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What is This?

Management of Prolonged Seizures and Status Epilepticus in Childhood: A Systematic Review

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Pediatric prolonged seizures and status epilepticus are medical emergencies necessitating immediate life-support and seizure-control measures. A systematic review of published data on the management of prolonged seizures and status epilepticus showed that buccal midazolam was significantly more effective than rectal diazepam, reaching a seizure-control rate of 70% and recurrence rate of 8%. Intranasal lorazepam was as effective as intramuscular paraldehyde in a cost-restrained setting. In refractory status epilepticus, both intravenous midazolam and valproate were equally effective to intravenous diazepam, with valproate exhibiting significantly faster seizure cessation and safer profile than diazepam, even in infancy. In conclusion, buccal midazolam is efficacious and safe thanks to its convenient route of administration, which may serve as first-line in the treatment of prolonged seizures. Intranasal lorazepam is an effective, easy-to-use, and safe drug for prolonged seizures. Intravenous valproate exhibits favorable efficacy and safety profile as third-line in status epilepticus, refractory to diazepam and phenytoin.

Keywords: status epilepticus; prolonged seizures; treatment; midazolam; lorazepam; valproate; systematic review; refractory; buccal; intranasal

S tatus epilepticus is by conventional definition a continuous seizure activity lasting longer than 30 minutes or two or more discrete seizures without interictal resumption of baseline mental status.[1-3] The intense controversy around which duration of seizure activity should be accepted as status epilepticus has led over the last years to a gradual decline from half an hour to 20 minutes,[4] 10 minutes,[5,6] and finally a 5-minute length has been proposed.[7-9] At the same time, new terms have been bestowed on status epilepticus, such as early or impending status epilepticus and established status epilepticus; the first 2 terms are based on the 5-minute definition to describe continuous or intermittent seizures lasting more than 5 minutes, without full recovery of consciousness between seizures,[10,11] while the latter one—established status epilepticus—is gradually replacing the conventional 30-minute definition.

This debate surrounding the definition of status epilepticus brings forth the need to identify and treat status epilepticus in a proper and timely manner; not too early as not all patients require aggressive anticonvulsant treatment but not too late either. Indeed, it has been shown that up to 40% of seizures lasting between 10 and 29 minutes abort spontaneously, without treatment.[12] Treatment delay, however, has been associated with delayed treatment response,[13] time-dependent pharmacoresistance,[6,14,15] and unfavorable overall mortality.[12]

Status epilepticus is classified into 2 major categories, namely convulsive status epilepticus and nonconvulsive status epilepticus. Convulsive status epilepticus is considered the most life-threatening type of pediatric status epilepticus, exhibiting case fatality rates of 2.7% to 8%.[16] Morbidity secondary to convulsive status epilepticus is also high; new neurological disorder occurs in 10% and 20% of cases among children with nonsymptomatic and symptomatic convulsive status epilepticus, respectively.[16] In general, neurological sequelae such as focal neurological deficits, cognitive impairment, and behavioral problems complicate 15% of pediatric convulsive status epilepticus.[17]

Table 1.   Final Eligibility Criteria

Inclusion
  1. Randomized controlled trials evaluating the therapeutic management of status epilepticus in children and/or adolescents
  2. Randomized controlled trials comparing an antiepileptic drug to another comparator (active and/or placebo) for the treatment of status epilepticus
  3. Randomized controlled trials evaluating the effects of antiepileptics in any type of status epilepticus: early/impending, established, or refractory status epilepticus
  4. Randomized controlled trials evaluating the effects of antiepileptics in prolonged seizure activity, defined as at least 5-minute duration
  5. Randomized controlled trials on the therapeutic management of status epilepticus in mixed population, with available data separately for the pediatric population
Exclusion
  1. Randomized controlled trials with no specific criterion regarding seizure duration, or randomized controlled trials that included seizure duration other than prolonged seizures and/or status epilepticus
  2. Nonrandomized, controlled clinical trials
  3. Randomized controlled trials on the therapeutic management of status epilepticus in mixed population, without available data separately for the pediatric population

Nonconvulsive status epilepticus, however, has been traditionally associated with better prognosis. It is further divided into 2 subgroups, the relatively benign absence status epilepticus and the complex partial status epilepticus[18,19]; both, and especially complex partial status epilepticus, exhibit high rates of underdiagnosis, accompanied by significant mortality and neurological morbidity.[20,21]

Prompt and accurate diagnosis and management of status epilepticus are therefore of great importance for the pediatrician in everyday clinical practice. One of the most challenging clinical issues to be addressed remains that of the optimal treatment algorithm. This article attempts to perform a systematic review of published literature regarding the therapeutic management of prolonged seizures and status epilepticus in childhood and, secondarily, to discuss treatment options on the basis of real-world clinical needs.

