South African National Essential Medicine List
Primary Health Care Medication Review Process
Component: Emergencies and injuries

1. Executive Summary

Date: 31 August2017
Medicine (INN): Midazolam, buccal (repeat dose)
Medicine (ATC): N05CD08
Indication (ICD10 code): G41.9
Patient population: Children < 12 years of age
Prevalence of condition: 17-23/100 000 in developed countries
2.3/1000 cases of convulsive status epilepticus in African multisite survey – 61% of these juveniles(1)
Level of Care: Primary Health Care
Prescriber Level: Emergency medicine – Nurse
Current standard of Care: Single dose of buccal midazolam or up to 2 doses of rectal diazepam. If no response, phenobarbital (phenobarbitone) is administered through nasogastric tube.
Efficacy estimates: (preferably NNT): N/A
Motivator/reviewer name(s): Dr Sandy Picken
PTC affiliation:n/a

2. Name of author(s)/motivator(s)

Dr Sandy Picken

3. Author affiliation and conflict of interest details

Affiliation: PHC Technical Sub-committee of NEMLC; Knowledge Translation Unit, University of Cape Town.

Conflict of interest: None

4. Introduction/ Background

Generalized convulsive status epilepticus (SE) is a serious and potentially life threatening medical emergency that requires prompt intervention.

Although the definition of SE has varied over time, for pragmatic clinical purposes of this review, the accepted definition of SE (early) will be a single unremitting seizure lasting longer than **five minutes** or frequent clinical seizures without return to the baseline clinical state. This corresponds with the time at which urgent treatment should be initiated.

Current standard treatment guidelines in South Africa recommend the following medicine treatment for the management of SE in children < 12 years old:

MEDICINE TREATMENT:
Children < 12 years of age

- Midazolam, buccal, 0.5 mg/kg/dose as a single dose. See dosing table, pg 22.6.
- Use midazolam for injection 5 mg in 1 mL undiluted.
- Draw up the required volume in a 5 mL syringe.
- Remove needle then administer midazolam into the buccal cavity (between gum and cheeks).
- **Note**: Buccal midazolam should not be used in infants < 6 months of age.

OR

- Diazepam, rectal, 0.5 mg/kg/dose as a single dose. See dosing table, pg 22.3.
- Use diazepam for injection 10mg in 2 mL undiluted.
- Draw up the required volume in a 2 mL syringe.
- Remove needle then insert the whole barrel of the lubricated syringe into the rectum and inject the contents.
- Remove syringe and hold buttocks together to minimise leakage.
- Maximum dose: 10 mg in 1 hour.
- May be repeated after 10 minutes if convulsions continue.
- Expect a response within 1–5 minutes.

If no response after one dose of midazolam or two doses of diazepam, and if the convulsion has lasted more than 20 minutes:

ADD

- Phenobarbital, oral, crushed and given by nasogastric tube, 20 mg/kg as a single dose. See dosing table, pg 22.7.

MIDAZOLAM

15.2 Seizures (convulsions/fits); 21.20 Status epilepticus.

- Midazolam, buccal, 0.5 mg/kg

Weight kg	Dose mg	Injection (buccal administration) 5 mg/mL	Age Months/years
>7–9 kg	4 mg	0.8 mL	>6–12 months
>9–11 kg	5 mg	1 mL	>12–18 months
>11–14 kg	6 mg	1.2 mL	>18 months–3 years
>14–17.5 kg	7.5 mg	1.5 mL	>3–5 years
>17.5–25 kg	10 mg	2 mL	>5–7 years
>25–35 kg	12.5 mg	3 mL	>7–11 years
>35 kg	20 mg	4 mL	>11 years

DIAZEPAM

15.2 Seizures (convulsions/fits); 15.2.3 Febrile convulsions; 21.20 Status epilepticus.

- Diazepam, rectal, 0.5 mg/kg/dose for convulsions as a single dose.

Weight kg	Dose mg	Ampoule 10 mg/2 mL	Age Months/years
>3–6 kg	2 mg	0.4 mL	<6 months
>6–10 kg	2.5 mg	0.5 mL	>6 months–1 year
>10–18 kg	5 mg	1 mL	>1–5 years
>18–25 kg	7.5 mg	1.5 mL	>5–8 years
>25–40 kg	10 mg	2 mL	>8–12 years

Midazolam is a short-acting benzodiazepine that has been clearly demonstrated to be an effective option for the acute management of epileptic seizures. It has the advantage of being water-soluble, with a rapid onset of action and it can be administered orally or intranasally, implementing an early intervention at the pre-hospital setting.

