First line management of prolonged convulsive seizures in children and adults – good practice points

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Article type: consensus paper and guideline

Running title: First line treatment of convulsive seizures

Abstract

Over the past decades, it has become clear that the most efficient way to prevent status epilepticus is to stop the seizure as fast as possible, and early treatment of prolonged convulsive seizures has become an integral part of the overall treatment strategy in epilepsy. Benzodiazepines are the first choice drugs to be used as emergency medication. This treatment in the early phases of a seizure often implies a 'pre-medical' setting before intervention of medically trained persons. In this paper, we propose "good practice points" for first line management of prolonged convulsive seizures in children and adults in a 'pre-medical' setting.

Key words: epilepsy, anti-epileptic drugs, benzodiazepines, seizures, emergency treatment, prolonged

Abbreviations:

BZP	benzodiazepines
DZP	diazepam
IB	intrabuccal
IN	intranasal
IM	intramuscular
IR	intrarectal
IV	intravenous
LZP	lorazepam
MDZ	midazolam

Introduction

In recent years, early treatment of prolonged convulsive seizures has become an integral part of the overall treatment strategy in epilepsy [1]. It is clear that the most efficient way to prevent status epilepticus is to stop the ongoing seizure as fast as possible, ideally within the first minutes. Chin *et al*. demonstrated that one of the major predictors for long lasting seizures and status epilepticus was inadequate or lack of use of benzodiazepines (BZP) in the early stages of the seizure [2]. It is recognized that early management should imply administration of treatment before the intervention of a medically trained emergency team or before arrival at the emergency department of the hospital. This 'pre-hospital' intervention in the community is considered the first and perhaps the most important phase in the treatment of an acute prolonged convulsive seizure, followed by a second phase with intravenous (IV) anti-epileptic drug administration, and eventually a third intensive care phase with anesthetic drugs if necessary [3]. In this paper we propose "good practice points" for the treatment of prolonged convulsive seizures in children and adults. The treatment of non-convulsive seizures and status epilepticus is not within the scope of this paper.

Methodology

A group of Belgian epilepsy experts, adult and pediatric neurologists, and an emergency/intensive care pediatrician, came together to review and discuss guidelines for the first line treatment of prolonged or repetitive convulsive seizures in children and adults in Belgium. Prior to this expert meeting, the scientific literature (Pubmed) was

searched for international treatment guidelines for seizures, and relevant controlled clinical trials. The discussion was based primarily on international guidelines published by the UK National Institute for Clinical Excellence (NICE, 2013) and the European Federation of Neurological Societies (EFNS, updated in 2011), and on the personal experience of the experts. The information in these published guidelines combined with the experts experience, was translated into good practice points for the use of emergency medication in the Belgian situation. All the members of the expert group read the first draft of the good practice points and discussed changes to reach an informative consensus.

Prolonged convulsive seizures: what, when and whom to treat?

Longer lasting seizures can cause direct damage to the brain by inducing brain edema and ischemia [4], but they also cause systemic effects such as rhabdomyolysis, metabolic dysregulation and acute disturbance of autonomic functions, including gastric paresis and cardiac arrhythmia. An almost linear relationship exists between the duration of the seizure and the risk for secondary brain damage [4]. It is generally accepted that convulsive seizures are more harmful than non-convulsive seizures. Clinical data indicate that spontaneous cessation of generalized convulsive seizures is unlikely after 5-10 minutes [5, 6]. The risk of a long-lasting seizure or status epilepticus (with considerable morbidity and mortality) is very significant whenever a convulsive seizure lasts for more than 5-10 minutes [6, 7]. Recent studies have elucidated a mechanism possibly underlying this phenomenon. It was shown in small animal models