Materials and Methods

The MEDLINE computerized bibliographic database was searched until July 9, 2008, with the use of a sensitive search strategy for randomized controlled trials in combination with search terms for status epilepticus and pediatric/adolescent population. Studies' final eligibility criteria for inclusion in the present systematic review are summarized in Table 1. No seizure type (convulsive or nonconvulsive), language, or date restrictions were applied. Assessments of eligibility criteria and data extraction were performed independently by 2 reviewers (K.S. and N.E.P.), with the use of a standardized data extraction form (Figure 1). Any discrepancies were resolved by consensus, and a third reviewer (R.K.) was consulted where necessary. As this was a systematic review of already published data, no institutional review board/ethics committee approval was required.

Results

A visual overview of the literature search and retrieval results is presented in Figure 2. From the 1179 papers initially retrieved, only 8 fully met the inclusion/exclusion criteria of the current systematic review.[22-29] As outlined in Table 2, 5 studies were conducted in the field of prolonged seizures or early/impending status epilepticus, while the remaining 3 were carried out in the refractory setting.

Diazepam is considered the most widely used antiepileptic medication for the acute management of seizures in both pediatric and adult populations.[30] Chamberlain and colleagues evaluated the effect of intravenous diazepam versus intramuscular midazolam in the treatment of motor seizures of at least 10-minute duration.[22] Both anticonvulsants were found equally effective in controlling seizures; however, through its intramuscular route of administration, midazolam exhibited faster initiation of treatment, leading to significantly more rapid cessation of seizure activity from arrival at the hospital (7.8 minutes vs. 11.2 minutes, $P = .047$).

Intranasal administration of midazolam has also been studied in the field of prolonged seizures. A randomized controlled trial performed by Lahat et al in 44 young children compared intranasal midazolam to intravenous diazepam in the treatment of febrile seizures of at least 10-minute duration.[24] Even though the time from drug administration to seizure control significantly favored the diazepam arm (2.5 minutes vs. 3.1 minutes, $P < .001$), the overall time to cessation of seizures after arrival at the hospital was significantly faster in the midazolam arm (6.1 minutes vs. 8.0 minutes, $P < .001$). Both treatments were found equal in terms of safety and risk of recurrence.

Midazolam and diazepam were further compared by Scott et al who studied different routes of drug administration in the treatment of prolonged seizures.[23] A total of 18 patients between 5 and 19 years of age with known severe epilepsy were randomized to receive either buccal midazolam or rectal diazepam for the cessation of longer than 5-minute seizure activity. In a total of 79 episodes,

Study ID	Author Surname		Reviewer ☐ KS ☐ NEP	Publication Details (Journal/Year/Issue/Page#)
RCT ☐ Yes ☐ No	Study Population [#] ☐ Pediatric [ ] ☐ Mixed [ ] Age Range (mean age):		Type of Seizures: ☐ Early or Impending SE ☐ Established SE ☐ Refractory SE ☐ Prolonged Seizures	
Design ☐ **Single Blind** ☐ **Double Blind** ☐ **Triple Blind** ☐ **Open Label**				
Antiepileptic Drug #1	Active substance:	Route of administration: IV, IM, IN, Rectal, Buccal		Mean Dose: Max Dose:
Antiepileptic Drug #2	Active substance: Placebo ☐	Route of administration: IV, IM, IN, Rectal, Buccal		Mean Dose: Max Dose:
Antiepileptic Drug #3	Active substance: Placebo ☐	Route of administration: IV, IM, IN, Rectal, Buccal		Mean Dose: Max Dose:
Treatment Outcomes				
Type of Outcome	Treatment #1	Treatment #2		Treatment #3
Successful seizure control				
Time to seizure control				
Seizure recurrence rate				
Mortality rate				
Resp. depression rate				
Hypotension rate				
ICU admission rate				
Other				
Authors conclusion				
Comments				
Study meets all final eligibility criteria:	☐ Yes ☐ No	Reviewers Initials:		Sign and Date:
The following section will be completed by the third reviewer, in case of consensus failure between the first two reviewers, after thorough evaluation of the study:				
Study meets all final eligibility criteria:	☐ Yes ☐ No	Reviewers Initials: Sign and Date:		