The recommendation for inclusion ofsingle dose midazolam, buccal to the PHC EML was supported by a medicine review, dated 28 May 2014 and the accompanying appendix of evidence (refer to the medicine reviewand appendix I for detailed information).

The purpose of this update of the initial review is to review the safety of a **second dose** of buccal midazolam in children.

5. Purpose/Objective i.e. PICO question:

-P *(patient/population):* Children< 12 years with status epilepticus
-I *(intervention):* Second dose of buccal midazolam
-C *(comparator):*N o repeat dose of midazolam [or enteral phenobarbitone]
-O *(outcome):* Efficacy (time to cessation of seizures), side effects (respiratory depression, respiratory arrest, death, neurological sequelae)

(P) Amongst children < 12 years old with status epilepticus, in whom seizures persist despite an initial dose of buccal midazolam, is **(I)** a second repeat dose of buccal midazolam compared to **(C)** placebo/no treatment *or* enteral phenobarbitone **(O)** safe and effective in terms of time to cessation of seizures, side effects (respiratory depression, respiratory arrest), neurological sequelae, death?

6. Methods:

a. Data sources: Pubmed

b. Search strategy

(((((("status epilepticus"[MeSH Terms] OR ("status"[All Fields] AND "epilepticus"[All Fields]) OR "status epilepticus"[All Fields]) OR ("seizures"[MeSH Terms] OR "seizures"[All Fields])) AND ("pharmacology"[Subheading] OR "pharmacology"[All Fields] OR "pharmacology"[MeSH Terms])) AND ("midazolam"[MeSH Terms] OR "midazolam"[All Fields]) OR ("benzodiazepines"[MeSH Terms] OR "benzodiazepines"[All Fields])) NOT ("ketamine"[MeSH Terms] OR "ketamine"[All Fields])) NOT (continuous[All Fields] AND ("midazolam"[MeSH Terms] OR "midazolam"[All Fields]))) AND (buccal[All Fields] OR oromucosal[All Fields] OR non-intravenous[All Fields] OR (non-parenteral[All Fields] AND routes[All Fields]))) AND ("safety"[MeSH Terms] OR "safety"[All Fields])

Adding the term enteral phenobarbitone retrieved no additional studies.

c. Out of the 30 citations identified, abstracts of 15 articles were assessed for eligibility based on likely relevance.8articles were excluded because the focus was either on intranasal midazolam with no repeat dosing examined or studies/reviews have been included in 2014 EML review with no additional information to add in context of repeat dose of midazolam. Of the remaining 7, 5 were reviews and 2 were evidence based guidelines with no individual studies found.

d.

	Author, date	Type of study	Reason for exclusion
1.	Zelcer et al, 2016 (2)	Literature review	Route of administration does not include buccal RoA and no reference to repeat/second dosing.
2.	Brigo et al, 2015 (3)	Meta-analysis	Indirect comparison of intranasal midazolam with buccal midazolam – not relevant to clinical PICO question
3.	McKee et al, 2015 (4)	Review	No access to full article
4.	McMullen et al, 2010 (5)	Meta-analysis	Included in 2014 EML review – no additional information to add in context of repeat dose.
5.	Mpimbaza et al, 2008(6)	RCT	Included in 2014 EML review – no additional information to add in context of repeat dose.
6.	Klimach et al, 2009(7)	Survey	Paediatrician and parent Questionnaires
7.	Appleton et al, 2008 (8)	Systematic Cochrane review	Primary focus of this review - intravenous lorazepam is at least as effective as intravenous diazepam. McIntyre study used to inform buccal MDZ conclusion and this was included in 2014 EML review – no additional information to add in context of repeat dose.
8.	McIntyre et al, 2005 (9)	Pseudo-randomised controlled trial	Included in 2014 EML review – no additional information to add in context of repeat dose.

e. Evidence synthesis –

The reviews included here add little in the way of evidence around repeat dosing of midazolam in the context of persistent seizures. They have been included for primary purpose of comparing adverse events between different benzodiazepines and different routes of administration as well as looking at strength of argument for non-intravenous management.

f. Given that available evidence related to the clinical PICO question is extremely limited – a search of UpToDate and International guidelines (WHO and NICE) were examined. Findings show that repeat dosing of buccal midazolam is generally advocated.

g. The Medicines Information Council (MIC) was also contacted and provided reference to an Australian Prescriber article which endorses and outlines repeat dosing of midazolam (10).

