Novel treatment (new drug/intervention; established drug/procedure in new situation)

Significant hypotension following buccal midazolam administration

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Summary

Buccal midazolam is a rescue medication to reduce the duration of or stop an epileptic seizure, and is used to prevent status epilepticus. It is available in various forms, including a buccal preparation with a strength of 10 mg/1 ml. Midazolam is a licensed medication, but the buccal formulation is currently used off-licence. The prescriber takes ultimate responsibility for its use in this way. Administered by a trained person, it is receiving widespread acceptance as an alternative and effective treatment to rectally-administered diazepam in the community. The commonest side effects of midazolam are drowsiness and somnolence, although respiratory depression and paradoxical reactions, for example, agitation, restlessness and disorientation, may also occur. Hypotension is said to be a rare side effect, but with no reported cases in people administered buccal midazolam. The authors report a case of significant hypotension associated with administration of buccal midazolam for seizure management.

BACKGROUND

Status epilepticus is a medical emergency which is associated with significant morbidity and mortality. Adequate treatment in the premonitory phase can prevent its emergence. Benzodiazepines are effective treatment agents at both the premonitory and established stages.¹ Buccal midazolam is gaining favour in community settings for the premonitory stage because it is less invasive than rectal diazepam.²

CASE PRESENTATION

A 24-year-old man with refractory epilepsy and recurrent episodes of status epilepticus was referred for drug changes. He had frequent focal seizures often generalising. The occurrence of ≥ 5 focal seizures within an hour would usually herald a convulsive episode. This criterion triggered a call to the emergency services.

On admission, he was on a combination of carbamazepine 500 mg, zonisamide 500 mg, lamotrigine 50 mg, phenytoin 375 mg and lacosamide 500 mg daily.

Apart from obesity, examination was normal. His routine blood investigations and electrocardiography were within normal limits (table 1).

Four days after admission, he experienced a cluster of two focal seizures and one secondarily generalised seizure within an hour. His blood pressure was 103/50 mm Hg and his pulse was regular at 90 beats per min (bpm). He was noted to be drowsy but was responding appropriately to painful stimuli. Examination was otherwise unremarkable. Within the following 20 min he had two further generalised seizures. Seizure activity subsided after 10 mg buccal midazolam. However, 15 min later, his blood pressure decreased remarkably to 83/68 mm Hg (figure 1) and he was placed in the recovery position. His vital signs were monitored continuously. Blood pressure increased back to 129/67 mm Hg 68 min after the medication was given. At

the time, ECG showed sinus rhythm and saturation was within normal limits (figure 1).

DISCUSSION

Midazolam can be administered intravenously, rectally, intranasally, intramuscularly and buccally. Its action usually starts within 2–3 min following intravenous administration and within 15 min by the rectal, intramuscular, nasal and buccal routes. All routes have been shown to be effective in emergency treatment of seizures.^{3–5}

The therapeutic and adverse effects of midazolam are due to its effects on γ -aminobutyric acid A (GABA-A) receptors. Midazolam does not activate GABA-A receptors directly but, as with other benzodiazepines, it enhances the effect of the neurotransmitter GABA on GABA-A receptors resulting in neural inhibition.⁶

Hypotensive episodes requiring treatment have occurred in people who have received a midazolam injection for therapeutic sedation, especially when administered rapidly.⁴ Intramuscular administration has been associated

Table 1 Physical parameters

BMI	48.04 kg/m ²
ECG, BP	Sinus rhythm, HR 67/min, rightward axis, RR 899 ms, PR 200 ms, QRS 124 ms, QT 370 ms, QTC 394 ms, 135/80 mm Hg
Blood tests	Sodium 142 mmol/l, potassium 3.6 mmol/l, urea 4.8 mmol/l, creatinine 93 μ mol/l, estimated GFR 87 ml/min, random glucose 4.1 mmol/l, calcium 2.3 mmol/l. Haemoglobin 15.0 g/dl, white cell count 4.8×10^9 /l, red blood count 4.82×10^{12} /l
Drug levels	Carbamazepine 5 μ mol/l Carbamazepine epoxide <1 μ mol/l Zonisamide 92 μ mol/l Phenytoin 45 μ mol/l Lacosamide 37 μ mol/l

BMI, body mass index; BP, blood pressure; GFR, glomerular filtration rate.

Figure 1 Clinical process.

with the same effect⁴ and indeed, the use of intramuscular midazolam for the emergency treatment of seizures was abandoned at the Chalfont Centre for Epilepsy in the early 1990s after the occurrence of three hypotensive episodes (JWS and JS Duncan, personal communication in Aug 2010). Hypotension following administration of buccal midazolam has been mentioned as a rare adverse event associated with pre-existing hyponatraemia. There have been no reported cases in people with epilepsy.⁶⁷

In our case, a patient with severe epilepsy experienced a significant drop in blood pressure after 10 mg buccal midazolam. Although blood pressure prior to 10 mg buccal midazolam administration was lower than usual, it markedly fell further afterwards (figure 1). It is highly unlikely that this was caused by another event, as there was no evidence for previous existing electrolyte disturbance, cardiovascular instability or appreciable co-morbidities (table 1). For subsequent seizure clusters, the patient was given only 5 mg buccal midazolam, with no further episodes of hypotension.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. British Medical Association, Royal Pharmaceutical Society of Great Britain: British National Formulary 59. British medical journal publishing group and pharmaceutical press, March 2010. <http://bnf.org/bnf/bnf/current/6601.htm> (accessed 21 September 2010).
2. Wilson MT, Macleod S, O'Regan ME. Nasal/buccal midazolam use in the community. *Arch Dis Child* 2004;**89**:50–1.
3. Walker M. Status epilepticus: an evidence based guide. *BMJ* 2005;**331**:673–7.
4. Bell DM, Richards G, Dhillon S, *et al*. A comparative pharmacokinetic study of intravenous and intramuscular midazolam in patients with epilepsy. *Epilepsy Res* 1991;**10**:183–90.
5. McIntyre J, Robertson S, Norris E, *et al*. Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial. *Lancet* 2005;**366**:205–10.
6. Penn Pharmaceutical Services. <http://www.pennpharm.co.uk> (accessed 21 September 2010).
7. Product Information – Epistatus. Buccal midazolam maleate solution equivalent to midazolam base 10 mg in 1 ml. Special Products Limited. <http://www.phebra.com.au/data/products/SOL041-pi.pdf> (accessed 21 September 2010).

Learning points

- ▶ Our case shows the potentially hypotensive effect of buccal midazolam.
- ▶ Clinicians who prescribe buccal midazolam for emergency seizure management should be aware of this.
- ▶ People who receive this agent may need careful monitoring to detect and manage hypotension as early as possible.
- ▶ If marked hypotension is seen, lower doses of buccal midazolam may be worth considering subsequently.

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