Figure 1.   Data extraction form. ICU, intensive care unit; IM, intramuscular; IN, intranasal; IV, intravenous; max, maximum; SE, status epilepticus.

buccal midazolam was shown to be at least as effective as rectal diazepam, with a response rate of 75% versus 59%, respectively ($P = .16$). Time to seizure control favored the midazolam arm (6 minutes vs. 8 minutes, $P = .31$), while hypotension was less prominent in the diazepam arm (decrease in systolic blood pressure of 6 mm Hg vs. 11 mm Hg, $P = .15$).

Another randomized controlled study of buccal midazolam versus rectal diazepam in the treatment of prolonged seizures was recently published by Mpimbaza and colleagues.[26] Among 330 children of 3 months to 12 years of age with convulsive episodes of longer than 5 minutes, 69.7% qualified as responders in the midazolam arm, as opposed to 57% in the diazepam arm ($P = .016$). Seizure recurrence rate at 1 hour

was significantly higher in patients treated with diazepam (17.5% vs. 8%, $P = .026$). As far as safety is concerned, respiratory depression was equally encountered in both arms, while an event of intense pruritus was evaluated as possibly related to midazolam treatment.

Another anticonvulsant administered intranasally, lorazepam, has been studied in African children presenting with protracted convulsions of more than 5-minute duration.[25] Ahmad et al showed that intranasal lorazepam provides slightly better seizure control when compared to intramuscular paraldehyde; response to treatment within 10 minutes was achieved in 75% of lorazepam-treated patients, while the respective percentage for paraldehyde was 61% ($P = .06$).
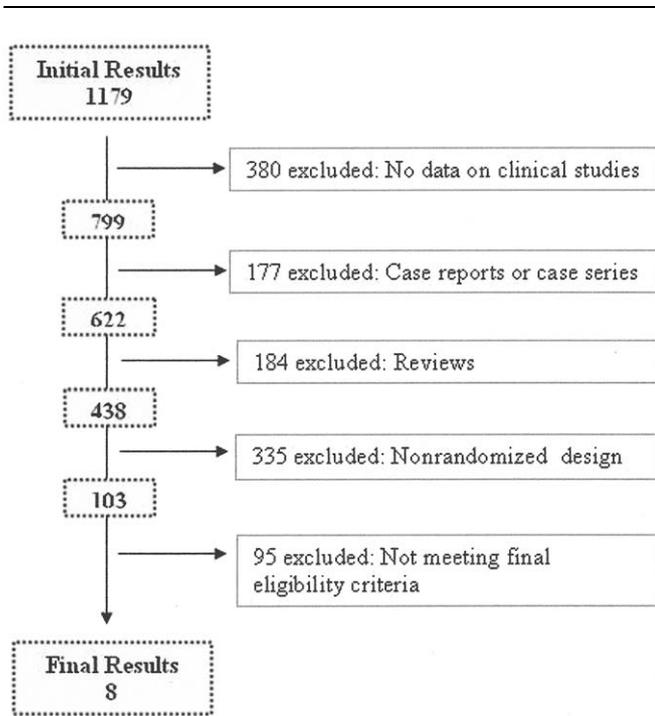
Figure 2. Literature search and retrieval results.

With respect to refractory status epilepticus, 2 of the 3 studies retrieved the use of intravenous diazepam as the active comparator. The first one was undertaken by Singhi and colleagues to include 40 children with motor seizures resistant to 2 consecutive doses of diazepam and phenytoin infusion.[27] When compared to diazepam, intravenous midazolam was found to be equally effective in seizure cessation; however, higher recurrence and mortality rates were attributed to midazolam treatment, largely associated with central nervous system infections. Respiratory depression and hypotension were equally prevalent in both treatment groups, reaching rates of 50% and 40%, respectively.

Another anticonvulsant agent with promising results in the therapeutic management of refractory status epilepticus is intravenously administered valproate. Its effect was compared to that of intravenous diazepam in a recent study by Mehta et al.[28] A total of 40 children, with status epilepticus uncontrolled after a bolus of diazepam and 2 consecutive doses of phenytoin, participated in the study. Both treatments were found to be equally effective in controlling seizures (seizure control within 30 minutes; 80% in valproate vs 85% in diazepam group, P not significant); however, valproate succeeding significantly faster cessation of convulsions (5 minutes vs 17 minutes, $P < .001$). Treatment with valproate was also shown to be significantly safer in terms of respiratory depression, hypotension, and intensive care unit admission rates, while being completely free of hepatotoxic adverse events.

