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Overview of clinical efficacy and risk data of benzodiazepines for prolonged seizures

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ABSTRACT – An historical overview is provided regarding the use of benzodiazepines for the treatment of acute prolonged convulsive seizures. It is clear that intravenous benzodiazepines remain a first step for the in-hospital treatment of prolonged seizures or status epilepticus. However, in the community, in a pre-hospital situation, intravenous administration is not possible. In recent years, it was shown that rectal, buccal, intranasal, and intramuscular administration of benzodiazepines is very effective as a first and safe treatment step. In many cases, rectal diazepam is not socially acceptable anymore, and therefore more emphasis is now put on buccal, intranasal, and intramuscular administration. At present, based on the available data, midazolam is the product of choice for the acute treatment of prolonged convulsive seizures.

Key words: epilepsy, acute prolonged seizures, benzodiazepine, midazolam, diazepam, status epilepticus

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The risks of acute and especially prolonged convulsive seizures are now well established. Apart from possible secondary injuries (*e.g.* head trauma, drowning, and burning), prolonged seizures can induce significant medical emergencies such as cardiac arrhythmias, lung congestion, liver failure, and rhabdomyolysis (Jovic *et al.*, 2011; Kravljanac *et al.*, 2011; Varelas *et al.*, 2013). Increased seizure duration is associated with increased morbidity. The effects of prolonged seizures on the epileptogenic process is still a matter of debate, but preliminary data from the FEBSTAT study indicate that a prolonged febrile seizure can entail MRI-visible changes in about 10% of the children scanned within 72 hours of their seizure (see also Van Landingham *et al.* [1998]). Some of these children will go on to develop mesial temporal sclerosis and concurrent refractory temporal lobe epilepsy (Shinnar *et al.*, 2012; Harden, 2013; Yoong *et al.*, 2013). By definition, a prolonged convulsive seizure is the start of an imminent status epilepticus and appropriate action to stop the seizure is therefore warranted. It is reassuring to see

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that many doctors now include an acute seizure treatment protocol in their overall epilepsy treatment plan (Lagae, 2011; Wait *et al*., 2013). Until recently, acute treatment was still reserved for a medical setting, such as an ambulance or the emergency department. Since a critical turning point for developing status epilepticus is at around 5-10 minutes of seizure activity, initial action in a medical setting might already be too late (Shinnar *et al*., 2001). Smith *et al*. (1996) showed that 80% of the seizures lasting for more than five minutes will continue for >30 minutes. Therefore, attention has shifted towards "pre-hospital" and "community-based" treatment options. This implies that a first-treatment action could also be administered by non-medically trained people, such as parents, teachers, or a partner of the patient. It is very clear from the community-based study of Chin *et al*. (2008) that pre-hospital treatment significantly reduces the duration of status epilepticus.

This first step in the treatment of a convulsing patient should therefore be effective, simple, and safe. In this review, we will therefore focus on the benzodiazepines (BZP), as these are the most potent and direct-acting drugs to stop an ongoing seizure. In particular, we will discuss the non-intravenous use of BZP, as these are the possible drug formulations for treatment in pre-medical community settings. The mechanism of BZP is well known; BZP activate the GABA-A receptor, thereby inducing a hyperpolarisation with a decrease of excitability (for a detailed review on BZP mechanism and GABA receptors, see, for instance, Galanopoulou [2008] and Sankar [2012]).

