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Benzodiazepine sedation in adult ICU patients

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General aspects

Critically ill patients need to be sedated for three main reasons: to tolerate artificial ventilation, to support the treatment of convulsions and to control agitation or anxiety [1–3]; the goal of sedation is the reduction of perception in the management of patients needing analgesia and sedation. In the most frequently used application of sedative drugs, namely in patients on the respirator, the attitude "how to sedate a patient" and the practical consequences have changed over the last 15 years. Initially complete sedation, mostly combined with relaxation, was thought to be necessary for fully controlled ventilation. More recently, after a few hours of controlled ventilation, partially spontaneous breathing is preferred. Consequently, sedation has changed from complete to partial sedation, combined with analgesia but generally without relaxation [4]. Among sedative drugs, benzodiazepines are the most commonly used drugs today for sedating critically ill patients. Instead of using long-acting drugs, such as diazepam with the danger of accumulation [5, 6], sedatives with a shorter half-life are at present preferred [3].

Degree of sedation and monitoring

The degree of sedation, and thereby the choice of drug including dosage and type of administration, depend on the strategy of sedation planned for an individual patient. The planned degree of sedation was investigated in 34 ICUs in Great Britain in 1981 [3], at a time when more or less complete sedation was still aimed for; 23 units wanted the patient to be "completely detached from the environment", 9 units tried to sedate the patient "to the point of no distress" and some units gave analgesic drugs "only for painful procedures". In our recent inquiry in 63 Swiss ICUs, called "Swiss Sedation 88", the extent of sedation aimed for was characterized by 43 ICUs (68%) as sedate to the point of "cooperation without distress", 13 units (21%) preferred "deep sedation, the patient reacting only to stimuli", 7 units named no general strategy of sedation. The required degree of sedation was mostly achieved in 49 units (78%), and rarely achieved in 11 (17%); for correction of prolonged coma following long term sedation with benzodiazepines 29 units (44%) used the benzodiazepine antagonist flumazenil.

This change from complete to partial sedation over the last few years is in parallel with the change in the ventilation technique, namely from complete controlled to only supportive ventilation, implying some spontaneous breathing effort by the patient. In addition, heavy sedation is not a benign treatment [1]; the disadvantages include respiratory muscle fatigue and all the complications threatening a comatose patient such as deep venous thrombosis, general muscle wasting, risk of compression injuries to peripheral nerves, infection and prolonged coma due to sedative overdose followed by weaning problems [7].

Objective parameters for monitoring depth of sedation are few and rarely investigated. Clinically, repeated examination of the quantitative and qualitative state of consciousness are sometimes performed using the Glasgow coma scale system [8], supplemented by questions concerning the orientation of the patient. Although this method might not be the most suitable to assess the degree of sedation in an intact, undamaged brain, the Glasgow coma score is still used for this purpose; other clinical scoring systems were described by Ramsey et al. [9], Bion et al. [10], Gerstenbrand et al. [11] and others. Physical examinations include the observation of the pupils, corneal reflex, reaction to stimuli, etc.; the nursing staff will estimate the degree of sedation additionally by the patients hemodynamic responses to invasive procedures; e. g. endotracheal suctioning. Drug monitoring, correlating plasma concentration and state of sedation, becomes possibly a part in monitoring sedated patients, although

Table 1. Use of drugs in sedating ventilated patients, 63 ICUs ("Swiss Sedation 88")

63 ICUs	
3	not using benzodiazepine regularly (all pediatric ICUs, 2 using opiates and 1 using barbiturates)
60	using benzodiazepines
8	using benzodiazepines alone in >50%
52	combining benzodiazepines routinely with analgesics or other sedatives, such as
49	morphine
22	pethidine
11	buprenorphine
11	fentanyl
9	barbiturates
9	etomidate

there exists a broad inter- and intra-individual pharmacokinetic variability; intermittent or continuous registration of the EEG will probably be the best parameter to evaluate objectively the degree of sedation [12, 13]; digital plethysmography testing the autonomic response to pain is not yet routinely used; in the future, measurement of pulse variability, probably combined with other parameters, might be of help in monitoring sedation.

Drugs for long-term sedation

The barbiturates, still indicated in patients with increased intracranial pressure, have almost completely been replaced by the benzodiazepines for sedating ventilated patients in ICU. In addition, benzodiazepines seem to be preferable also to neuroleptic agents and to opiates because of their anxiolytic and sedative properties [14]. In view of the well known central-nervous effects of benzodiazepines, namely the anxiolytic, sedative, muscle relaxant and anticonvulsant effect, they seem at present to be the drugs of choice.