Appendix I: May 2017 update

	Type of study	n	Population	Comparators	Primary outcome	Relevant re Comments
Systematic reviews/ meta-analyses						
Jain et al, 2016(11)	Systematic Review	26 studies -RCTsand quasi-randomized controlled trials, irrespective of blinding included.	> 1 month old (children and adults)	1. Time to administration 2. Time to seizure termination 3. Rate of treatment failure 4. Prevention of seizure recurrence 5. Patient and caregiver treatment satisfaction 6. Adverse events realted to BDZ treatment or RoA 7. Respiratory adverse events	Proportion of children with clinical seizure cessation within 10 minutes of drug administration	› Signif and w › 'Mod comp o › The re but th time t lower cessat admin
Haut et al, 2016(12)	Systematic Review	75 unique citations 30 specifically for MDZ	Search terms for seizures + benzodiazepines	DZP - Diazepam LZP - Lorazepam MDZ - Midazolam CLB - Clobazam CZP - Clonazepam	- Safety and efficacy outcomes -Patient/care-giver satisfaction	- 100% of t buccal MD - Almost ha termination terminated Lower trea compared
Chin et al, 2014(13)	Non-systematic Review	-	-	· IN MDZ versus PR DZP · IN MDZ versus IV DZP · Buccal MDZ versus PR DZP · Buccal MDZ versus IV DZP · IM MDZ versus IV DZP · IM MDZ versus IV LZP · IM DZP versus placebo	· Buccal MDZ superior to PR DZP. · Buccal MDZ vs PR DZP: In all the studies, respiratorydepression was similar or less frequent with treatmentwith buccal MDZ, compared to treatment withPR DZP. Buccal MDZ vs IV DZP: time to dosing quicker with buccal; time from administration quicker with IV. For up to 10 minutes posttreatment, no patients in either group had unusual	Examines t stability in drug absor and safety,

				· Ease of delivery route and social acceptability	CNS depression, respiratory depression, apnoea, orcardiac dysrhythmia.	
Anderson, 2013(14)	Non-systematic Review	7 citations in efficacy comparison	Many studies spanning efficacy, safety, and patient/caregiver acceptability	N/A	N/A	- Five studies compared its efficacy against that of rectal diazepam. In all of these, buccal midazolam was found to be as effective or more effective - Respiratory depression reported in two of the comparative trials with an incidence of 0.6%–5%. This was not increased compared with that seen in the diazepam-treated groups.
Sofou et al, 2009 (15)	Systematic review	8 studies		· IM MDZ vs IV DZP · Buccal MDZ vs PR DZP · IN MDZ vs IV DZP · IN LZP vs IM paraldehyde · Buccal MDZ vs rectal placebo vs PR DZP vs buccal placebo · IV MDZ vs IV DZP		**Buccal MDZ vs PR DZP** · Equally effective in the treatment of prolonged seizures · All participants had known severe epilepsy · Time from arrival to drug administration was 2 min · Hypotension was slightly more prominent in the midazolam arm **Buccal MDZ vs rectal placebo vs PR DZP vs buccal placebo** · Buccal midazolam was safe as and more effective than rectal diazepam in prolonged seizures · Majority of patients with severe malaria, which also accounted for 50% of deaths · One SAE of intense pruritus deemed possibly related to midazolam
Guidelines (evidence based)						
Shah et al, 2014(16)	· Using a National Prehospital EBG Model and GRADE methodology, a paediatric seizure guideline has been developed that emphasizes the routine assessment of capillary blood glucometry and the use of buccal, IM, or intranasal benzodiazepines over IV or rectal routes for seizure cessation.				Recommendation #7: We recommend that prehospital protocols for seizure management in children utilize alternative (non-IV) routes of drug administration as first-line therapy for treating children with status epilepticus. Evidence quality: Moderate; Recommendation strength: Strong Recommendation #8: We recommend buccal midazolam over rectal (PR) diazepam for prehospital seizure cessation and control. Evidence quality: Low; Recommendation strength: Strong	
Glauser et al, 2016(17)	Guideline based on literature review	38 RCTs split into adult and paediatric	RCTs of anticonvulsant treatment for seizures longer than 5 minutes	· N/A	-- A meta-analysis of six class III pediatric studies found non-IV midazolam (IM/intranasal/ buccal) was more effective than diazepam (IV/rectal) at achieving seizure cessation (relative risk [RR] =1.52, 95% CI: 1.27–1.82) with similar respiratory complications (RR = 1.49; 95% CI: 0.25–8.72). - Only one study found a significantly shorter time to seizure	Choose 1 of the following for 1st line: i. IM midazolam, single dose (10mg >kg, 5mg for 13-40kg) OR ii. IV lorazepam, may repeat once) OR iii. IV diazepam, may repeat once) If none of these available: choose 1 of: i. IV phenobarb, single dose ii. PR Diazepam, single dose iii. Buccal midazolam, IN midazolam

