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CLINICAL APPROACHING OF PEDIATRIC EPILEPSY MANAGEMENT

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ABSTRACT

Seizures are characterized as brief episodes of symptoms brought on by the abnormal, excessive, or synchronous brain neuronal activity that is marked by sudden and involuntary movement of the skeletal muscles. Early detection, therapy, and specialized medical assistance must be carried out in order to avoid Status Epilepticus (SE). Onset of seizures, particularly in children population, is associated with particular risk factors such as fever, infections, and positive family history. From infancy to adolescence, pediatric epilepsy can strike at any age. Diagnosis is typically predicated on the detection of persistent or recurrent seizures, but if a SE condition is suspected, an electroencephalogram (EEG) evaluation may be helpful. The aim of treatment is to reverse the pathological process that takes place in SE prior to neural Cells sustain permanent damage. As per the most recent International Guidelines and Seizure-related disease recommendations, a multi-stage, schematic pharmacological and in particular, a diagnostic approach is suggested for the treatment of SE and its associated causes in kids. The first steps should concentrate on administering medications promptly and appropriately at sufficient dosage, airway control, vital sign monitoring, and the pediatric intensive care unit (PICU) acknowledgment and treatment of anxiety in parents.

KEYWORDS: Seizures; status epilepticus; children, antiepileptic treatment.

INTRODUCTION

A medical emergency known as convulsive status epilepticus (CSE) is characterized by a tonic-recurrent convulsions or persistent convulsions lasting longer than five minutes.[1] Previous rules for the Evidence based guidelines have taken the place of established CSE treatment.[2] [3-4]

The American Epilepsy Society (AES) recommended antiseizure medications (ASMs) in 2016. The first step in treating established CSE is to administer an intravenous (IV) bolus, according to guidelines[3]: lorazepam, diazepam, phenobarbital, or intramuscular (IM) midazolam (MDZ; level and efficient), followed by the administration of an IV phenytoin loading dose and subsequent maintenance doses (PHT), fosphenytoin (level A, effective), valproic acid (VPA; level C, potentially effective), or Levetiracetam (LEV; level U, insufficient data). About one-third of patients have CSE persists even when the proper initial ASMs are used.

Among CSE-affected adults, a US veteran administration trial showed that the first ASM was effective in 55.5% of cases, while the second ASM was effective in an additional 7.0%, and only 2.3% of patients responded to the third ASM.[5] In kids, the second ASM seems to be less successful than the first, and there is no information regarding the third ASM.[3]

An SE that persists in spite of treatment with both benzodiazepine (BDZ) and a second ASM that has been carefully chosen and dosed is known as refractory status epilepticus (RSE).[6] About 23% to 43% of SE patients develop status epilepticus, which results in death in 17% to 39% of adults (a lower rate in children), and causes the neurological condition to return to its initial state in a minority, longer hospital stays, and a greater need for rehabilitation among many patients.[7-8]

Clinicians frequently use continuous infusions of anesthetizing ASMs like MDZ, pentobarbital (PTB), or propofol (PRO) as third-line therapy to help prevent complications of convulsive refractory status epilepticus (CRSE); however, concerns have been raised regarding their serious adverse effects (AEs). Even after adjusting for age and SE severity, a class III study discovered that IV anesthetic ASM use was linked to a 3-fold relative increased risk of death and a 4-fold increased incidence of infection.[9] A 7-fold relative increased risk of new disability, a 9-fold increased risk of death, a 4-fold increased risk of infection, and one-week longer hospital stays were discovered in another class III study of IV

anesthetic ASMs.[10] In that large study, TC was more frequently used in patients with refractory SE, higher Status Epilepticus Scale Score (STESS)[11], and younger age. It was also linked to longer hospital stays but not higher mortality. Shorter but deeper TC was linked to fewer in-hospital complications and worse outcomes, according to a recent retrospective observational study.[12]

Recently approved commercial preparations of MDZ and DZP nasal sprays have become available for the treatment of seizure clusters, and there is growing evidence supporting the use of pharmacy-manufactured MDZ preparations for seizures and SE. The application in SE is still unknown, though.

In this review, we discuss the commonly used BZDs, with a focus on their pharmacodynamics, pharmacokinetics, metabolism and available formulations, and we summarize the published data on their efficacy, safety and routes of delivery in the clinical management of seizures, seizure clusters and SE.

