice is difficult because of a lack of data in this group of patients. Propofol is a

Table 1 Distribution of ICUs surveyed. Two hundred and fifty-one completed forms were returned. Out of 213 adult general units 32 also accepted children (27 DGH, 4 teaching hospital). The units that listed themselves as adult general/neurological or adult general/cardiac have been listed in the adult general row. Units that classified themselves as neurological or cardiac are counted in the special category. Three units returned insufficient information and are not included in this table. Numbers in parentheses represent the inter-quartile range for the number of beds in the hospital of that type.

Patients taken	Teaching hospital		District general hospital	
	Number of units	Median no. of beds (inter-quartile range)	Number of units	Median no. of beds (inter-quartile range)
Adult general	46	8 (7–11)	165	5 (4–6)
Special	13	10 (8–11.5)	3	[a]
Paediatric	19	7 (6–9)	2	[b]
Total	78	8 (6–11)	170	5 (4–6)

[a]Units responding had four, six, and eight beds
[b]One unit failed to provide data on number of beds; the other had three beds

popular drug for intensive care sedation in adults and was used widely in children in Britain until 1991 [1]. The reporting of five fatal cases of myocardial failure after propofol infusion in children [2] led to recommendation that it be abandoned for paediatric sedation [3]. Lack of suitable alternative licensed agents led us to believe that it may be still used. Not all children in Britain are managed in dedicated paediatric ICUs. We asked our respondents about their use of propofol in children.

Earlier reviews of sedation in ICUs in the UK [4, 5] have been performed. Since then there have been many alterations in intensive care practice such as the introduction of new modes of ventilation [6], the introduction and widespread acceptance of percutaneous tracheostomy [7], and the increased numbers of physicians with a dedicated interest in intensive care. There has also been the introduction of new drugs such as propofol and alfentanil and the abandonment of several older drugs such as nitrous oxide and phenoperadine. We decided that it was important to establish the current practice of sedation employed in British ICUs.

Materials and methods

We designed a questionnaire (Appendix A) to determine sedation practice employed in an ICU and collect basic data about the respondent unit. Initially, we attempted to communicate with the named director of the British ICUs listed in the Directory of Emergency and Specialist Care Units [8]. If we did not receive a reply a follow-up letter and questionnaire was addressed to 'The Director' of the unit. The initial questionnaire was sent out in November 1997, the follow up was sent out in February 1998, and the last reply was received by the end of April 1998.

We suspected that some units might change sedative regimens on long-term patients so we requested information about drugs used in the first 72 h and those afterwards; this is an arbitrary time point.

Finally, we asked if cost was important in choice of agents used for sedation. We then determined if units that rated cost as important used different drugs from those that did not rate it as important.

Nurse staffing levels may be expected to effect the way in which patients are sedated. This data was not sought as in Britain ICUs are expected to provide 1:1 nursing levels.

All answers were processed and recorded, including those from partially completed questionnaires. The data was analysed using Microsoft Excel 7.0 running on Microsoft Windows 95.

Results

We identified a total of 323 units from the directory and received a response from 255 units. This represents an overall response rate of 79 %. Four units were excluded from the overall analysis, three did not admit ventilated patients, and one form was returned blank. Neurological and Cardiac ICUs are classified together for convenience as they represent different groups of patients to the general intensive care population. They are examined separately in some areas such as sedation scores and the use of neuro-muscular blocking agents.

The distribution of ICUs in our study is shown in Table 1. Three units provided incomplete information and are not included in this table.

The number of beds in teaching hospital ICUs [median = 8 (inter-quartile range 6–11)] is significantly larger then those in district general hospitals [median = 5 (inter-quartile range 4–6)]; Mann-Whitney U-test $P < 0.001$.

