Peripheral infusion of Diazemuls

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Diazemuls is a very powerful anxiolytic agent with sedating and anti-epileptogenic properties. Unfortunately, until now it has not been possible to give Diazemuls accurately and safely as an infusion. A new delivery system ensures that, as an infusion, this drug is potentially very effective in treating patients with terminal agitation, status epilepticus, drug and alcohol withdrawal.

Diazemuls (Dumex Ltd, Whiddon Valley, Barnstaple) is an effective drug, licensed for sedation before procedures, premedication before anaesthesia, control of acute muscle spasm resulting from tetanus or poisoning, control of convulsions, status epilepticus and management of severe acute anxiety or agitation including delirium tremens (ABPI Compendium, 1998).

The therapeutic action is rapid when given as a bolus intravenous injection. However, when the patient's condition is more chronic, such as status epilepticus, alcohol or drug withdrawal and severe agitation, administration is more difficult.

It has previously been recommended that if the drug is to be given as an infusion that it should be mixed with 5% or 10% dextrose and then infused within 6 hours. The dosage of Diazemuls received over the 6 hours will be unpredictable because of strong adherence of the drug to polyvinyl chloride in the bag and the giving set (Martens et al, 1990; Winsnes at al, 1981; Hancock and Black, 1985).

INFUSING DIAZEMULS

A simple and safe delivery system has been developed for infusing Diazemuls through a peripheral line, which has been used in patients with terminal illness whose uncontrolled agitation was very distressing for them. The infusion has also been used to treat status epilepticus, alcohol and drug withdrawal and to control very violent patients.

Diazemuls is an oil in water emulsion containing diazepam. This formulation reduces the risk of localized pain and thrombophlebitis (Von Dardel et al, 1983). Diazepam and its principal metabolite, desmethyldiazepam, are very potent anxiolytic agents (Jack and Colburn, 1983; Greenblatt et al, 1988). Diazepam also has anticonvulsant and sedative effects.

The decision to start the intravenous infusion of Diazemuls is taken by the consultant physician responsible for the patient. In all cases the decision is fully discussed with the relatives and, when possible, with the patient. A peripheral cannula is inserted. Undiluted Diazemuls is drawn up into a 50 ml syringe (e.g. polyethylene Plastipac syringe from Becton Dickinson UK Ltd, Cowley, Oxford). Depending on the dosage required, the syringe does not always need to be completely filled. A low sorbing extension set (IVAC G30303, IVAC® UK Ltd, Basingstoke, Hants) is attached to the syringe and an IVAC 711 or equivalent infusion pump is used (IVAC® UK Ltd, Basingstoke, Hants). When possible the Diazemuls is drawn up under aseptic conditions in the hospital pharmacy department and a 5 μm filter is used to remove any possible splintered glass because of the large numbers of ampoules that are required. At other times the syringes are made up on the wards. *Table 1* outlines the peripheral infusion of Diazemuls.

TERMINAL AGITATION

Terminal agitation is a very unpleasant state, which can be caused by many conditions. This problem is likely to be more severe in the hospital situation than in a hospice. Metabolic encephalopathy is usually a result of electrolyte imbalance, nutritional disorders and sepsis. The condition tends to be more acute in hospital and is often complicated by problems such as fitting and alcohol withdrawal. In the hospice situation up to 40% of terminal patients develop restlessness and/or agitation in the last 24–48 hours and do not die peaceful deaths (Saunders, 1989; Lichter and Hunt, 1990). About 12% of dying patients develop jerking or twitching (Lichter and Hunt, 1990).

Even uraemia, which is considered one of the least unpleasant ways of dying, can sometimes

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be very unpleasant for the patient, family, nursing and medical staff. Terminal agitation can include delirium, severe confusion and paranoia, and often in renal patients, twitching and fits. The patient may be unable to get comfortable because of aching, severe itching, or breathlessness. The patient may be terrified.

The patients have been divided into two groups, those with renal failure (group A) and those with normal renal function (group B). These patients were all severely distressed and some were fitting. They were being cared for on general medical and renal woards. The patients were divided into two groups to see if there was a difference in the dosage andduration of infusion required.

In group A, there were 8 patients with chronic renal failure in whom dialysis was withdrawn, 2 patients with acute renal failure in whom short term dialysis was withdrawn, and 6 patients with chronic renal failure who were not considered appropriate for dialysis. In the chronic dialysis patients, the mean time from withdrawal of dialysis to death was 8.1 days, with a range of 2–22 days.