Intravenous valproate has also been compared to intravenous phenytoin in the treatment of refractory status epilepticus.[29] This study by Agarwal and colleagues was performed in a mixed population of both children and adults with impending status epilepticus resistant to diazepam. The only available data that were exclusively referred to the pediatric population showed valproate to successfully control 90.9% of cases as opposed to 75% of cases which responded to phenytoin (P value not available).

Discussion

Failure to diagnose and treat status epilepticus in a prompt and accurate manner has been shown to result in significant overall mortality and neurological morbidity of 3% to 7% and 9% to 28%, respectively.[31,32] As soon as status epilepticus is diagnosed, further course relies on consistent and vigorous treatment. The choice of the therapeutic management should be directed toward 3 fronts: (*a*) choice of the most effective antiepileptic agent both in succeeding seizure control and minimizing seizure recurrence, (*b*) choice of the fastest and most reliable route of administration, and (*c*) choice of the drug with the optimal safety and tolerability profile.

With regard to efficacy in controlling prolonged seizures, buccal midazolam was the only drug that presented statistically significant results in our systematic review. It should be taken into account that the study of Mpimbaza et al is limited by the fact that the majority of the study population suffered from malaria; however, midazolam's superiority versus rectal diazepam was documented in children without a diagnosis of malaria at the time of seizure presentation.[26] In the previous study by Scott and colleagues, the 2 agents were found equally effective in the treatment of 79 episodes of prolonged seizures, when studied in a special population of children and adolescents already diagnosed with severe epilepsy.[23] Buccal midazolam has been shown to be an effective and safe alternative to rectal diazepam as a rescue therapy for acute seizures.[33] As far as personal/family preference regarding anticonvulsive treatment is concerned, both buccal and intranasal midazolam have been preferred over rectal diazepam in prehospital administration, mainly on the basis of consideration for personal dignity, social acceptance, ease of administration in wheelchair users, and faster response than rectal diazepam.[34] Another advantage of using a nonrectal route of administration is to overcome potentially unpredictable absorption, in the event of constipation or bowel movement disorders. Both buccal and intranasal midazolam exhibit high bioavailability resulting from absorption without a hepatic first-pass effect.[35] Because of the greater surface of the buccal mucosa, bucally administered midazolam would be expected to show significantly faster absorption than intranasal administration;