Drugs used

The majority of units which responded to our survey indicated that during any patient episode more than one sedation regimen may be used and that more than one drug was used as part of the sedative regimen. Propofol, midazolam, fentanyl, alfentanil, and morphine are the most widely used drugs in adult intensive care, whilst in

Table 2 Drugs used for sedation in British ICUs. Results are expressed as the number of ICUs, which use a drug for sedation during the stated time period. Numbers in parentheses represent the percentage of units using the given drug

Drug	Number of teaching hospitals using a drug for sedation (%)		Number of district general hospitals using a drug for sedation (%)	
	0–72 h	> 72 h	0–72 h	> 72 h
Alfentanil	16 (37)	11 (26)	68 (42)	28 (17)
Diamorphine	2 (5)	2 (5)	6 (4)	7 (4)
Fentanyl	9 (21)	7 (16)	34 (21)	24 (15)
Midazolam	23 (54)	33 (77)	89 (54)	139 (85)
Lorazepam	0 (0)	1 (2)	0 (0)	4 (2)
Morphine	26 (61)	28 (65)	85 (52)	113 (69)
Propofol	35 (81)	33 (77)	139 (84)	56 (34)
Others	0 (0)	1 (2)	6 (4)	18 (11)

Table 3 Drugs used for sedation in 18 British paediatric ICUs. Results are expressed as the number of ICUs, which use a drug for sedation during the stated time period.

Drug	Number of units using drug in first 72 h	Number of units using drug after 72 h
Morphine	16	12
Midazolam	18	13
Triclofos	3	4
Chloral hydrate	3	6
Fentanyl	3	3
Trimeprazine	1	5
Others	2	4
Propofol	0	3
Isoflurane	0	2

paediatric practice morphine, midazolam, and chloral hydrate are the most widely used drugs (see Tables 2 and 3).

Neuromuscular blockade

The results in Table 4 demonstrate that atracurium is the most widely used neuromuscular blocking agent in intensive care practice.

The commonest indications for neuromuscular blockade were difficulty in oxygenation and neurological protection. Other reasons quoted (all less then 10%) include this for protection of the patient, for patient transport, for procedures, for initial stabilisation, and for difficult-to-sedate patients. Indications mentioned rarely included tetanus (six units), rabies (one unit), and hypothermia (two units).

We asked respondents to indicate how many of their patients received therapeutic paralysis. In the general adult ICU a median of 10% of patients are paralysed (inter-quartile range 5%–20%); in the neurological ICU a median of 15% of patients are paralysed (inter-quartile range 10%–28%); and in paediatric ICU the median is 32.5% (inter-quartile range 17.5–60).

It is standard practice in Britain to sedate all patients receiving neuromuscular blocking drugs because of concern about awareness [9], therefore we did not specifically explore this issue.

Sedation and sedation scoring

Several different sedation scoring systems have been described, including the Cook [10], the Addenbrookes [11], the Ramsay [12], and the Sheffield [13] systems. The Cook sedation score is similar to the Glasgow Coma Scale with four items of assessment graded between 1 and 4, or 5, and loading for spontaneous communication leading to a score between 19 and 4. This score is then used to derive a level of sedation between 1 = awake and 6 = anaesthesia. The Ramsay score was developed in the assessment of patients sedated with alphaxalone-alphadone. It has six levels of sedation, three awake (1 = anxious/agitated, 2 = co-operative and orientated, and 3 = respond to commands) and three asleep (4 = brisk response to stimuli, 5 = sluggish response to stimuli, and 6 = no response). The Addenbrookes score is similar, but describes seven levels of sedation (1 = agitated, 2 = awake, 3 = roused by voice, 4 = roused by suction, 5 = unrousable, 6 = paralysed, and 7 = asleep). The Sheffield score is a six point system (1 = awake and agitated, 2 = awake and comfortable, 3 = opens eyes to voice, 4 = opens eyes to touch, 5 = re-

Table 4 Drugs used for neuromuscular blockade in British ICUs. Results are expressed as the number of ICUs that use a drug. Units indicated more than one drug in many instances. Numbers in parentheses represent the percentage of the units replying that use a given neuromuscular blocking agent