RISK FACTORS

Positive family relationships are the main risk factors for seizures in children. History[13], elevated body temperature[14], mental impairment[15], postponed NICU discharge or premature birth[13], smoking and alcohol abuse by the mother during pregnancy double the risk of incidence of seizures.[16] Additionally, in 30% of kids, once the initial seizure episode happens, the likelihood of recurrent episodes rises. Rather, the following are risk factors for recurrent febrile seizures: small age and length of the initial episode of seizures, a feverish first period, and a positive family history of febrile seizures. Seizures start in a first-degree relative short timeframe after temperature elevation.[13] Patients who have all of these risk factors have a greater than 70% chance of experiencing another episode of seizures; contract patients who do not have any of them are more likely to experience another episode of less than 20% of seizures.[17-18]

Risk factors for childhood epilepsy

- Head trauma
- Development delay
- New born distress
- Brain infections
- Prenatal injuries
- Brain abnormalities
- Family history of epilepsy

MORTALITY

People with epilepsy have a mortality rate that is two to four times higher than the general population. And five to ten times greater in kids. Children without neurological comorbidity have an early death risk that is comparable to that of the general population. Additionally, many deaths are caused by preexisting neurological disabilities rather than seizures. Systemic complications and deadly neuro-metabolic changes are the causes of this increased risk (result of neuro-disability), seizure-related death. Sudden Unexpected Death in Epilepsy (SUDEP), which represents the most common cause of death for children with epilepsy: Although rare, the risk of death rises up until young adulthood if epilepsy is present.[15-16] Seizures could be another cause of death. Brain tumors are examples of natural causes; suicide or unintentional death are examples of non-natural causes. According to SUDEP, the annual global mortality rate is between 2.7 and 6.9 deaths per 1000 children. The annual child mortality rate is approximately 1.1-2 cases per 10,000 children.[16]

PATHOPHYSIOLOGY

It's unclear exactly how seizures start. A lack of neuronal inhibition or an overabundance of excitatory stimuli could be the cause. The majority of authors contend that a deficiency in neuronal inhibition, specifically y-Aminobutyric acid (GABA) deficit[19], the most significant neurotransmitter in the central nervous system; alternatively, it depends on a change in GABA function, which establishes a high-intensity, prolonged stimulation. N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid, two glutamate receptors—the most significant excitatory receptor in the central nervous system—have been shown in other studies to be involved in seizure physiopathology in experimental animal models.[19]

Young children with a lower convulsive threshold are susceptible to febrile seizures. Children are more likely to contract viral infections that cause fever, otitis media, and respiratory high tract infections.[20,21] Inflammatory mediators such as IL-1 may play a major role in the development of febrile seizures and an increase in neuronal stimulation, according to animal models.[20] Although preliminary research on children appears to support this theory, its clinical and pathological significance is still unclear. A serious pathological condition such as meningitis, encephalitis, or cerebral abscess may be highlighted by febrile seizures.[20]

The pathophysiology of seizures appears to involve viral infections. According to recent research, 20% of patients experiencing their first febrile seizures may have Rubivirus and HHV-6 (Human herpesvirus-6).[21-22] Lastly, additional reports indicate that febrile seizures have been linked to gastroenteritis caused by Shigella.[23]

CURRENT RECOMMENDATIONS FOR HANDLING SEIZURE EMERGENCIES

Benzodiazepines are the preferred medication for rescue therapy, which is used to stop a seizure, stop it from progressing to a longer episode, or stop it from happening again. When qualified medical professionals are available, the Neurocritical Care Society advises using IV lorazepam to treat status epilepticus. According to Society guidelines, benzodiazepines can be given by IM, rectal, intranasal (IN), or buccal routes when IV

therapy is not practical. Rectal diazepam gel, however, is the only rescue therapy product available in the US.

Clinicians outside of Europe, where buccal midazolam is approved for patients up to the age of 17, may consider the off-label use of diazepam or midazolam oral solutions given buccally or injectable formulations administered intranasally when patients refuse rectal therapy until FDA-approved IM and IN formulations are available. Nevertheless, there is uncertainty regarding the effectiveness of these treatments and the best dosage schedules because they have not been tested in controlled trials.

IDEAL MEDICATION PROPERTIES FOR SEIZURE

Medications used to treat seizure emergencies need to have a broad therapeutic index and be strong enough to allow for low dosage volumes. They should show an intermediate duration of action (hours) and a quick onset of action (minutes). Drug administration ought to be quick, simple, and secure. When using an extravascular route to treat seizure emergencies, the formulation should show high, consistent, and quick (minutes) absorption.