The gold standard: intravenous benzodiazepines

The study of Alldredge *et al*. (2001) is a pivotal study that illustrates the efficacy of intravenous BZP in status epilepticus. In this study, 258 adults with a status epilepticus were randomly assigned to three treatment groups: lorazepam (2 mg), diazepam (DZP) (5 mg), or placebo. This pre-hospital treatment was given by trained ambulance personnel. In about 30% of the two active study groups, a second similar dose of the study drug was given. This was similarly performed for 50% of the placebo group. One of the primary outcome parameters was the cessation of the status epilepticus upon arrival at the emergency department of the hospital. In both active treatment groups (lorazepam and DZP), the mean duration of the prolonged seizure was around 30 minutes (lorazepam: 34±17.8 minutes; DZP: 31.3±14.5 minutes; placebo 46.7±38.8 minutes), indicating that indeed the majority of patients suffered from a status epilepticus, if one accepts the 30-minute-duration definition of status epilepticus. More than 50% of all patients were known to have epilepsy and one of the most frequent causes (in overall around 20%) of their status epilepticus was a chronic antiepileptic drug level in the blood that was too low, probably illustrating the well known, but underestimated, low treatment compliance in epilepsy. In the three groups, it took around 16 minutes to get to the emergency department. In the lorazepam and DZP groups, the status epilepticus was terminated in 59.1 and 42.6%, respectively. In the placebo group, spontaneous cessation was observed in only 21.1%. Although this difference between active treatment and placebo is very clear, one should not ignore that a large group continued to have a status epilepticus even after BZP treatment. One of the most likely explanations is the delayed administration of adequate rescue drugs, again a strong argument to start treatment in the community, before the arrival of medically trained personnel. Further analysis showed that lorazepam was significantly more effective than DZP. This finding represented the start to promote intravenous lorazepam as the first step in the majority of treatment protocols of status epilepticus. The study also demonstrates the high morbidity of status epilepticus; 47.8% (DZP group), 56.9% (LZP group), and 63% (placebo group) of patients had to be admitted to intensive care for further diagnosis and treatment. Neurological deficits at hospital discharge were observed in around 16%. Perhaps even more illustrative were the mortality data; in the LZP and DZP groups, this was 7.7 and 4.5%, respectively, but as high as 15.7% in the placebo group.

Influential non-intravenous BZP studies

Probably, the first study using rectal DZP for the treatment of acute seizures was published in 1979 by Knudsen (1979). Rectal DZP (<3 years: 5-7.5 mg; >3 years: 7.5-10 mg) was given to 44 children with 59 seizure episodes. Children were between six months and five years and all seizures were generalised convulsive seizures. Of the 59 seizures, 35 were febrile seizures. With regards to febrile and non-febrile seizures, the results were the same, and 80% of the treated seizures (43/54) stopped within 5 minutes. Another 7/54 of the seizures stopped after subsequent intravenous administration of DZP. A post hoc analysis showed that earlier administration of rectal DZP was associated with a higher chance of success; if given before 15 minutes of seizure duration, seizures were stopped in 96%. Later treatment (>15 minutes) was successful in 57%, which is indeed comparable to the data reported in the Alldredge study. In the Knudsen study, the rectal DZP administration did not cause any significant respiratory depression.

Respiratory depression clearly is the most important possible side effect to deal with, but, as was already shown in this DZP study, it should not be overemphasized. In this respect, the study of Chin *et al*. (2008) clearly showed that respiratory depression can be observed only after two or more dosages of BZP. This was also confirmed in a recent study by Spatola *et al*. (2013). Therefore, when necessary, it is advocated to give a second dosage of BZP, but under medical supervision and best in a setting where respiratory support can be given.

The study of Dreifuss *et al*. (1998), albeit using a different study design and outcome parameters, basically confirms the Knudsen study. In the Dreifuss study, feasibility of rectal DZP gel for prolonged seizures in a home-based setting was studied. Rectal DZP (0.5 mg/kg for children 2 to 5 years of age, 0.3 mg/kg for children 6 to 11 years of age, and 0.2 mg/kg for patients 12 or older) was compared to placebo. One of the efficacy outcome parameters was the recurrence of a seizure within an observation period following administration (12 hours for children). In the DZP group, 62% remained seizure-free in the next 12 hours, whereas this was the case in only 24% in the placebo group. The time to first seizure recurrence was significantly longer in the DZP group than in the placebo group. Concerning side effects, respiratory depression was not reported in the patients receiving DZP. Only somnolence was observed more frequently in the DZP group (33%) than in the placebo group (11%). The fact that somnolence was also observed in the placebo group illustrates that this is a possible and well-known post-ictal phenomenon, and that not all sleepiness or somnolence should be attributed to BZP treatment. This Dreifuss study was very influential, and rectal DZP has since become the non-intravenous standard against which all other BZP preparations are compared.