Drug	Neuro (%)	General (%)	Paediatric (%)	Cardiac (%)
Atracurium	16 (80)	171 (84)	13 (60)	4 (40)
Cis-atracurium	3 (15)	16 (8)	3 (14)	1 (10)
Pancuronium	2 (10)	14 (7)	6 (28)	3 (30)
Rocuronium	0 (0)	12 (6)	3 (14)	3 (30)
Vecuronium	5 (25)	68 (34)	9 (41)	1 (10)
Number of units replying	20	203	22	10

Table 5 Frequency of use of sedation scoring system and ideal level of sedation using the Addenbrookes system[a] in different types of ICUs. Numbers in parentheses represent the percentage of units replying that use a sedation score

	Scoring system used (%)	Median level of sedation	Interquartile range
Adult units	142 (67)	3	3–3.5
Paediatric units	8 (47)	4	3.5–4
Neurological units	0 (0)	–	–
Cardiac units	5 (56)	3	3–3.5

[a]Addenbrookes score: 0 = agitated, 1 = awake, 2 = roused by voice, 3 = roused by tracheal suction, 4 = unrousable, 5 = paralysed, 6 = asleep

sponds to suction and 6 = unrousable). All four scores increase as sedation increases, and the latter three describe agitation at level one (see Table 5).

Only general adult ICUs listed the different sedation scoring systems that they used; these were: Ramsay, 40 units; Addenbrookes, 13 units; Cook, 11 units; Sheffield, eight units. Five other systems were named by one unit each. Only four neurological ICUs gave a sedation score to which they aimed to sedate their patients.

Cost

The cost of sedative drugs can become a significant part of the drug bill for any ICU. Of the 246 units which answered this question, 127 (52%) said that cost was important and 119 (48%) said it was not important. Of the 208 replies from general adult ICUs 111 (53%) said that cost was important. This compared with only six out of 21 paediatric ICUs and six out of nine cardiac ICUs which rated cost as important. There were no significant differences ($P > 0.05$; Chi squared test) in the frequencies of propofol, alfentanil, fentanyl, morphine or midazolam used in either group in both time periods, nor was there any difference between teaching hospital and non-teaching hospital replies.

Propofol usage in children

Two hundred and forty-six units replied to the question "Do you use propofol for the sedation of children YES/NO?". Fifty units replied affirmatively;, eleven of these were paediatric ICUs. Five of the paediatric units gave the youngest age of a child that they would use propofol on as 3, 3, 3, 8, and 12 years of age; the others did not state an age. Of the five units that replied that they would not use propofol in children and stated a lower age where they would use it, two stated 12 years of age and one stated 10 years. Thirty-nine non-paediatric ICUs stated that they use propofol for the sedation of children. Twenty-nine stated a lower age [median of 5 years (inter-quartile range 3–10 years)]. Of the 179 units that replied they did not use propofol for the sedation of children, 92 stated a lower age limit of 12 years of age (inter-quartile range 10.5–16 years).

There was no significant difference (Chi squared test) between teaching hospital and district general hospitals in their use of propofol in the paediatric population, in non-paediatric ICUs.

Discussion

In 1981, [4] the commonest first line drugs were benzodiazepines or opioids alone or in combination, the most frequently used being phenoperadine (62%), papaveretum (32%), and morphine (26%). Relaxants were used in 91% of patients. Diazepam was used in 64%, lorazepam 32%, and nitrous oxide in 26% of patients. Opioids were used in 81% of patients, benzodiazepines 29%, and there was an increase in midazolam usage. Two units used althesin, but only 16% of units used neuromuscular blocking agents frequently. In 1987, Bion and Ledingham [5] received 189 replies from 357 questionnaires, of which 40% reported a sedation policy. 60% of replies reported the use of an opioid plus benzodiazepine, whilst 37% reported the use an opioid alone.