DIAGNOSIS

Status epilepticus is the most difficult condition to treat in an emergency. As a result, this clinical state is the focus of the sections on diagnosis and treatment. Status epilepticus manifests clinically in a variety of ways. The pediatric patient's prior state conditions, stage, and type of seizures all play a role. Continuous or recurrent seizures are the basis for the diagnosis, which is simple to identify during the clinical manifestation. It is challenging to rule out non-epilepticus continuous status after persistent status epilepticus, even when motor symptoms go away. When SE first manifests clinically, complicated SE, comorbidity, or infants are involved, a comprehensive instrumental evaluation may be requested.[24]

According to published research, serologic tests are not warranted in pediatric age routines due to the low frequency of abnormal values. Hypoglycemia is the only abnormal test found in over 20% of patients.[24] When an infectious etiology is suspected in patients with status epilepticus and a body temperature greater than 38.5°C, a lumbar puncture may be considered. Even in the absence of central nervous system infections, SE may exhibit temperature, leukocytosis, and pleocytosis in cerebrospinal fluid. According to American Academy of Pediatrics (AAP) guidelines, lumbar punctures and other diagnostic tests should not be routinely performed on pediatric patients experiencing febrile seizures unless the condition warrants it.[22]

For all patients under one year old who exhibit fever and seizures, a lumbar puncture is strongly advised.[17] According to American College of Emergency Physicians (ACEP) guidelines, lumbar punctures should be requested in cases of recent CNS infections, persistent seizures, clinical signs of meningitis, and immune compromise.[22]

When seizures first appear clinically and when there are clinical circumstances that could raise the risk of complications, computerized tomography (CT) is requested. The first test suggested for diagnosing neoformations, head injuries, hemorrhages, and/or cerebral infarcts is an encephalic CT scan without contrast media. To confirm a suspected diagnosis of brain tumors or subdural hematomas, a CT scan using contrast media may be required. According to a study, a positive CT scan is uncommon in children with complex febrile seizures and a normal clinical examination, as well as in children with febrile seizures without a clear acute cause in anamnesis. Therefore, this test may be delayed.[17]

EEG is only used for differential diagnosis in emergency rooms. Every time SE is suspected, EEG should be taken into consideration. Since the best course of treatment involves preventing recurrent SE, research into the causes of SE should be conducted concurrently with treatment.

TREATMENT

Stopping seizures before irreversible damage to neural cells is the primary objective of therapy during SE. It is crucial to begin an early target pharmacological treatment because SE is challenging to control as the duration increases. The most crucial aspect of pharmacological treatment is the quick execution of a precise protocol that modifies dosages according to the patient's weight. As a result, treatment for refractory SE should proceed as quickly as feasible. Pharmacological treatment and time are related in the 2017 ILAE recommendations.[25] Thus, the following three time points are described.

a) T1 is the time frame during which SE emergency treatment should begin.

b) T2 is the time frame following which seizures may cause functional deficiency, changes in neural networks, and death of neural cells. T3 is typified by refractory SE, which persists in spite of treatment. Hospitalization and PICU admission are advised in this situation.

c) Additionally, there is a time frame known as T4. It is distinguished by a super refractory SE that lasts longer than twenty-four hours. Advanced life support is required in this situation.

Most commonly used Anti-epileptic Drugs are

1. Carbamazepine

Monotherapy: In a Class III double-blind RCT comparing topiramate (TPM) (100 or 200 mg/day) with either valproate (VPA 1250 mg/day) or carbamazepine (CBZ 600 mg/day), the proportion of seizure-free patients during the final six months of treatment in the pediatric partial-onset seizure subset, the time to first

seizure, and the time to exit based on clinical response.[26] Of the 67 patients in the subgroup with partial-onset seizures, 17 received CBZ. The patients ranged in age from 1 to 16. Another Class III study compares CBZ or phenytoin (PHT) with clobazam (CLB). A meta-analysis compared oxcarbazepine (OXC) and CBZ as initial monotherapy. However, children were not included in the only clinical trial with sufficient outcome measures. Therefore, it is impossible to draw any conclusions about the effectiveness of CBZ versus OXC in children.[27]