Rectal administration of medication is not always easy and is no longer socially acceptable, especially for older children or adults. Other routes of administration and other BZP were therefore examined. Scott *et al*. (1999) compared buccal midazolam (MDZ) (at a dosage of 10 mg; 40 seizures in 14 patients) with rectal DZP (at a dosage of 10 mg; 39 seizures in 14 patients). All patients were children or adolescents, older than five years, presenting with prolonged seizures. Basically, this study clearly showed equal efficacy for both drugs; 75% of the seizures treated with buccal MDZ and 59% of the seizures treated with rectal DZP were responsive to the treatment. The median time between drug administration and end of the seizures was somewhat shorter for buccal MDZ (median: 6 minutes; range: 4-10 minutes) than for rectal DZP (median: 8 minutes; range: 4-12 minutes), but this difference was statistically not significantly different (p=0.31).

The study of McIntyre *et al*. (2005) examined in more detail, and in a larger patient group, the efficacy of buccal MDZ *versus* rectal DZP; 109 prolonged seizure episodes were treated with buccal MDZ and 110 with rectal DZP. In this study, the time to stop the seizures was significantly shorter for buccal MDZ (median: 8 minutes; range: 5-20) than for rectal DZP (median: 15 minutes; range: 5-31 minutes; p=0.01). In the MDZ group, 65% of the seizures stopped within 10 minutes, whereas this was the case in 41% of the DZP group. This difference in efficacy is also reflected in another outcome parameter; whereas subsequent intravenous lorazepam was required in 33% of the MDZ group, it was required in 57% of the DZP group. In addition, this study also investigated how many seizures recurred within one hour after initial success, defined as seizure cessation within 10 minutes. Again, there was clear difference between the two groups; early recurrence was observed in 14% in the MDZ group and in 33% in the DZP group. In this study, respiratory depression was carefully monitored and was defined as a fall in oxygen saturation or decrease in respiratory effort, sufficient to require assisted breathing. The rate of respiratory depression was very similar in both groups; 5 and 6% in the MDZ and DZP group, respectively.

The largest study comparing buccal MDZ to rectal DZP was performed in Uganda (Mpimbaza *et al*., 2008) and included 330 patients, 50% assigned to rectal DZP and 50% to buccal MDZ. The dosage for both drugs was similar: 2.5 mg for 3-11 months of age, 5 mg for 1-4 years, 7.5 mg for 5-9 years, and 10 mg for 10-12 years. The direct cause for the prolonged seizure was malaria in more than 60% in both groups. Similar outcome parameters to those used in the McIntyre study were included; seizure cessation 10 minutes after drug administration. Overall, there were no significant differences between the two treatment arms, but buccal MDZ was more effective in the non-malaria group; seizures treated with buccal MDZ stopped within 10 minutes in 74% (36/49), whereas this was the case in only 45% in the rectal DZP group (26/59; p=0.02). Looking in more detail, the median time for cessation of the seizure was around 4.5 minutes in the overall population and was not different between the MDZ and DZP groups. However, as in the McIntyre study, recurrence within one hour after initial success of the drug was higher in the DZP group (17.5%) than in the MDZ group (8%; p=0.026). Recurrence rate within 24 hours after initial success was also investigated, and was in fact relatively high in both groups; 46.3 and 39.1% in the DZP and MDZ group, respectively. Recurrence occurred earlier in the DZP group (median: 1.81 hours) than in the MDZ group (median: 5.11 hours; p=0.001). Although this study indeed dealt with a rather unique population, it basically confirms the McIntyre study, with data showing a better overall efficacy of MDZ.