that during a seizure the postsynaptic inhibitory GABA-A receptors get internalized in the cell. At the same time, more excitatory glutamate receptors appear on the cell surface making the cell more excitable [8, 9]. These dynamic processes occurring during a seizure are important to understand treatment options and possible treatment failures in prolonged seizures. However, this principle remains to be proven in clinical practice in humans. The window of opportunity to give the classic GABA-ergic drugs (*e.g.* benzodiazepines (BZP)) is probably in the early phase of a seizure, being the first 5 to 10 minutes. Therefore, it is proposed to give a first dose of emergency medication when the convulsive seizure does not stop after 5 minutes. This implies that most often a non-medically trained person has to administer the emergency medication in the community (e.g. at home, at work, at school or in a sports club). Therefore, parents, grandparents, teachers, caregivers, partners and other people who are in close contact with the patient, should be educated.

These good practice points should always be considered in case of convulsive seizures in patients known with epilepsy, and with a history of prolonged (lasting more than 5 minutes) or repetitive (3 or more in an hour) convulsive seizures. It was shown by Shinnar *et al.* [6, 10] that in children the duration of a subsequent seizure correlates very well with the duration of the first seizure, making it possible to define a high risk group for whom it is advisable to prescribe acute treatment. We do not usually recommend prescription of emergency medication to any patient who experienced a short (less than 5 minutes) convulsive seizure of any type. For instance, in benign rolandic epilepsy, childhood absence epilepsy or juvenile myoclonic epilepsy, the risk for

prolonged convulsive seizures is known to be low. Therefore, an individualized care plan should be made for every patient, based on the epilepsy syndrome diagnosis, the type or duration of the usual seizure, and the experience of the treating physician. Emergency treatment could also be considered for prolonged febrile seizures. Other target populations are non-compliant patients and the group of patients with a history of prolonged seizures in whom one tapers anti-epileptic drugs after a long period of seizure freedom. During tapering and in the first months after stopping of the drugs, there is a risk for recurrence of seizures.

General management of prolonged convulsive seizures

When a person experiences a convulsive seizure that lasts longer than 5 minutes, airway/breathing/circulation (ABC) management comes at the first place. Lay care givers should check if the mouth of the patient is empty, and position the head and body of the patient so to enable a free airway. Breathing should be assessed by feeling with the cheek and looking for chest expansion. If breathing is absent, or only gasping is present, cardiopulmonary resuscitation should be started. In any case of prolonged convulsive seizures emergency medical services should be alerted (European emergency number 112). Safety of both the patient and caregiver themselves should be guaranteed: objects that could hurt the patient should be removed, restraining garments should be loosened, the environment should be safe,…

Benzodiazepines

First line medication to be administered in the community should be effective (fast action), safe, easy and socially acceptable to administer, and stable for conservation during a long period. There is consensus about the use of benzodiazepines (BZP) to treat prolonged convulsive seizures. Their working mechanism is well known. BZP activate the binding of GABA to the post-synaptic inhibitory ionotropic GABA-A receptor, thereby opening a chloride channel and hyperpolarizing the postsynaptic neuron, leading to a decreased neuronal excitability [11, 12]. BZP typically reach the brain within minutes. Studies in rodents showed that the ictal discharges disappear within 5 to 10 minutes, together with the onset of post-ictal slow waves on the EEG. However, there are subtle but perhaps clinically important differences between BZP. The onset of effect is faster for midazolam (MDZ) than for lorazepam (LZP) and diazepam (DZP), but the duration of the effect is much longer for LZP than for MDZ and DZP. This may also explain why the hangover effects like drowsiness, sleepiness or abnormal behavior may last longer for LZP than for MDZ. The risk of respiratory depression is a real issue but should not be over-estimated, as was shown in several studies [2, 13, 14]. The seizure itself may cause respiratory depression. This is supported by the observation that respiratory depression occurs more frequently with placebo [13]. Furthermore, the BZP-related risk of respiratory depression is related to individual sensitivity and dosage. In clinical practice, a single correct dosage of BZP poses only a very minimal risk for respiratory depression [2, 15].