Adjunctive Therapy: In patients with partial-onset seizures who were not responding to barbiturates, one study assessed PHT and CBZ as adjunctive therapy. However, this study used a before-and-after comparison design[28] and discovered that approximately two-thirds of the patients had no seizures over the course of the six-month study period, with superior efficacy in secondary generalized seizures. The trial is still uninformative because it did not report differential efficacy or PHT versus CBZ as an outcome.[28]

2. Clobazam

Retention on CLB for the first 12 months of treatment was found to be comparable to standard therapy (either CBZ or PHT) in a Class III double-blind RCT. This result was presented for all children with either partial-onset or primary generalized seizures in the study cohort, which included both untreated and previously treated children. Although the data for partial-onset seizures were not shown separately, there was no difference between CLB[63] and CBZ[52] for the retention on therapy for the first 12 months in the untreated subgroup (n=115).[29] The use of CLB as an adjuvant therapy in a pediatric age group is not supported by any systematic research.

3. Clonazepam

The sample size for each group (CBZ-6, CLN-8) in the sole Class III double-blind study comparing CBZ with clonazepam (CLN), was insufficient to draw any conclusions about efficacy or effectiveness.[32] The use of CLN as an adjuvant therapy in a pediatric age group is not supported by systematic research.

4. Gabapentin

Monotherapy: In one clinical study, children with benign epilepsy who experienced centrotemporal spikes were treated with gabapentin (GBP) alone. In this Class III double-blind, placebo-controlled, forced-exit study, 225 children with benign epilepsy with centrotemporal spikes were given either GBP (n=113) or a placebo (n=112). Two statistical analyses of the study produced somewhat different findings: one GBP was more effective than a placebo (Wilcoxon test, p=0.0395), while the other revealed a trend (log rank test, p=0.06).[30] This research has only been published in abstract form.

Adjunctive Therapy: In a 12-week double-blind, placebo-controlled trial, a single Class I study assessed the effectiveness of GBP as an adjunctive therapy in 247 children aged 3-12 years who had refractory partial seizures. The dose was up-titrated to 23-35 mg/kg/day.[31]

5. Lamotrigine

Monotherapy: In a Class III open-label trial, lamotrigine (LTG) demonstrated comparable efficacy/effectiveness to CBZ for the monotherapy of new-onset or untreated partial seizures.[33] Furthermore, LTG versus CBZ monotherapy for epilepsy has been the subject of two meta-analyses; however, the total number of children examined was too small to make any firm conclusions.[34,35]

Adjunctive Therapy: In 199 children with partial seizures between the ages of 2 and 16, one Class I study compared the effectiveness of adjunctive LTG versus a placebo.[36] Depending on the baseline medication or medications at the time of randomization, the target dose of LTG changed: 1-3 mg/kg/day for VPA alone, 1-5 mg/kg/day for an enzyme-inducing AED (PHT, CBZ, or phenobarbital [PHB]) combined with VPA, and 5-15 mg/kg/day for a child using an enzyme-inducing AED alone.

6. Levetiracetam

Monotherapy: Levetiracetam (LEV) has not been used in any Class I monotherapy RCTs for children with untreated partial-onset seizures or new-onset seizures.

Adjunctive Therapy: Using an 8-week baseline and a 14-week double-blind treatment period, a Class I multicenter RCT assessed the effectiveness and tolerability of LEV as an adjunctive therapy in children aged 4-16 years with medically refractory partial-onset seizures.[37] Patients were given either a placebo or adjunctive LEV (up-titrated to 60 mg/kg/day) during the double-blind phase (198). Adjunctive LEV significantly reduced weekly seizure frequency compared to placebo therapy (26.8%; p=0.0002; 95% CI 14.0%) up to 37.6%. 44.6% of the LEV group (45/101) experienced a >50% reduction in weekly seizure frequency, compared to 19.6% (19/97) receiving a placebo (p=0.0002). Somnolence (23%), vomiting (15%), anorexia (13%), behavioral hostility (12%), cough (11%), anxiety (10%), asthenia (9%), diarrhea (8%), dizziness (7%), and emotional instability (6%) were the most frequent treatment-emergent adverse events. In each group, a comparable proportion of patients needed a dose reduction or left the study due to an adverse event. The effectiveness and tolerability of adjunctive LEV in infants and younger children (aged 1 month to 4 years) with partial-onset seizures that were not sufficiently controlled with fewer than two AEDs were assessed in another multicenter, double-blind, randomized, placebo-controlled Class II study.[38]

7. Oxcarbazepine

Monotherapy: OXC and PHT have been shown to be differently effective in a single Class I study.[39] In this multicenter study, children with partial or generalized seizures between the ages of 5 and 18 were randomly assigned to receive either PHT or OXC in a 1:1 parallel-group design. Of the 151 children in the subgroup with partial-onset seizures, 73 were taking OXC. The weak flexible titration period (beginning dose 150 mg/day OXC or 50 mg PHT, increased gradually based on clinical response) lasted 48 weeks.