The overall mean length of time on the Diazemuls infusion was 3.5 days, with a maximum of 14 days and a minimum of 6 hours.

The overall mean dose was 5.1 mg/hour, with a maximum of 10 mg/hour and a minimum of 2.5 mg/hour. Six of the 16 patients required 2.5 mg/hour. In patients who were very agitated at night, but not during the day, the infusion rate was increased each night (e.g. 2.5 mg/hour during the day and 10 mg/hour during the night). It was rarely necessary to increase the dose of Diazemuls after control of symptoms was obtained.

In 3 patients in this group, diamorphine and haloperidol had been instituted for pain, but were not controlling the patient's agitation and distress. Within 2 hours of starting the Diazemuls infusion, the diamorphine and haloperidol were no longer required. In all cases, care was taken to ensure that the sedative effect of Diazemuls did

TABLE 1.
Administration of peripheral diazemuls

Preparation	Undiluted Diazemuls* in a 50 ml Plastipak syringe (Becton Dickinson UK Ltd, Cowley, Oxford)† using a low sorbing extension set (IVAC G30303, IVAC® UK Ltd, Basingstoke, Hants) via an IVAC 711 pump (IVAC® UK Ltd, Basingstoke, Hants)	
Rate of infusion	Most adults	Commence at 2.5 mg (0.5 ml) per hour
		Increase in increments of 2.5 mg/hour until control achieved
	Elderly	Commence at 1.25 mg (0.25 ml) per hour
		Increase by increments of 1.25 mg/hour until control achieved
		Nursing staff 'fine tune' the dosage
	Violent or severely agitated patients	Commence at 5 mg (1 ml) per hour and increase by increments of 5 mg every 30 minutes until control achieved
Safety issues	Most adults	Infusion to be administered as sole drug through the intravenous cannula
		If patient is not for terminal care, pulse oximetry should be used
		Usual maintenance dose < 7.5 mg/hour‡
	Elderly	In the event of respiratory depression, reverse with flumazenil (Anexate)
		Discuss with consultant if patient requiring >20 mg/hour

*Diazemuls should not be mixed with any other solution except rarely with 10% or 20% Intralipid; †Change syringe and giving set every 24 hours; ‡Maximum therapeutic dosage so far recorded: 40 mg/hour

TABLE 2.
Terminal agitation: normal renal function

Patient no	Age (years)	Medical condition	Days on Diazemuls	Maximum dose of Diazemuls
1	69	Metastatic bladder and prostate cancer. Very agitated despite diamorphine 80 mg and haloperidol 5 mg. Diazemuls added	7	5 mg/hour
2	63	Systemic sclerosis, rheumatoid arthritis, pseudomembranous colitis, bleeding leg ulcers, ischaemic heart disease, polycystic kidneys, status epilepticus	6	15 mg/hour
3	77	Pneumonia/pleurisy, severe chronic obstructive pulmonary disease, left ventricular failure not responding to therapy. Very agitated despite diamorphine for 8 days. Diamorphine stopped, diazemuls started	1	5 mg/hour
4	78	Disseminated cancer of the stomach, unable to eat or drink. Very distressed	9	5 mg/hour
5	57	Alchoholic liver disease, hepatic encephalopathy, pseudobulbar palsy, osteomyelitis, *Staphylococcus aureus* septicaemia	4	10 mg/hour
6	67	Wegener's granulomatosis, methicillin-resistant *Staphylococcus aureus* infection of large lung granuloma despite partial lobectomy no response to treatment	9	5 mg/hour
7	84	Dense right hemiparesis, very agitated, history of alcohol excess	5	17.5 mg/hour
8	73	Cancer of lung, metastases in bone. Very agitated despite diamorphine and haloperidol	3	4.5 mg/hour
9	71	Motor neurone disease, continuously choking. Unable to sleep	1	2 mg/hour
10	69	Respiratory failure caused by pulmonary fibrosis. Cheyne Stokes respiration. Very agitated despite diamorphine. Diamorphine stopped. Diazemuls alone showed dramatic improvement	3	5 mg/hour

not mask the patient's pain. These patients all died comfortable, non-agitated deaths.

The patients in Group B comprised the first 10 patients with normal renal function who were treated with the Diazemuls infusion. They had a number of other conditions (*Table 2*), which can result in patients becoming severely agitated when dying. Many were confused and frightened.