Table 2. Overview of Retrieved Randomized Controlled Clinical Trials

Study	No. of Participants	Age Range	Type of Seizures (Prolonged or Status Epilepticus)	Comparative Treatments	Successful Seizure Control	Time to Seizure Control	Seizure Recurrence Rate	Mortality Rate	Respiratory Depression Rate	Hypotension Rate	Intensive Care Unit Admission Rate	Authors Conclusion	Commentary
Chamberlain et al[22]	n = 24	9 mo-13.75 y	Prolonged seizures	IM midazolam vs. IV diazepam	92.3% / 91%	7.8 min / 11.2 min (P = .047)	30% / 36% (P: NA)	0% / 0%	0% / 0%	NA / NA	0% / 0%	Equally effective in cessation of motor seizures; more rapid seizure control with IM midazolam because of faster administration	• Time to seizure cessation from drug administration was less in the diazepam arm (3.4 min vs. 4.5 min, P = .32) • Seizure recurrence was defined at 60 min
Scott et al[23]	n = 18 (no. of episodes, n = 79)	5 y-19 y	Prolonged seizures	Buccal midazolam vs. Rectal diazepam	75% / 59% (P = .16)	6 min[a] / 8 min[a] (P = .31)	NA / NA	NA / NA	NA / NA	NA / NA	NA / NA	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
Lahat et al[24]	n = 44 (no. of episodes = 52)	6 mo-40 mo	Prolonged seizures	IN midazolam vs. IV diazepam	88.5% / 92.3% (NSS)	6.1 min / 8 min (P < .001)	0.05% / 0.05%	0% / 0%	0% / 0%	0% / 0%	0% / 0%	Equally effective and safe in the treatment of prolonged febrile seizures	• All participants with febrile seizures • Time to seizure cessation from drug administration was less in the diazepam arm (2.5 min vs. 3.1 min, P < .001)
Ahmad et al[25]	n = 160	2 mo-12 y	Early/impending status or prolonged seizures	IN lorazepam vs. IM paraldehyde	75% / 61% (P = .06)	7.5 min / 8 min (P = .06)	10% / 14% (P = .46)	19% / 16% (P = .68)	NA / NA	18.7%/15% / 20%/5%	NA / NA	Lorazepam is effective, safe, and less invasive than paraldehyde	• Successful seizure control was defined at 10 min and based solely on clinical assessment • Almost half the patients with cerebral malaria as the underlying cause
Mpimbaza et al[26]	n = 330	3 mo-12 y	Prolonged seizures	Buccal midazolam plus rectal placebo vs. Rectal diazepam plus buccal placebo	69.7% / 57% (P = .016)	4.8 min / 4.4 min (P = .518)	1st h: 8%; 24th h: 39.1% / 1st h: 17.5% (P = .026); 24th h: 46.3%	4.8% / 7.3% (P = .356)	1.2% / 1.2%	NA / NA	NA / NA	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
Singhi et al[27]	n = 40	2 y-12 y	Refractory status epilepticus	IV midazolam vs. IV diazepam	86% / 89% (NSS)	16 min / 16 min (NSS)	57% / 16% (SS)	38% / 10.5% (NSS)	50% / 50% (NSS)	40% / 40% (NSS)	NA / NA	Equally effective in refractory status epilepticus; higher recurrence and mortality rates in midazolam group	• Refractory status epilepticus defined as motor seizures uncontrolled after 2 doses of diazepam and phenytoin infusion

(continued)

Table 2. (continued)

Study	No. of Participants	Age Range	Type of Seizures (Prolonged or Status Epilepticus)	Comparative Treatments	Successful Seizure Control	Time to Seizure Control	Seizure Recurrence Rate	Mortality Rate	Respiratory Depression Rate	Hypotension Rate	Intensive Care Unit Admission Rate	Authors Conclusion	Commentary
Mehta et al[28]	n = 40	5 mo-12 y	Refractory status epilepticus	IV valproic vs	80%	5 min[a]	NA	17.5%	0%	0%	55%	Equally effective in refractory status epilepticus; valproic safer in terms of respiratory depression and hypotension	• No hepatotoxicity found with valproic
				IV diazepam	85% (NSS)	17 min[a] (P < .001)	NA	17.5% (NSS)	60% (P < .01)	50% (P < .01)	95% (P = .008)		
Agarwal et al[29]	n = 38 (mixed population: n = 100)	10.6 y-18 y	Refractory status epilepticus	IV valproic vs	90.9%	NA	NA (mixed population: 12%)	NA (mixed population: 8%)	NA (mixed population: 0%)	NA (mixed population: 0%)	NA	Equally effective in the treatment of status epilepticus refractory to IV diazepam; IV valproate better tolerated	• Not solely pediatric population • Operational status epilepticus definition of 5-min duration
				IV phenytoin	75%	NA	NA (mixed population: 16%, NSS)	NA (mixed population: 8%)	NA (mixed population: 8%)	NA (mixed population: 12%)	NA		• Refractory to IV diazepam; SGPT elevation with valproate (8% in mixed population)

IM, intramuscular; IN, intranasal; IV, intravenous; NA, not applicable; NSS, nonstatistical significance; SAE, serious adverse event, SGPT, serum glutamic pyruvic transaminase; SS, statistical significance; vs, versus.
a. Time to seizure control from drug administration.

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nevertheless, buccal midazolam has been shown to reach the maximum plasma concentration in 30 minutes, in comparison to a time to maximum plasma concentration of 10 minutes following intranasal administration.[36] This has been attributed to pronounced salivation, which is often encountered in buccal administration. However, a direct comparison between the 2 routes showed that sublingual midazolam is much better tolerated than intranasal midazolam, possibly due to its bitter taste, which can lead to decreased compliance to the medication.[37] Intranasal route of delivery may be preferred in cases of excessive salivation but not in the event of nasal congestion or upper respiratory tract infections, where there might be a risk of limited absorption; in the latter cases, buccal route can be superior.