Adjunctive Therapy: One double-blind, placebo-controlled study (n=1267, OXC 138, placebo 129) with a target dose of 30-46 mg/kg/day has produced Class I evidence for the effectiveness of OXC as an adjunctive therapy in children aged 3-17 years.[40] Children receiving OXC had a 50% responder proportion of 41%, compared to 22% for those receiving a placebo (p=0.0005). Children taking OXC showed a median decrease in seizure frequency of 35% compared to 8.9% for those taking a placebo (p=0.0001). The OXC group experienced a 10% discontinuation rate due to adverse effects, compared to 3% in the placebo group.

8. Phenobarbital

In Class III open-label trials, PHB monotherapy was comparable to CBZ, PHT, and VPA in terms of efficacy and effectiveness in children with partial-onset seizures.[41-42] The status of PHB as monotherapy is still unclear because none of these other AEDs have Class I efficacy/effectiveness data as initial monotherapy. The effectiveness, tolerability, and efficacy of PHB as an adjunctive treatment for children with refractory partial-onset seizures have not been thoroughly studied.

9. Phenytoin

The efficacy (62% of patients with seizure freedom during the maintenance period) and tolerability (14 adverse effect-related withdrawals) of PHT in children with partial-onset seizures were reported in the study by Guerreiro et al.[39] According to this study, rash (n=4, one of whom also had acute cerebellar syndrome) and hypertrichosis and/or gingival hyperplasia (n=10) were the primary causes of withdrawal. Overall, there was no statistically significant difference in the efficacy results between the compounds; however, PHT's effectiveness and tolerability were lower than those of OXC. The effectiveness, tolerability, and efficacy of PHT as an adjunctive treatment for children with refractory focal seizures are not supported by any systematic research.

10. Stiripentol

Stiripentol (STP) has not been used in any Class I monotherapy RCTs for children with untreated partial-onset seizures or new-onset seizures as a supplemental treatment. With 'orphan designation' for other indications, STP is authorized in Europe for the treatment of severe myoclonic epilepsy of infancy (Dravet's syndrome). The effectiveness of adjunctive STP in children receiving CBZ for refractory partial-onset seizures was investigated in a Class III open-label study.[43] 32 responders (50% reduction in seizure frequency compared with baseline during the third month of the open period) were randomly assigned for two months to either continue STP (17) or withdraw to placebo (15) among the 67 children who entered a 4-month open-label adjunctive STP period after a 1-month single-blind baseline in an enrichment-withdrawal design.

11. Topiramate

Monotherapy: 63%, 59%, 53%, and 39% of children receiving TPM 100 mg/day, TPM 200 mg/day, VPA, and CBZ, respectively, had no seizures during the final six months of double-blind treatment in the Class III study comparing TPM/CBZ/VPA described by Wheless et al.[26] For these same four groups, the incidence of adverse events severe enough to result in stopping study treatment was 11%, 18%, 32%, 2%, and 4%, respectively. Children with partial seizures, who made up 56.3% (67/119) of the entire study population, did not have these results reported separately.[26] The pediatric partial-onset seizure subset of two high- versus low-dose forced-exit TPM RCTs did not report any efficacy or effectiveness outcome data.[44,45]

Adjunctive Therapy: In children aged 2-16 years (n=86, TPM-41, placebo-45) with partial-onset seizures, one study found that TPM was more effective as an adjunctive therapy than a placebo.[46] The TPM dosage was increased from 25 mg/day to 125-400 mg/day during this 16-week trial. Children taking TPM had a 50% response rate of 39%, while children receiving a placebo had a 50% response rate of 20% (p=0.08). For the TPM and placebo groups, the median decrease in seizure frequency was 33% and 10.5%, respectively (p=0.034). While two children in the placebo group stopped taking TPM due to unbearable side effects, no child taking TPM did so. Purpura or other bleeding issues (15%), somnolence (12%), anorexia (12%), emotional instability (12%), rash (12%), mood issues (10%), aggression (10%), anxiety (10%), and diarrhea (10%) were among the subsequent adverse effects reported.