Early treatment implies that administration should be kept simple and easy (Table 1 and flowchart). On the spot calculation of the dosage and complex handling procedures of

the product should be avoided. Intrabuccal (IB) LZP (0.05-0.1 mg/kg or 0-2 years : 1 mg and >2 years : 2.5 mg) and IB MDZ (0.2-0.5 mg/kg, maximum 10 mg in one dosis) are the medications of choice [16, 17] for first line treatment of prolonged or repetitive convulsive seizures. Intramuscular (IM) MDZ (0.1-0.2 mg/kg, maximum 10 mg) is another safe and effective option [14], particularly in patients who have hypersalivation or spitting during seizures, leading to inadequate dosing. However, this can only be administered by a medically trained person. Intranasal (IN) MDZ can also be given (0.2-0.5 mg/kg, maximum 10 mg). Although effective, intrarectal (IR) administration of DZP (0.5 mg/kg, maximum 10 mg) cannot be advocated anymore, since it is not only socially unacceptable, but it is also more difficult to administer in a seizing person and there is a high risk of spillage of the product. However, in certain situations, *e.g.* in babies or infants, in cases where no IV access can be obtained, when MDZ or LZP are not available, IR DZP might still be considered.

Most experts use an immediate release of IB LZP (Temesta Expidet® 1 or 2.5 mg) that can be given sublingually. It very rapidly diffuses to the blood through the oral mucosa. Evidence-based data for this formulation are lacking however. A prescription for MDZ should be handled with care, as multiple dilutions exist on the Belgian market: Dormicum®, Midazolam B Braun®, Midazolam Mylan®, each in 15 mg/3 ml, 5 mg/5 ml or 50 mg/10 ml. For evident reasons of volume to be given (IB/IN/IM) the first dilution (15 mg/3 ml) should be used. A ready-to-use IB MDZ oromucosal solution (Buccolam® 2.5 mg/0.5 ml, 5 mg/0.5 ml, 7.5 mg/0.5 ml and 10 mg/0.5 ml) is available in several European countries, and this product is supposed to be launched on the Belgian market.

The first dose of BZP can be given by the parents, grandparents, partners or educated caregivers in the community (Table 1 and flowchart). If needed, a second dose should be given by medically trained people, being the general practitioner, a doctor arriving with the emergency team, or a doctor in the emergency room. This second dosage of BZP, preferentially IV LZP (0.05-0.1 mg/kg) or DZP (0.1-0.3 mg/kg), should be administered with more intensive monitoring (Table 2 and flowchart). If IV access can not be obtained, another dose of IB/IN/IM MDZ, IB LZP or IR DZP can be given [14]. See Table 1 and Table 2 for preparations, formulations and dosages.

Recommendations for treatment

- In a patient with a well-established epilepsy diagnosis and with a history of prolonged (lasting 5 minutes or longer) convulsive seizures, including repetitive seizures (3 or more in an hour), it is good practice to prescribe and explain emergency BZP treatment. Parents, grandparents, partners and caregivers should be educated about the use of these emergency drugs.
- Whenever a patient with known epilepsy experiences a convulsive seizure lasting longer than 5 minutes, BZP should be given to avoid a pending status epilepticus.
- Care should be taken to secure the person's airway and assess respiratory and cardiac function.
- IB MDZ and IB LZP are recommended as first line treatment for children and adults with prolonged or repetitive seizures in the community. IR administration

is not preferred anymore, but can be used as an alternative. Another alternative is IN or IM MDZ.

- After a first BZP dosage, a medical professional should decide on the next treatment step when the seizure did not stop within 10 minutes. This should be a second dosage of BZP, preferentially IV LZP or DZP.
- If 2 dosages of BZP fail, second line treatment in a hospital setting with intensive monitoring of vital functions is mandatory. In most protocols, IV phenytoin, levetiracetam or valproate, followed by general anesthesia with continuous MDZ, thiopental or propofol are preferred [18]. In some guidelines, IV phenobarbital is still recommended, but its place in the treatment algorithm has become controversially.