Propofol is now the most widely used drug for intensive care sedation, in combination with another drug. However, in patients sedated for greater than 72 h in district general hospitals, there is a significant fall in its use. 84.8% of units report its use in the initial period compared to 34.1% after 72 h, whereas in teaching hospitals the figures are 81.4% and 76.7%, respectively (a midazolam-based regimen becomes more popular after 72 h in both teaching and district general hospitals). There are several possible reasons for this, including differences in the case-mix of patients, the incidence of organ failure, and concern over the accumulation of metabolites, differences in the timing of tracheostomy, and differences in cost. In Britain, drug budgets are usually devolved to individual ICUs, but often held by managers who do not always have direct control of prescribers. The introduction of new drugs is reviewed locally by the hospital drug and therapeutics committee. Hospitals are often able to negotiate directly with drug manufacturers which can effect the price paid. Thus, large purchasers can negotiate significant discounts. The parent speciality of the consultant in charge of the unit was identified in this survey; the vast majority (more than 90%) classified themselves as anaesthetists. No correlation was demonstrated between this and the drugs used for sedation.

There is no significant difference between the sedative regimens used in those units which stated cost was important and those which said it was not important.

Barrientos-Vega et al. [14] reported that while the drug cost of a propofol regimen may be more expensive compared to a benzodiazepine regimen, the cost saving disappears once increased time to discharge is taken into account. Differences in accounting practices mean that such savings may not be attributable to the drug budget in some countries such as Britain. It is also difficult to quantify these costs without complex costing systems that are not present in the majority of British ICUs.

A survey of the drugs given to 50 patients in one unit in 1980 showed that 96% of patients received pancuronium [15]. The 1981 [4] study of sedation practice showed that pancuronium was used in all units, of which 91% (31) used it frequently. By 1987 [5] the use of neuromuscular blocking agents had changed markedly with only 16% using the drugs frequently and 71% using them rarely. The results we have obtained show that the minority of patients now receive neuromuscular blockade during their stay on intensive care and that atracurium is the most widely used drug. The reasons patients receive therapeutic paralysis are in accordance with previously published guidelines [16].

There are many reasons for the less frequent use of neuromuscular blocking drugs, including greater awareness of critical care myopathy, especially with steroids, loss of respiratory muscle function, an inability to clear secretions, and the risk of awareness. Other reasons include different ventilator techniques, the use of different sedative drugs, and a more clearly defined indication for paralysis in intensive care.

The introduction of the newer neuromuscular blocking agents offer several advantages over pancuronium; these include shorter duration of action, fewer cardiovascular side effects, and novel methods of inactivation not dependent on either liver or renal function. Organ dysfunction can alter the elimination and metabolism of all drugs administered to the critically ill, resulting in unintended and prolonged effects. Midazolam has a prolonged effect in patients with liver and renal failure due to decreased metabolism and decreased excretion of active metabolites [17]. The sedative effect of propofol, however, appears to be minimally influenced by liver or renal failure, possibly making it a more suitable agent in these patients [18, 19]. A recent systematic review of sedation in intensive care has indicated a shorter time to extubation in patients sedated with propofol compared to those sedated with midazolam [20].

The reason for the difference in adult and paediatric rates of neuromuscular blockade is unclear; it may represent different severity of illness, increased difficulty in ventilation or inadequacy of available sedative drugs.

The use of propofol for sedation in paediatric intensive care was first reported in 1987 [21]. Its use in Britain was dramatically reduced following a report in 1992 [2], which discussed the deaths of five children who had received propofol for sedation and suffered fatal myocardial failure with no clinical or pathological evidence for a septic or viral source. The paper demonstrated no direct link between the use of propofol and the deaths. Shortly after the appearance of this article the UK Committee on the Safety of Medicines issued a serious adverse warning suggesting the immediate abandonment of propofol in paediatric intensive care. Since then several other authors have reported cases of myocardial failure and death in patients receiving propofol in paediatric ICU [22].