12. Valproate

VPA and TPM had comparable efficacy and effectiveness in the Class III study by Wheless et al.[26] VPA has been compared with CBZ[47,48], PHT[49,50], both CBZ and PHT[51], and CBZ, PHT, and PHB[52] in additional multiple Class III open-label trials. The reported estimates of efficacy and effectiveness in these studies did not differ statistically. The use of VPA as an adjunctive treatment for children with partial-onset seizures has not been the subject of any pertinent trials.

13. Vigabatrin

Vigabatrin (VGB) and CBZ as monotherapy have comparable efficacy and effectiveness, according to three Class III studies.[53-54] 459 patients from 44 European

centers were randomly assigned to either VGB (2.5 g/day, n=229) or CBZ (600 mg/day, n=230) in a primarily adult study that included an unknown number of adolescents aged 12-18 years.[53] Time to withdrawal due to side effects or lack of efficacy did not vary between groups according to intention-to-treat analysis. Regarding the amount of time needed to reach the 6-month seizure remission period, there was no discernible difference between VGB and CBZ. However, compared to the VGB group, the CBZ group's time to first seizure six weeks after randomization was significantly longer (p=0.0001). There are no pertinent studies on the use of VGB as a supplemental treatment for kids who have focal seizures.

14. Zonisamide

Low (3-4 mg/kg/day, 65) and high (6-8 mg/kg/day, 59) doses of zonisamide (ZNS) were compared in a Class III open-label RCT for children with newly diagnosed epilepsy, 81% of whom were classified as having localization-related epilepsy. On intention-to-treat analysis, the percentage of patients attaining the primary outcome measure (seizure-free rate for six months) was similar in both groups (63.1% vs 57.6%, respectively, p=0.66).[55] There are no pertinent studies on the use of ZNS as a supplemental treatment for kids with partial-onset seizures.

15. Midazolam

Midazolam is a 1,4 BDZ that increases the opening of the chloride ionophore by binding to synaptic GABA receptors with subunits. Since midazolam is water-soluble at lower pH levels and does not require propylene glycol as a vehicle, it can be administered by continuous infusion. However, other BDZs (like lorazepam) cannot be infused because propylene lactic acidosis may be brought on by glycol.[64] Because MDZ is lipophilic at physiological pH, it quickly penetrates the central nervous system.[65]

The primary active metabolite of midazolam, 1-hydroxymidazolam, is produced by intestinal and hepatic CYP3A4. Midazolam is highly (94%-97%) protein-bound. After being glucuronidated, its metabolites are subsequently eliminated by the kidneys. MDZ elimination is biphasic, with a faster initial phase (probably into adipose tissue) and a slower terminal phase with a t1/2 that is shortest in infancy, lasting 1 to 4.5 hours in children and 1.8 to 6.8 hours in adults.[66-68] The parent compound MDZ and 1-hydroxymidazolam are comparable in single-dose investigations. Long-term use causes hepatic metabolism to increase five to ten times.[67,68,70-71] Enzyme-inducing ASMs like carbamazepine, phenobarbital, and PHT lower MDZ serum levels; however, despite hepatic induction, its t1/2 is prolonged up to 24 hours with high-dose, long-term use.[69]

