Midazolam: an effective intravenous agent for seizure control

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SUMMARY

Midazolam maleate, a water soluble 1,4 benzodiazepine, was used intravenously in 20 patients suffering seizures, of whom 12 were in status epilepticus. In all cases, midazolam in a dose of 2.5–15 mg rapidly terminated the seizure. There were no complications from the use of midazolam. The causes of the seizures were varied but alcohol-withdrawal seizures were the single largest cause. Thirteen patients were taking some form of anticonvulsant medication but only three were in the therapeutic range. Midazolam is seen to be an effective agent in the emergency treatment of seizures.

INTRODUCTION

Tonic-clonic seizures are a neurological emergency and need to be terminated quickly. Status epilepticus is defined as a seizure lasting more than 30 min or where a normal alert state is not regained between seizures. Clinical and experimental studies show that it is important to terminate tonic-clonic status epilepticus as soon as possible as it has been associated with brain damage and death (Delgado-Escueta *et al.*, 1982).

Benzodiazepines in seizure control

Many sedatives, tranquillizers and anaesthetic agents have been shown to terminate seizures. In the 1920s, barbiturates became established as potent anti-convulsant agents. Naquet *et al.* (1965) reported the successful use of diazepam in experimental animals and man. Gastaut *et al.* (1965) published their results of the clinical use of diazepam in terminating seizures and from that time diazepam has been used extensively. The place of diazepam in seizure control was reviewed by Delgado-Escueta *et al.* (1982). Two other benzodiazepines, clonazepam and lorazepam have been used in

seizure control. Clonazepam is effective as an oral agent in myoclonic epilepsy and has been used intravenously in status epilepticus (Davidson, 1980). Lorazepam has a longer half-life than diazepam and has been used in the control of refractory neonatal seizures (Deshmukh *et al.*, 1986). All benzodiazepines appear to modify excitability of neuronal membranes by binding to specific receptor sites. The major effect of benzodiazepines in seizures is potentiation of the GABA (inhibitory) pathway (Meldrum & Chapman, 1986; Sunao *et al.*, 1983).

Diazepam has a long elimination half-life, (21–37 h), is water insoluble and requires organic solvents to remain in solution. These solvents cause venous irritation and thrombophlebitis (Brown *et al.*, 1979).

Recently, a water-soluble 1,4 benzodiazepine, midazolam, has become available for clinical use in Australia. Midazolam has an elimination-phase half-life of approximately 2 h and 30–40% of a single I.V. dose is recovered in a conjugated form in the urine in the first 12 h. The effect of midazolam on E.E.G. recordings is similar to that of diazepam and Brown *et al.* (1979) suggested that the anticonvulsant properties of diazepam and midazolam would be similar and recommended further study to clarify these points. Midazolam has been shown to protect mice from local-anaesthetic induced convulsions (DeJong & Bonin, 1981). A case report in 1983 showed that midazolam was effective in controlling status epilepticus in a 14-year-old girl (Sunao *et al.*, 1983). This trial was designed to test the efficacy of midazolam in seizure control.

MATERIAL AND METHODS

Twenty adult patients (13 years and over) who suffered seizures in the emergency department or who arrived in status epilepticus were treated with intravenous midazolam. An initial dose of midazolam of 2.5 mg was followed by increments until the seizure was controlled. Blood was drawn from patients for blood alcohol and serum anticonvulsant levels.

Table 1 Details of patients and dose of midazolam

Patient	Age	Sex	Weight (kg)	Status (yes/no)	Midazolam dose (mg)	Aetiology of seizure	Anticonvulsants	Comments
01	45	F	59	No	5.0	Post-traumatic	Phenytoin Phenobarbitone	
02	40	M	62	No	5.0 + 5.0 (10 min later)	Idiopathic epilepsy	—	First seizure: 10 min later patient suffered second seizure which required more midazolam
03	74	F	50	Yes	5.0	Previous C.V.A.	—	—
04	26	F	55	Yes	3.0	Hypoxic birth injury	Carbamazepine ¹ Phenobarbitone Clonazepam ¹	—