According to the inquiry of Merriman et al. [3] 31 of 34 units used diazepam to sedate ventilated patients, at least until 1981. Two years later we demonstrated some cases of prolonged coma due to sedation with diazepam in therapeutic high doses [6, 7]. In addition to the advantages of a rapid passage through the blood-brain barrier, of a broad therapeutic range and rather rare side effects, the benzodiazepines have certain disadvantageous pharmacokinetic properties. The plasma half-lives of the almost 40 different types of benzodiazepines available in Europe range from 3 to more than 24 h. When benzodiazepines are used repeatedly, especially in elderly patients with retarded elimination and/or reduced liver function, accumulation may lead to prolonged coma following withdrawal of the drug [7]. Among the newer benzodiazepines with shorter half-lives, midazolam is preferred [15, 16] and corresponds to the habits in the different Swiss ICUs (Table 1). Midazolam, a water-soluble imidazole benzodiazepine has several advantages over diazepam [17, 18]: potency is twice that of diazepam, onset of hypnosis is more rapid, the half-life is only 2–3 h and the metabolites are inactive, making the drug suitable for continuous intravenous infusion. The initial short duration of action due to redistribution from the brain to other tissues with lower perfusion necessitates the application of a loading dose. Within individuals there is a good correlation between pharmacokinetics and pharmacodynamic effects, Persson et al. [19] showed a good relationship between plasma levels of midazolam and clinical response. Between individuals, however, the drug shows a wide variability [20].

Midazolam in continuous infusion

The clinical use of midazolam by i.v. infusion is reported so far in 9 efficacy and safety studies (Table 2); in 355 cases the mean duration of midazolam sedation ranged from 1.7–11.3 days. The loading doses used were

Table 2. Midazolam for long-term sedation, efficacy and safety reports on 355 cases

Authors	No. of cases	Age	Duration (days)	Loading dose (mg)	Maintenance dose (mg/h)	Dose-adjustments per patient (*n*)	Antagonisation by flumazenil (*n*)
Maintenance of anesthesia:							
Gesztes et al.	73	19–65	–	8–25	5.0	–	–
Intensive care:							
Geller et al.	89	15–95	days	1–16	5.0	3.2	23
Ritz et al.	6	33–64	11.3	28–33	6.5	4.9	0
Nicolan et al.	20	29–94	1.7	5–15	3.5	–	–
Suter et al.	10	22–53	2.0	1.7	2.1	2.2	–
Malacrida et al.	11	18–70	2.0	15.0	9.0	1.2	11
Park et al.	50	4–76	4.4	1–70	3.0	–	–
Ledingham et al.	18	19–81	3.0	–	3.0	2.9	–
Bursztein et al.	45	16–71	days	3–15	3–14	–	–
Postoperative sedation:							
Bloch et al.	33	12–58	–	–	3–5	–	–
Total	355	4–95	1.7–11.3	1–70	2.1–14	1–4.9	34

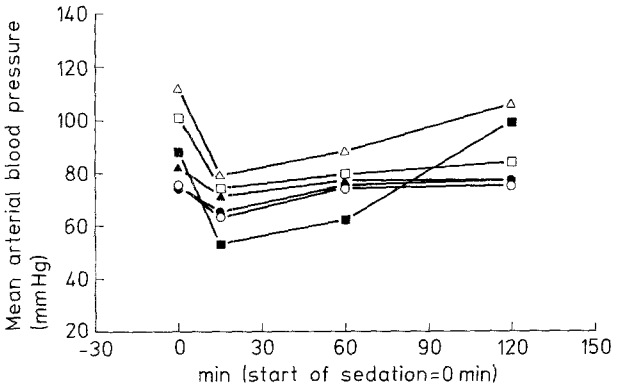

Fig. 1. Controlled study of 6 ventilated ICU patients sedated with midazolam; course of mean arterial pressure during loading dose (30 mg/70 kg over 15 min) and maintenance dose (6 mg/h/70 kg)