Conclusions

In this consensus paper, we emphasized the importance of early treatment of acute prolonged or repetitive convulsive seizures. BZP are recommended as first choice emergency treatment to be used in the community by non-medically trained persons. The risk for side effects (especially respiratory depression) is much smaller than the potential benefit of preventing status epilepticus. In children and adults, IB MDZ or IB LZP are recommended as first line treatment. The second dose of BZP should preferentially be IV LZP or DZP administered by a medically trained person.

Acknowledgements

This work was supported by an unrestricted grant from Viropharma, Belgium. Viropharma facilitated the organization of the expert meeting, but was not involved in the discussion or the actual preparation of the consensus guidelines.

L. Lagae and P. Boon chaired the expert meeting. This paper has been prepared under the endorsement of the Belgian League against Epilepsy, and the Belgian Society for Emergency and Disaster Medicine (BESEDIM).

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Table 1: Benzodiazepine formulations and dosing proposal for first administration (IB or IN) in prolonged and repetitive convulsive seizures in children and adults.

Product	**Route**	**Children**	**Adults**
diazepam (DZP) (Valium® 10 mg/2 ml)	IR	**0.5 mg/kg** (max. 10 mg) < 2 years: 2.5 mg 2-5 years: 5 mg >5 years: 10 mg	**10 mg**
lorazepam (LZP) (Temesta Expidet® 1 mg, 2.5 mg)	IB	**0.05-0.1 mg/kg** (max. 5 mg) 0-2 years: 1 mg >2 years: 2.5 mg	**2.5 mg**
midazolam (MDZ) (Dormicum® 15 mg/3 ml, Midazolam B. Braun® 15 mg/3ml, Midazolam Mylan® 15 mg/3 ml, Buccolam® 2.5 mg/0.5 ml, 5 mg/0.5 ml, 7.5 mg/0.5 ml, 10 mg/0.5 ml)	IB/IN	**0.2-0.5 mg/kg** (max. 10 mg) 3 months-1 year: 2.5 mg 1-5 years: 5 mg 5-10 years: 7.5 mg 10-18 years: 10 mg	**10 mg**