Intranasal lorazepam is another promising agent in the treatment of prolonged seizures, which apart from its efficacy, safety, and ease of administration confers a cost advantage of great importance in the Third World countries. Lorazepam administered intranasally is an appealing antiepileptic medication in settings where most seizure episodes are associated with central nervous system infections, and therefore, a longer duration of anticonvulsive action is required. Intranasal lorazepam exhibits approximately 4-fold duration of action when compared to that of intranasal midazolam and is therefore considered better for preventing seizure recurrence.[38,39]

The gold standard of status epilepticus treatment, intravenous diazepam, has been compared to intranasal and intramuscular midazolam in 2 different randomized controlled trials,[22,24] which both showed equal efficacy in controlling prolonged seizures and preventing recurrent seizure activity. Furthermore, midazolam was associated with significantly more rapid seizure control in both studies. Even though intravenous diazepam acts faster in controlling convulsions, obtaining intravenous access was quite time-consuming, resulting in significantly delayed seizure control from arrival at the hospital in the diazepam arms. Indeed, it has been shown that the time saved by not having to secure intravenous access prior to treatment is greater than the difference in onset of action between intravenous and nonintravenous route of administration.[40]

In the refractory setting, intravenous midazolam was accompanied by significantly higher recurrence rates when compared to intravenous diazepam. Even though the safety profile of the 2 drugs was similar in terms of respiratory depression and hypotension rates, mortality rate was found to be slightly elevated in the midazolam arm. Valproate, however, exhibited a favorable profile in the treatment of refractory status epilepticus, acting in less than one third of the time required by diazepam to cease epileptic activity. Although being as effective as diazepam, valproate presented a significantly safer profile, with zero incidence of respiratory or cardiovascular adverse reactions and zero hepatotoxicity. The superior profile of intravenous valproate has also been demonstrated in the treatment of status epilepticus resistant to diazepam, where valproate was found to be more effective than intravenous phenytoin in the pediatric population, with a better tolerability profile. These data are consistent with the results of previous studies showing intravenous sodium valprate to be highly effective and relatively safe in treating status epilepticus in children.[41-44] Its use, however, should still be exercised with caution in children with underlying liver or mitochondrial diseases and especially in the very young group of patients of less than 3 years of age.[45]

These results coincide to a great extent with the recently published, evidence-based review undertaken by the Cochrane Collaboration to compare the efficacy and safety of midazolam, diazepam, lorazepam, phenobarbitone, phenytoin, and paraldehyde in treating acute tonic-clonic convulsions and convulsive status epilepticus in hospital-treated children.[46] In this review, Appleton et al concluded that intravenous lorazepam is at least as effective as intravenous diazepam and is associated with fewer adverse events in the treatment of acute tonic-clonic convulsions and that in the event of unavailable intravenous access, buccal midazolam should be the treatment of choice. It should be taken into account that the review by Appleton et al studied only convulsive seizure activity, irrespective of the duration of the convulsions and that a cutoff point at July 2007 was applied in the literature search. Our systematic review, however, was not restricted to a specific type of seizures and included only prolonged seizure activity or status epilepticus (Table 1), with a cutoff point at July 9, 2008, thus resulting in the review of 8 trials in comparison to 4 trials retrieved by Appleton et al.[46]

In conclusion, there is a narrow window of opportunity of 30 minutes to treat a child with status epilepticus in an effective and safe manner; failure to do so can lead to cerebral metabolic decompensation and threaten the child's life. The route of administration therefore plays a crucial role in succeeding rapid initiation of treatment. In early/impending status epilepticus, buccal midazolam provides a highly efficacious choice as first-line treatment, with simple and fast route of administration, without the various social issues and acceptability constraints involved in rectal administration. The rapid seizure control, safety, and ease of administration, as well as the suitability of use in the extrahospital milieu—especially in the more "socially sensitive" group of adolescents—allow both the patient and the family to pursue a better quality of life. Intranasal lorazepam, however, is a quick-acting antiepileptic agent of long-lasting effect and a relative inexpensive one, which may serve as an optimal prehospital treatment. The treatment of refractory status epilepticus must be more efficacy-focused, as failure of the first 2 medications usually results in a very poor outcome. Safety concerns should also be taken into account, mainly regarding arterial hypotension that compromises cerebral blood flow. Intravenous sodium valproate seems

to offer a promising choice in the management of status epilepticus resistant to diazepam and phenytoin, both in terms of efficacy and safety. Its role as a second-line treatment, immediately after diazepam failure, requires further investigation in well-controlled pediatric trials.

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