1–70 mg, the mean maintenance doses varied from 2.1–14.0 mg/h and, according to the clinical judgement by the nurse at bedside, 1–5 dose adjustments were necessary. Beside some situations with a minor drop of systolic blood pressure following the loading dose no significant hemodynamic or respiratory adverse reactions or other side effects were registered. The positive results using midazolam in critically ill patients were confirmed by several publications [21–24]. In our own intensive care unit, 3 years ago, we first studied in detail the pharmacokinetic properties in the clinical application of midazolam in 6 ventilated patients. Beside morphine only midazolam was used for intubation and initiation of ventilation, therefore a rather high loading dose of 30 mg/kg midazolam was infused over 15 min at that time (Table 2). We thereby observed some remarkable but short lasting initial decreases of systolic arterial blood pressure and cardiac index (Fig. 1). With a mean maintenance dose of 6.5 mg/h midazolam over 11.3 days in the 6 ventilated patients, sedation was good, but needed repeated dose adjustments; further adverse reactions or side effects were not observed. In addition, we recently reviewed our sedation protocol over the three years. In 152 consecutive ventilated patients sedated with midazolam the mean loading dose was 7.8±6.9 mg infused over 15–20 min, supplemented mostly by morphine for analgesia. The mean maintenance dose of midazolam per day ranged from 5.9–10.3 mg/h (first day, $n = 152$) up to 36.0–40.0 mg/h (21st day, $n = 3$) with constant need of increasing doses, raising the question of tolerance (Fig. 2). It is important to mention that these high doses of midazolam were needed according to the clinical judgement of the nurses at the bedside; it is unknown so far if these doses include disadvantages for the patient and if the sedative drug should be changed at a certain point. No definite conclusion can be drawn from these data, since on day 21 only 3 of the 152 patients were still on the ventilator. In 16% of these 152 midazolam sedated patients the benzodiazepine antagonist flumazenil was used during the weaning phase (2.3±4.5 mg/h).

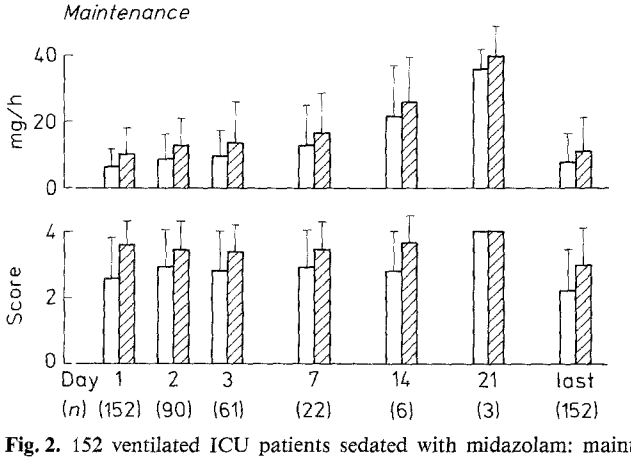

Fig. 2. 152 ventilated ICU patients sedated with midazolam: maintenance doses (mg/h); mean±SD of the highest (*right columns*) and lowest (*left columns*) doses on day 1 ($n = 152$), 2 ($n = 90$), 3 ($n = 61$), 7 ($n = 22$), 14 ($n = 6$), 21 ($n = 3$), and the last day ($n = 152$) on the respirator, respectively. *Below*: awakeness score (1 = awake, 2 = drowsy, 3 = reacting on painful stimuli, 4 = comatose); mean±SD of the highest (*right columns*) and lowest (*left columns*) score on that day

In general, after a loading dose, midazolam should be administered by continuous infusion rather than by intermittent injections [25], usually in combination with analgesics to sedate ventilated patients. If the degree of sedation is not adequate the serum level of midazolam should at the same time be raised by 1–3 small bolus i. v. injections and by increasing the infusion rate, since the stepwise increase of a continuous infusion without bolus injections may lead to accumulation of the drug.

The ideal agent for prolonged sedation should include advantageous pharmacokinetic properties, i. e. a broad therapeutic range and a short half-life, a rapid passage through the blood-brain barrier, no effect on the respiratory and cardiovascular systems, no interactions with other drugs, and should be metabolized by pathways independent of renal and hepatic function. This drug does not exist. Optimal sedation can probably only be reached using several sedative and analgesic agents in combination. Today short-acting agents such as propofol [26], the opioid alfentanil [27] or a short-acting benzodiazepine such as midazolam seem to be the drugs of choice. In case of cumulation midazolam has the additional advantage of the existence of the benzodiazepine antagonist flumazenil; the titration of these 2 drugs might lead to an optimal and balanced sedation in ventilated intensive care patients in the future [28, 29].

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