					cessation for buccal midazolam compared with rectal diazepam.	

International guidelines and synthesized evidence products	
WHO(18)	GIVE MEDICATION TO STOP CONVULSIONS IF NO I.V. ESTABLISHED Give: diazepam rectally (adult 10 mg, child 1 mg/year of age) OR midazolam buccally/intranasally (5-10 mg adult, child 0.2 mg/kg) Have the convulsions stopped within 10 minutes of 1st dose of emergency medication? No GIVE 2nd DOSE OF EMERGENCY MEDICATION Have the convulsions stopped? No REFER URGENTLY TO HEALTH FACILITY DO NOT GIVE MORE THAN 2 DOSES OF EMERGENCY MEDICATION
NICE(19)	Administer intravenous lorazepam as first-line treatment in hospital in children, young people and adults with ongoing generalised tonic–clonic seizures (convulsive status epilepticus). Administer intravenous diazepam if intravenous lorazepam is unavailable, or buccal midazolam if unable to secure immediate intravenous access. Administer a maximum of two doses of the first-line treatment (including pre-hospital treatment).
UpToDate Management of convulsive status epilepticus in children	When IV access is unavailable, alternative agents include: • Buccal midazolam 0.2 mg/kg, maximum 10 mg • IM midazolam 0.1 to 0.2 mg/kg, maximum 10 mg • Rectal diazepam 0.5 mg/kg, maximum 20 mg Benzodiazepine: second dose given after further 5 – 10 minutes
Smith et al, 2017 (10)	Current guidelines recommend an initial buccal or intranasal dose of 0.3 mg/kg to a maximum of 10 mg. Each drop of the 5 mg/mL solution contains approximately 0.3 mg midazolam. Absorption takes approximately 1–3 minutes and midazolam can take up to 10 minutes to abort the seizure. The dose can be repeated after five minutes if seizures persist.

Discussion

In practical terms, it has been observed that the longer the status epilepticus persists, the more resistant it becomes to treatment and more is the risk of neuronal injury (20). Pre-hospital treatment by a non-intravenous route is therefore most desirable since IV access poses a major challenge in a child experiencing seizures, particularly in children under the age of 5 years, when convulsive status epilepticus is most common.

Midazolam is a relatively novel seizure medication. A growing wealth of literature has demonstrated its efficacy and safety in paediatric populations. Buccal administration of midazolam in particular has been demonstrated a popular, socially acceptable, and clinically appropriate seizure medication. A previous medicine review has demonstrated that midazolam, when compared to alternative seizure medications, such as diazepam, and alternative methods of administration, such as IV or rectal delivery is either as effective or more effective than comparators, hence its inclusion in the last review of STG. Upon revisiting the evidence, these studies did not use a second dose of buccal midazolam – if the seizure persisted beyond 10 minutes or recurred within 1 hour, the child was categorized as having treatment failure and treated with intravenous benzodiazepines. There seems to be a dearth of evidence specifically examining the safety of buccal midazolam in the context of a second dose.

When reviewing the lack of safety data for buccal midazolam, it is important to note that the review by Glauser et al (17) showed that the rate of respiratory depression in patients with convulsive status epilepticus treated with benzodiazepines is lower than in patients with convulsive status epilepticus treated with placebo indicating that respiratory problems are an important consequence of untreated convulsive status epilepticus.