The mean dosage of Diazemuls required to control the symptoms of these patients was 7.4 mg/hour, with a minimum dosage of 2 mg/hour and a maximum dosage of 17.5 mg/hour. The mean time that the patients required the Diazemuls infusion was 4.2 days, with two patients on the infusion for 9 days and two patients on the infusion for 1 day.

It can be seen from *Table 2* that patient 7 required 17.5 mg Diazemuls per hour. This patient had a massive cerebral infarct affecting his dominant side. He was extremely agitated. A safe environment could not be maintained because the patient was constantly trying to get out of bed. He continuously tried to remove his catheter. The patient had a very long history of alcohol excess. Once stable on 17.5 mg/hour of Diazemuls, this patient remained comfortable. Any attempt to lower the dosage caused his problems to recur. Patient 5 also had a long history of alcohol excess and required 10 mg/hour to control symptoms.

Patient 2 had systemic sclerosis, and developed intractable fits at a time when it had already been decided that further treatment would be inappropriate. Despite weighing less than 60 kg, this patient required 15 mg/hour to control her symptoms and fits.

Patient 9 had very severe motor neurone disease and was choking on her own secretions. She was terrified of choking and had been unable to sleep for a number of days. After full discussion with the patient and her family, she was started on the Diazemuls infusion. She fell asleep about 2 hours later and had a very comfortable night. She died comfortably the following day.

Four patients in this group were on diamorphine and haloperidol. Two of these patients no longer required this when the Diazemuls was started, and the other two required no further increase in the dose of haloperidol and diamorphine.

Most of the patients continued to eat and drink until shortly before they died. If a patient was not able to take oral fluids, then a nasogastric tube feed was instituted. All drugs, except those for symptomatic benefit, were stopped at the time of starting the infusion of Diazemuls if the patients were being treated for terminal agitation. It is important to ensure that sedation does not mask pain, and to treat pain effectively if it is present.

STATUS EPILEPTICUS

Diazepam is a very useful and potent drug in the treatment of epilepsy and status epilepticus (Booker and Celesia, 1973; Hvidberg and Dam, 1976).

An infusion of Diazemuls has been used for the control of status epilepticus. The first two patients treated by this method were on haemodialysis. One developed severe ketoacidosis, pulmonary oedema, and started fitting. This patient required bolus injections of Diazemuls, but when the fits did not resolve, she was started on a Diazemuls infusion at 2.5 mg/hour for 24 hours. The other patient had a very severe vasculitis, particularly affecting his kidneys, bowel and brain. He developed severe status epilepticus, and was treated with the Diazemuls infusion at a maximum dosage of 17 mg/hour for 7 days. In both of these patients, if bolus injections of Diazemuls had been given, the patients would almost certainly have required ventilation on the intensive care unit. Instead they were safely nursed on the renal ward (*Table 3*).

This treatment has been used in other patients with status epilepticus without problem. The patients have been monitored by pulse oximetry, but the Diazemuls infusion has not needed to be reversed in any case. Using a stepped dosage infusion of Diazemuls results in the patient's conscious level being much lighter than if bolus doses of Diazemuls are used.

A number of the patients with terminal agitation were fitting and the Diazemuls infusion controlled the fits in these patients.

VIOLENCE, ALCOHOL AND DRUG WITHDRAWAL

There is a dramatically increasing incidence of violent patients being admitted to hospital. In Wolverhampton the number of attacks on community nurses and medical staff increased by 12% in the year ending March 2000. Staff employed by the Wolverhampton Health Care Trust reported 171 assaults by patients, as well as five 'near misses' and two assaults by 'others'. Many of these will either have taken alcohol or drugs, or will be withdrawing from alcohol or drugs.

Diazemuls has been used as a peripheral infusion in these patients. The patients who were treated by this method were not being controlled by any other drugs.

A patient who became violent following cerebral hypoxia caused by a cardiac arrest was controlled by this method for 8 days. He was particularly agitated and violent at night. He was controlled by 2.5 mg/hour during the day and 10 mg/hour at night. He made a full recovery.