Talukdar and Chakrabarty (2009) compared the efficacy of buccal MDZ (*n*=60) to intravenous DZP (*n*=60). This study allows us to look at the time differences induced by the necessary handling and preparation of the medication. It is expected that preparation of an intravenous drug will take more time than that for a drug for buccal administration. Essentially, both treatments were overall equally effective; seizures were controlled in 93% in the intravenous DZP group and in 85% in the buccal MDZ group. *Post-hoc* analysis did show a significant difference when different convulsive seizure types were considered, and complex partial seizures reacted better to intravenous DZP than to buccal MDZ; 100% *versus* 63.6%, respectively (p=0.01). For generalised tonic-clonic seizures, no differences were found (efficacy was measured at around 90% for both). The treatment initiation time (the time to deliver the medication) was, as expected, significantly longer for the intravenous preparation than for the buccal preparation; it took about twice as long to get the intravenous preparation ready. On the other hand, and again not surprising, the time for the drug to take effect was much shorter in the intravenous DZP group; mean time of 1.1 minutes for the intravenous DZP group *versus* 1.6 minutes for the buccal MDZ group ($p<0.001$). Overall, however, the time from seizure start to cessation was shorter in the MDZ group (mean: 2.39 minutes *versus* 2.98 minutes; p=0.004), indicating that the shorter preparation time of the medication significantly contributed to the success rate. However, one should not over-emphasize these, albeit small, time differences. The authors did conclude that their common practice to use intravenous medication as a first-line approach could indeed be replaced by the much easier buccal administration, if intravenous access was not easily possible.

Another way to deliver MDZ is the intranasal route, and in some countries this way of delivering MDZ is clearly preferred. In 2010, Holsti *et al*. published a study with a classic design, comparing intranasal MDZ (0.2 mg/kg; *n*=50) to rectal DZP (0.3-0.5 mg/kg; *n*=42) (Holsti *et al*., 2010). In the intranasal MDZ group, there was a shorter median cessation time compared to the DZP group (1.3 minutes faster; p=0.09). Further analysis also showed that intranasal administration is safe, although more children in the intranasal group (6%) needed extra oxygen compared to the intrarectal group (2%). This difference was not statistically significant.

Lahat *et al*. (2000) published their small randomised study, comparing intranasal MDZ (0.2 mg/kg) to intravenous DZP (0.3 mg/kg). In this study, BZP were used to treat febrile seizures in young children. Overall, both medications were equally effective if one looked at seizure cessation at 10 minutes; 23 of 26 seizures responded to initial treatment with intranasal MDZ and 24 of 26 responded to intravenous DZP. None of the treated children had clinical signs of respiratory depression. As in the Talukdar study, it took longer for the intravenous formulation to work, only because of the time needed to prepare drug administration.

In 2012, the first results of the RAMPART study (Rapid Anticonvulsant Medication Prior to Arrival Trial) were published (Silbergleit *et al*., 2012); the largest study on the use of BZP for the treatment of pre-hospital status epilepticus. This study was performed in children and adults and compared intramuscular MDZ (10 mg if body weight >40 kg) with intravenous lorazepam (4 mg). With regards to intention to treat, 448 patients were listed in the MDZ group and 445 patients in the lorazepam group. For this study, an autoinjector device was designed for rapid intramuscular injection of MDZ. Looking at the aetiologies of long-lasting seizures, about 30% were due to non-compliance or discontinuation of the prescribed antiepileptic drugs, and therefore, perhaps theoretically, preventable.

Seizures were arrested without additional rescue medication at arrival at the hospital (=primary outcome) in 73.4% in the intramuscular MDZ group and 63.4% in the intravenous lorazepam group. Here also, detailed timing analysis of the different treatment steps was provided. Time to administration of active treatment was significantly lower in the intramuscular MDZ group than in the intravenous lorazepam group (1.2 *versus* 4.8 minutes). On the other hand, time from active treatment to cessation of seizures was significantly shorter in the intravenous lorazepam group (1.6 *versus* 3.3 minutes), but this did not make up for the much faster preparation of the drug; overall, time from opening the box to cessation of the convulsions was still shorter for the intramuscular MDZ group. However, importantly, the large majority of seizures stopped well before 10 minutes in both groups.