North American intensivists use propofol as sedation in paediatric intensive care and its use has been successfully reported in large numbers of paediatric patients. The FDA announced in 1992 that "propofol has no direct link to paediatric deaths in hospital ICUs and no identifiable cardiac adverse events in children and adults" [23]. The use of any agent for sedation in British paediatric practice is further complicated as no drug currently has a British license for long-term sedation. It is interesting to note the number of units that said they did not use propofol for the sedation of children and yet stated an age of less than sixteen as the minimum age they would use it.

Previous surveys of paediatric sedation have been restricted to identified paediatric ICUs. At the time of our survey many other units were accepting children and were responsible for sedating them. Whilst we did not enquire specifically about what agents were used for the sedation of paediatric patients, we did look at the use of propofol in all units for paediatric sedation and the youngest age in which units used propofol.

It does not appear that there are major differences between teaching hospitals and district general hospitals in their use of propofol in the paediatric population. It appears that despite the warning from the regulatory authority in Britain and the manufacturers, propofol continues to be used for the sedation of children in British ICUs.

In 1987, Bion reported that 40% of 189 ICUs had a formal sedation policy. In 86 out of 189 units, the choice of sedative agents used was made by individual consultants without an agreed policy and in 25 units the regimen was left to the junior staff. The replies we received showed that 109 (43%) units had a formal sedation policy, 129 (51%) had an informal policy, and 16 (6%) had neither.

It has become uncommon for an ICU to not use a sedation policy (only 17 units had neither a written or unwritten policy). This may indicate a greater number of trainees rotating through intensive care. It may also be due to a greater consensus amongst physicians about techniques of sedation, a general increase in guidelines used in medicine or a bias in our results. Units that employ guidelines may be more likely to respond to questionnaires of this nature.

Sedation of the critically ill patient is different from anaesthesia in that it is not an all or none effect. This has led to the development of scoring systems to assess the level of sedation for a given patient. These are at present crude ways of assessing patients' levels of consciousness and demonstrate the lack of efficacy of techniques such as processed EEG [24], and auditory evoked potentials which have been adopted from methods used to measure anaesthetic depth. Whilst over half of all units use a sedation scoring system, the variety of systems used seems to indicate little agreement on how sedation should be scored. A survey of Danish ICUs in 1996/7 showed that only 16% (8 units) used a sedation score. In all units this was the Ramsay score [25]. There does, however, seem to be agreement that patients should be less sedated than in the past. This suggests that the aim of a lightly sedated co-operative patient is now viewed as the ideal rather than the deeply sedated or paralysed patient of 20 years ago.

Appendix: Intensive care sedation questionnaire

About the unit you work at

1 How would you describe the hospital at which you work?
   District general hospital
   Teaching hospital
   Other (please specify)
2 What type of patients does your unit generally take?
   General adult
   Paediatric
   Cardiac
   Neurological
   Other (please specify)

Concerning sedation

1 Which drug(s) do you routinely use for sedation in the first 24–72 h after admission?
2 Which drug(s) do you routinely use for sedation after 72 h of admission?
3 How often do you use neuromuscular blocking agents? . .. .%
4 Which neuromuscular blocking agents do you routinely use in intensive care?
   Atracurium
   Cis-atracurium
   Vecuronium
   Pancuronium
   Rocuronium
   Other (please specify)
5 What indications do you have for neuromuscular blockade?
6 Does your unit have a written sedation policy? Yes/No (if you do have a written sedation policy could you possibly send me a copy?)
7 Do you consider that your unit has an unwritten sedation policy/guidelines? Yes/No
8 Does your unit use a sedation scoring system? Yes/No
9 What level of sedation do you aim to keep your patients at? Please use the Addenbrookes scoring system (0 = agitated, 1 = awake, 2 = roused by voice, 3 = roused by tracheal suction, 4 = unrousable, 5 = paralysed, 6 = asleep)
10 Does your unit use propofol for sedation in children? Yes/No
11 If no what is the lowest age of patient that you would use propofol in?
12 Does cost play an important part in the choice of sedation policy? Yes/No

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