TABLE 3.
Diazemuls infusion: full recovery including status epilepticus

Patient no	Age (years)	Condition and progress	Dose of Diazemuls (mg/hour)	Length of treatment
1	73	Disinhibited and dangerous following a cardiac arrest. Intensive therapy unit then coronary care and then medical ward. Full recovery	5 day 10 night	7 days
2	36	Severe diabetic ketoacidosis. Haemodialysis and pulmonary oedema. Developed severe status epilepticus requiring more than 5 mg Diazemuls intravenously as a bolus every 30 minutes. Settled on a continuous infusion. Full recovery	2.5	24 hours
3	19	Henoch–Schönlein purpura, severe vasculitis, acute renal failure. Cerebral vasculitis. Haemodialysis. Developed status epilepticus, required Diazemuls infusion 10 mg/hour for 48 hours. Started on phenytoin. 4 days later status epilepticus recurred. Required Diazemuls infusion up to 17 mg/hour to control the fits. Also on diamorphine 40 mg and haloperidol subcutaneously every 24 hours for abdominal pain. Developed respiratory depression, immediate response to naloxone. Diazemuls infusion stopped 12 hours later. No further fits.	10 17	2 days 5 days
4	30	Drug abuser. Cocaine, heroin + 3 LSD dots. Violent. Controlled by 70 mg Diazemuls and 10 mg haloperidol over 2 hours. Controlled by Diazemuls infusion	7.5	36 hours
5	41	Acute psychotic confusion following grand mal fit	3	36 hours
6	32	Status epilepticus not controlled by 25 mg Diazemul as 5 mg bolus injections Infusion 2.5 mg/hour complete control, return of fits if dose dropped over first 3 days. Patient remained conscious and aware on the infusion. Started on phenytoin 150 mg twice daily on first day. Fitting restarted day 5, Diazemuls infusion 2.5 mg/hour. Lamotrigine commenced — side effects. Valproic acid started. Diazemuls infusion stopped day 7. No further fits	2.5 2.5	3 days 2 days

Another patient with a history of heroin and cocaine abuse took 3 LSD dots. It required three policemen to control him. Other medications had no effect. He settled on Diazemuls 7.5 mg/hour for 36 hours. Six hours after the infusion was stopped he was fully recovered, and walked off the ward in police custody.

An alcoholic patient became very violent, and refused any medication. A 15 mg bolus of Diazemuls was given followed by Diazemuls infusion. The patient required 35 mg/hour to control his violence. This did not result in significant respiratory depression. The infusion was required for 5 days until the patient was controlled on oral chlormethiazole.

It was not possible to control one very violent patient, despite very large doses of intravenous Diazemuls and large bolus injections of midazolam. This patient had a long history of drug and alcohol abuse and had taken crack cocaine.

This treatment has been used in a number of other patients. No cases of respiratory depression have been reported in patients who were not being treated for terminal agitation. In patients who are at risk of respiratory depression, high dependency type monitoring should be considered.

CONCLUSIONS

The continuous infusion of Diazemuls by our method has proved effective in our patients. Patients dying with terminal agitation are much more comfortable and are no longer agitated. The treatment does not appear to hasten death, and we suspect that those patients who were previously on diamorphine and whose symptoms were not properly controlled, lived longer on the Diazemuls infusion than if they had remained on the narcotic agents. The dosage of Diazemuls used in these two groups was exactly comparable with the dosage used in patients with remediable conditions who made a full recovery. The patient, relatives and nurses were much happier when the patient's symptoms were properly controlled.

This treatment seems to be very effective at treating status epilepticus, and because there are no 'peaks and troughs' as a result of repeated bolus injections of Diazemuls, but rather a 'stepped' dosage, it should be much safer (*Figures 1* and *2*).

The violent hospital patient is an increasing problem; this method seems to work well in most violent patients. It is apparent that patients with a long history of alcohol abuse may require much larger doses of Diazemuls than other patients.

This method of infusion of Diazemuls could potentially be used for alcohol and drug withdrawal; the author has not seen any significant complications.

The nursing staff have found the system very easy to set up, and the patients are much easier to nurse, once the infusion has been started. Diazemuls is legally classified as a controlled drug, Schedule 4, part 2. As such, the full controlled drug handling requirements associated with narcotic agents (controlled drug schedule 2) are avoided and nursing time reduced, which means that the logistical problems for nurses are much less than with narcotic agents.

The drug acts quickly, and once the patient is stabilized, it is rarely necessary to alter the

dosage. We have not had any problems with superficial thrombophlebitis over and above those we would have anticipated with any normotonic infusion.