Safety was assessed as one of the secondary endpoints. In both groups, about 14% required endotracheal intubation within 30 minutes after arrival at the emergency room. Most likely, this reflects the fact that the seizures did not stop in all patients and that more intensive care and second/third-line agents were needed to stop the seizures in these patients. It is therefore difficult to understand in how many patients this ventilatory support was needed because of pure drug side effects. Recurrence of seizures within 24 hours, again, was not different between both groups; 11.4 and 10.6% in the MDZ and lorazepam group, respectively. This large study clearly shows that intramuscular administration of MDZ is also a valuable option for treating long-lasting seizures. A primary condition remains the availability of a well-designed autoinjector with adjustable dosages for infants, children, and adults.

In 2010, McMullan *et al*. published a meta-analysis comparing DZP to MDZ for the treatment of status epilepticus in children and young adults (McMullan *et al*., 2010). All routes of drug administration were considered (intravenous, intramuscular, intrarectal, and intranasal). This study was undertaken before the publication of the RAMPART study. It should be noted that the definition of status epilepticus was variable but included definitions such as convulsions of >5 or 10 minutes, or convulsions upon entering the emergency room. This study therefore focused more on the effect of medication for prolonged seizures than for "classic" status epilepticus (>30 minutes duration of seizures). At that time, only six publications fulfilled the criteria for an adequate meta-analysis. Taking into account the small number and heterogeneity of the studies (especially with regards to route of administration), this analysis nevertheless confirmed that MDZ was superior to DZP (the risk ratio for MDZ to be superior was 1.52 [95% CI: 1.27-1.82]). Moreover, DZP was not effective in 170/386 seizures, and MDZ was not effective in 112/388 seizures. Respiratory safety was also analysed. Both drugs were equally safe in that respect; respiratory depression occurred in 3/375 seizures treated with DZP and in 2/375 seizures treated with MDZ.

Although almost no studies have been performed with intravenous or rectal MDZ, there is also limited experience with other diazepines and especially lorazepam (for an overview see Anderson and Saneto [2012]). Because of the superior results with intravenous lorazepam, it is indeed logical also to consider this product for non-intravenous use.

In 2011, Arya *et al*. (2011) published the results of their study comparing intravenous lorazepam (70 children) *versus* intranasal lorazepam (71 children). Dosage for both routes of administration was 0.1 mg/kg (max: 4 mg). Randomisation occurred at hospital entrance, hence the duration of the ongoing seizures was very variable but comparable in both groups. Both routes of administration were equally effective; seizure termination occurred within 10 minutes in 80 and 83.1% in the intravenous and intranasal group, respectively.

Ahmad *et al*. (2006) also found intranasal lorazepam to be a valid alternative for the treatment of prolonged seizures. They compared intranasal lorazepam with intramuscular paraldehyde and reported seizure cessation within 10 minutes in 75% in the intranasal lorazepam group *versus* 61.3% in the intramuscular paraldehyde group. Furthermore, in the lorazepam group, fewer patients required additional anticonvulsant agents compared to the paraldehyde group. They also confirmed the cardio-respiratory safety in both treatment arms.

Concluding remarks

This short review of the clinical use of BZP for the treatment of long-lasting convulsive seizures illustrates that we do have effective drugs to stop the ongoing seizures in the majority of cases. Since early treatment to prevent status epilepticus is mandatory, non- intravenous use should be advocated. Rectal administration is no longer preferred, mainly because of social reasons, but also because of overall lower efficacy. MDZ is nowadays the drug of choice, with buccal, intranasal, or intramuscular routes of administration. For the use of possible alternative drugs, further details can be found in the review of this supplement by Chin (2014). Because first-line treatment should also be given by non-medical specialists, any treatment option should be simple and easy to use, with minimum handling and without any calculations to determine dosage. Only then can we hope for an earlier and more effective treatment of prolonged convulsive seizures, with eventually less status epilepticus and co-morbidities. There is an ongoing debate about who should be selected for acute treatment. Should every patient with epilepsy be informed and instructed about acute treatment options or should this be reserved for only those epilepsy syndromes with a high likelihood of developing long-lasting seizures? This debate should not be used as an argument to avoid discussion of acute treatment options for the majority of epilepsy patients. □

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