05	65	M	62	No	10.0	Idiopathic epilepsy	—	—
06	53	M	65	Yes	7.5	Alcohol withdrawal	—	—
07	20	M	50	Yes	4.0	Friedrich's ataxia and mental retardation	Phenytoin ¹	—
08	31	M	81	Yes		Previous cerebral abscess	Phenytoin	—
09	55	M	43	No	5.0	Alcohol withdrawal	Phenytoin	
10	61	F	72	No	5.0	Cerebral metastases (Ca Lung)	—	—
11	25	M	73	Yes	10.0	Myoclonic epilepsy	Valproate ² Phenytoin ² Clonazepam ²	Drug levels not measured
12	71	F	43	Yes	15.0	Cerebral metastases (unknown primary)	—	—
13	55	M	43	No	2.5	Alcohol withdrawal	Phenytoin	
14	39	M	52	Yes	9.0	Post-traumatic epilepsy	Phenytoin	Patient had been convulsing for 50 min prior to Midazolam
15	38	F	26	No	5.0	Mental retardation chromosome 4-9 translocation	Phenytoin Carbamazepine ¹	
16	64	M	110	Yes	7.5	Metabolic (hypoglycaemia)	—	—
17	52	M	75	No	5.0	Alcohol withdrawal	Phenytoin	—
18	74	M	120	Yes	5.0	Alcohol withdrawal	Phenytoin	—
19	45	M	60	Yes	7.5	Alcohol withdrawal	Phenytoin	—
20	49	F	56	Yes	7.5	Alcohol-associated epilepsy	Phenytoin ³	Phenytoin level in toxic range (38.0 mg/ml); intoxicated B.A.L. 0.12 g/dl

¹Patients anticonvulsant level within the therapeutic range.

²Patients anticonvulsant levels not measured.

³Patients anticonvulsant level within the toxic range.

RESULTS

Control of seizures was achieved in less than one minute in all 20 patients, of whom 12 were in status epilepticus.

No patient suffered any significant cardio-respiratory depression. Of the 13 patients taking anticonvulsants, only three had serum levels in the therapeutic range. One patient was in the toxic range for phenytoin and intoxicated with alcohol (patient 20) (Table 1).

DISCUSSION

Previous studies have suggested that midazolam would share anticonvulsant properties with diazepam. In this study, midazolam has been shown to be an effective agent for emergency seizure control. It was effective over a wide range of ages (20–74 years) and weights (26–120 kg). The effective dose of midazolam lay between 2.5 and 15 mg with a mean dose of 8.25 mg.

Further studies are being undertaken.

REFERENCES

- Brown C. R., Sarnquist F. H., Canup C. A. & Pedley T. A. (1979) Clinical, electroencephalographic and pharmacokinetic studies of a water-soluble benzodiazepine, midazolam maleate. *Anesthesiology* **50**, 467–70.
- Davidson D. L. W. (1980) Anticonvulsant drugs. *British Medical Journal* **286**, 2043–5.
- DeJong R. H. & Bonin J. D. (1981) Benzodiazepines protect mice from local anaesthetic convulsions and death. *Anaesthesia and Analgesia* **60**, 385–9.
- Delgado-Escueta A. V., Wasterlain C., Treiman D. M. & Porter R. J. (1982) Current concepts in neurologic management of status epilepticus. *New England Journal of Medicine* **306**, 1337–40.
- Deshmukh A., Wittert W., Schnitzler E. & Mangurten H. H. (1986) Lorazepam in the treatment of refractory neonatal seizures. *American Journal of Diseases of Children* **140**, 1042–4.
- Gastaut H., Naquet R., Poire R. & Tassinari C. A. (1965) Treatment of status epilepticus with diazepam (Valium). *Epilepsia* **6**, 167–82.
- Meldrum B. S. & Chapman A. G. (1986) Benzodiazepine receptors and their relationship to the treatment of epilepsy. *Epilepsia* **27** (Supplement), S3–S13.
- Naquet R., Soulayrol R., Dolce G., Tassinari C. A., Broughton R. & Loeb H. (1965) First attempt at treatment of experimental status epilepticus in animals and spontaneous status epilepticus in man with diazepam (Valium). *Electroencephalography and Clinical Neurophysiology* **18**, 424–7.
- Sunao Kaneko, Kozo Kurahashi, Seiichi Fujita, Yutaka Fukushima, Tokijiro Sato & Hill R. G. (1983) Potentiation of GABA by midazolam and its therapeutic effect against status epilepticus. *Folia Psychiatrica et Neurologica Japonica* **37**, 307–9.