In patients who are not being terminally cared for pulse oximetry is used. Using this system we have only had one case of significant respiratory depression. That individual had acute renal failure, severe abdominal pain and developed status epilepticus as a result of a severe vasculitis. He was having diamorphine for his abdominal pain, and a Diazemuls infusion for his status epilepticus. His respiratory depression responded rapidly to naloxone, and was probably caused by the diamorphine.

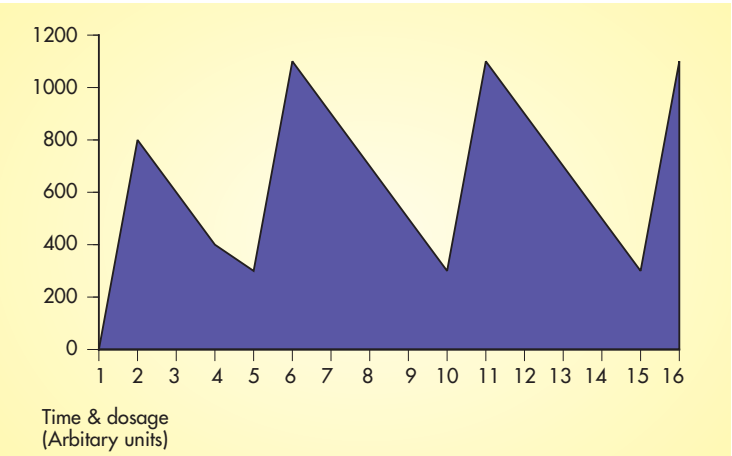

Figure 1. 'Peaks and troughs' following bolus injections of Diazemuls.

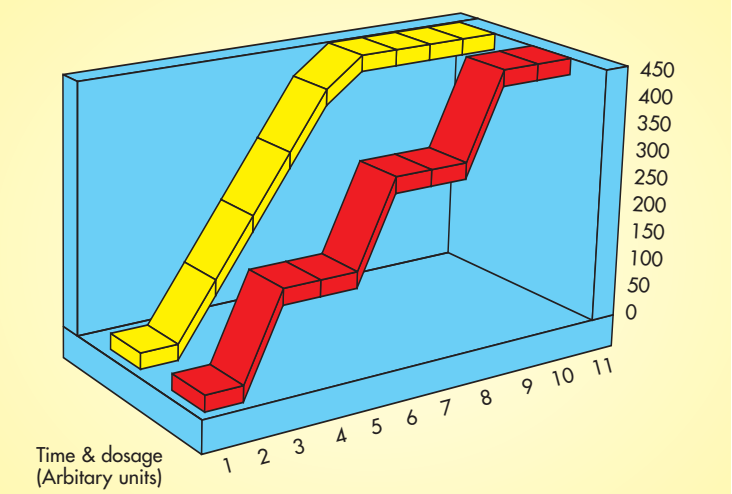

Figure 2. Stepped dosage increase or smooth transition with intravenous Diazemuls.

KEY POINTS

- An infusion of Diazemuls is quick and easy to set up.
- It gives rapid relief of symptoms of severe agitation and appears to have a wide therapeutic range.
- Diazemuls often obviates the need for narcotics or prevents the dosage of narcotic agents needing to be increased.
- Diazemuls can quickly be reversed by flumazenil and can be used to quickly and safely control patients who are a danger to the staff, and themselves.
- It is a schedule 4 controlled drug, which means it is less of a logistical problem for the nursing staff when treatment is instituted.
- Because the patient is less agitated and distressed, less nursing time is required.
- If the patient is comfortable the relatives are less likely to be distressed.

In contrast to chlormethiazole, for which there is no effective antidote, the sedative effect of diazepam in this formulation can easily be reversed with flumazenil.

The manufacturer's stability data shows that Diazemuls can be stored at 4°C in a polyethylene syringe for 28 days. This means that the syringes can be made up in the aseptic suite of the pharmacy department.

There has been a lot of recent concern with the way that doctors manage dying patients and the use of narcotic agents in these patients (Gillon, 1999; Doyal, 1999).

In the author's opinion this is an appropriate and very effective, simple and inexpensive way of looking after patients who are otherwise going to die an unpleasant death with terminal agitation. It is also an effective and safer way of treating status epilepticus than bolus injections. This method of infusing Diazemuls has been found to be an effective and safe way of controlling some violent patients. **HM**

Conflict of interest: Dr Jackson has a consultancy agreement with Dumex. A patent for this method of infusing Diazemuls has been jointly applied for by the Royal Wolverhampton Hospital Trust and Dumex.

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