Various evidence based guidelines (16) and International accredited guidelines including WHO and NICE, routinely include a second dose of benzodiazepine, regardless of route of administration (including buccal midazolam) for persistent seizures.

There is an argument that a second dose of benzodiazepine may inappropriately delay optimal second line treatment, however in the context of the PHC STG, this second line treatment is oral phenobarbital, crushed and given via a naso-gastric tube, the placement of which may in itself pose a risk. The IV formulation of phenobarbitoneremains a Section 21 item.

The European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP) assessment report provides the following commentary regarding a second dose of midazolam:
"The posology section of the SmPC of rectal diazepam recommends administration of a second dose in refractory cases whereas efficacy of buccal midazolam has been demonstrated for single use only, and the proposed SmPC recommends single use. In the Mpimbaza study (6) the rate of recurrence of seizure activity within one hour was 8% for midazolam and 17.5% for rectal diazepam (p=0.026) and recurrence within 24 hour 39,1% and 46,3% respectively.
Although this indicates less need for retreatment under midazolam in case of treatment failure, the Applicant calculated that a second dose administered at 10, 30 and 60 minutes after the first dose results in an increase of the Cmax with an factor 1.6 to 2 after 10 minutes, 1.2 to 2 after 30 minutes and a less pronounced increase of Cmax after 60 minutes. Therefore re-treatment of midazolam in case of non-response is not recommended and can only take place under medical supervision in emergency medical setting.
The clinical studies were all performed in an emergency room or residence setting. However, the rates of observed respiratory depression were similar for Buccolam and rectal diazepam. As rectal diazepam has been safely used in the community on an extensive scale, midazolam can be expected to show similar safety."

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [X] Not confident [ ] Uncertain [ ]	
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [ ] No [X] List the members of the group. List specific exclusion from the group: Lorazepam excluded from primary health care settings due to high cost and the challenges associated with the need for locked refrigeration.	Rationale for therapeutic alternatives included: References: Rationale for exclusion from the group: References:
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	
RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [ ] Uncertain [X]	Cost of medicines: **Medicine** / **Cost (ZAR)*** Midazolam 1mg/mL 5mLampoule — R3.53 Midazolam 5mg/mL 10mL Vial — R14.82 Diazepam 5mg/mL 2 mL ampoule — R 2.40 *Contract circular HP06-2017SVP **Additional resources:**

EQUITY	**Would there be an impact on health inequity?** Yes: X No: Uncertain:	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes: X No: Uncertain:	

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☐	☐	**X**

Recommendation: The Primary Health Care Committee recommends a second dose of buccal midazolam if seizures persist for more than 5 mintues after the initial dos, with urgent referral of the child and a caution box that prompts the healthcare worker to monitor for respiratory depression.

Rationale: Status epilepticus is relatively common in children, and failure to terminate seizures rapidly can lead to cerebral metabolic decompensation and is life-threatening. Obtaining IV access is difficult in a young fitting child, hence the recommendation of buccal and rectal formulations of benzodiazepines. Historically, the PHC STG has recommended a second dose of rectal diazepam.

Despite limited evidence, in the context of a persistently fitting child, the risk–benefit ratio favours a second dose of buccal midazolam too, given the following:
1) The risk of prolonged seizures probably outweighs the risk of benzodiazepine-associated respiratory depression, even in a PHC setting. The available evidence shows that significant adverse effects of buccal midazolam, including respiratory depression, were infrequently reported, and, when present, were similar to diazepam, Thus, the safety profile of buccal midazolam is expected to be similar to rectal diazepam. According to the Ideal Clinic Policy (April 2017), all PHC facilities must be equipped to manage respiratory depression (i.e. emergency trolley should have a manual bag valve mask/ manual resuscitator or self-inflating bag with compatible masks for paediatrics).
2) The current recommendation for second line treatment is crushed oral phenobarbitone via NGT, which is supported by a small pharmacokinetic study in a hospital setting which used phenobarbitone only after two doses of benzodiazepines failed to terminate the seizure (21). The placement of a nasogastric tube in a fitting child may be challenging in primary health care settings.

Level of Evidence: III Guidelines, Expert opinion

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
	X	

VEN status:

Vital	Essential	Necessary
X		

Monitoring and evaluation considerations

Research priorities

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