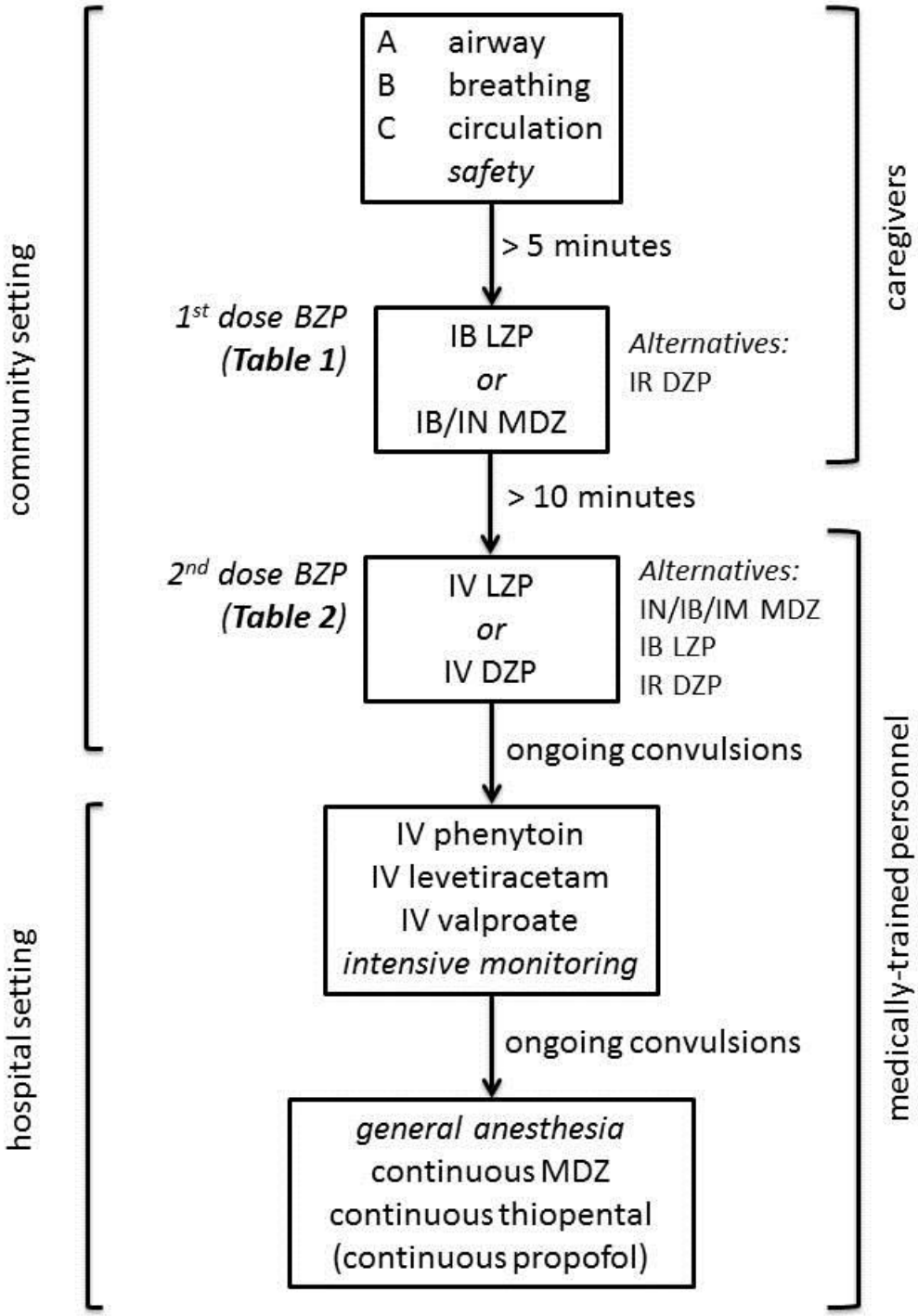
DZP: diazepam, LZP: lorazepam, MDZ: midazolam, IB: intrabuccal, IN: intranasal, IR: intrarectal, kg: kilogram, max: maximum, mg: milligram

Table 2: Benzodiazepine formulations and dosing proposal for second administration (IM or IV) in prolonged and repetitive convulsive seizures in children and adults.

Product	**Route**	**Children**	**Adults**
diazepam (DZP) (Valium® 10 mg/2 ml)	IV	**0.1-0.3 mg/kg** (max. 5 mg)	**10 mg**
lorazepam (LZP) (Temesta® 4 mg/ml, Tavor® 2 mg/ml)	IV	**0.05-0.1 mg/kg** (max. 2 mg)	**5-10 mg**
midazolam (MDZ) (Dormicum® 15 mg/3 ml, Midazolam B Braun® 15 mg/3 ml, Midazolam Mylan® 15 mg/3 ml)	IM IV	**0.1-0.2 mg/kg** (max. 10 mg) 13-40 kg: 5 mg >40 kg: 10 mg **0.1-0.3 mg/kg** (max. 10 mg)	**10 mg**

DZP: diazepam, LZP: lorazepam, MDZ: midazolam, IM: intramuscular, IV: intravenous, kg: kilogram, max: maximum, mg: milligram, min: minute

Flowchart: Management of prolonged convulsive seizures.



DZP: diazepam, LZP: lorazepam, MDZ: midazolam, IB: intrabuccal, IM: intramuscular, IN: intranasal, IR: intrarectal, IV: intravenous