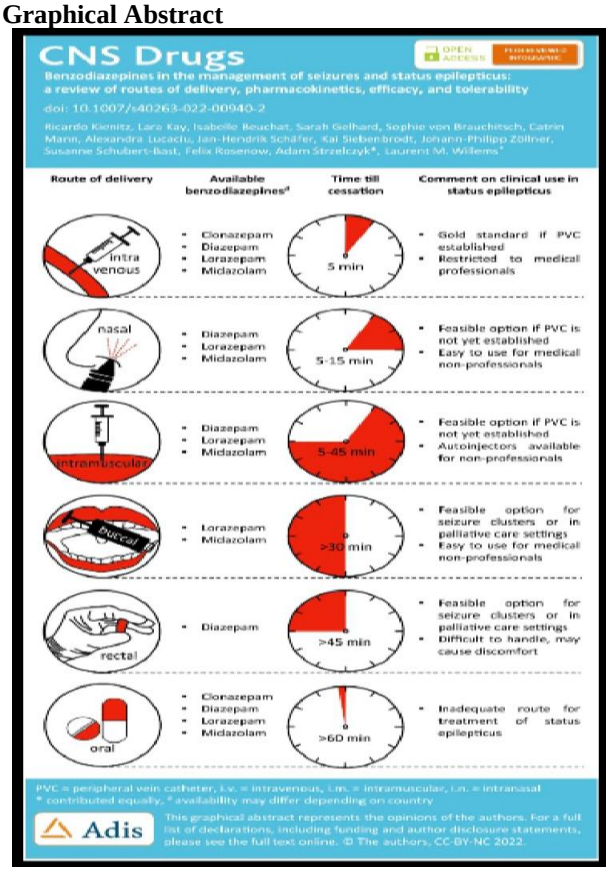
MDZ clearance is prolonged by renal insufficiency and CYP3A4 inhibitors, which may cause prolonged sedation.[72] Erythromycin, diltiazem, and verapamil are moderate CYP3A4 inhibitors; ketoconazole, itraconazole, and clarithromycin are strong inhibitors.[69] Due to the prevalence of hypotension and issues brought on by the protracted course of PTB, reports on the use of MDZ for RSE appeared in the late 1980s and early 1990s. 33 of the 479 articles found through literature searches discussed the use of continuous IV MDZ infusions for the treatment of RSE.[73-74] Reports that used bolus IV MDZ, intranasal, buccal, or IM as the initial treatment for SE were not included.

16. Additional Substances

Despite the lack of published Class I or II level evidence in studies, some AEDs have been approved for use in the pediatric age group. Nevertheless, there aren't any published trials specifically for TGB in children.[56-57] Similarly, although primidone is authorized for use in children, there is no controlled evidence of its effectiveness in pediatric trials.[58]

The FDA has approved felbamate (FBM) for the treatment of seizures in the context of Lennox-Gastaut syndrome, but its status for partial-onset seizures outside of this context is unclear. FBM has only open-label uncontrolled efficacy data (Class IV) for adjunctive treatment in children with refractory partial-onset seizures, which are not reviewed further. FBM has been tested as monotherapy and adjunctive therapy in adults with partial-onset seizures.[59-60]

Graphical Abstract

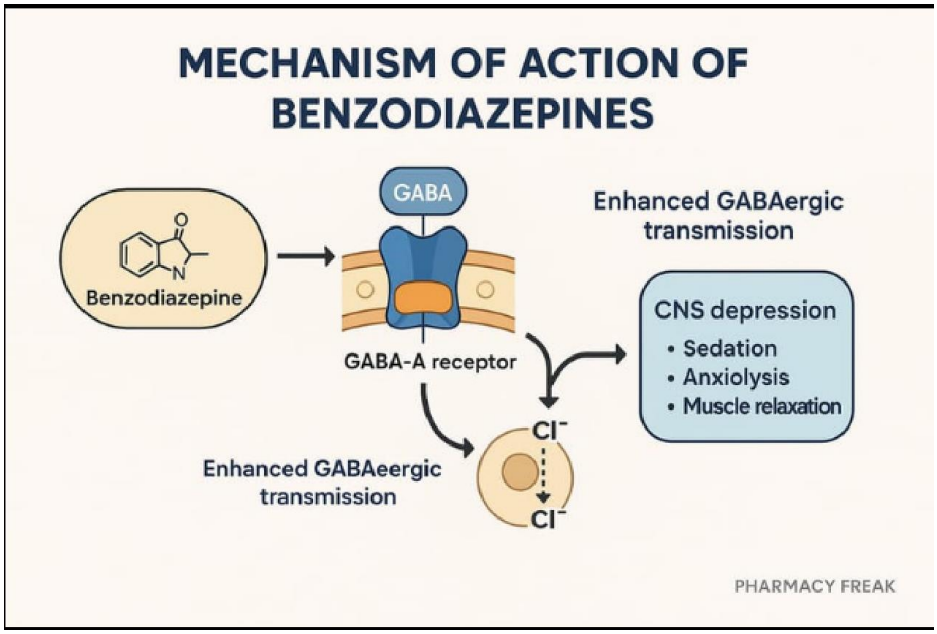


Anticonvulsant Drugs in Emergency

Guidelines in the treatment of SE give the basis to manage SE optimally in the emergency room; 80% of patients with simple convulsion respond to initial treatment, including those who will develop an SE. The most important factor is to use effective drugs at the appropriate dosages. Therapy can be optimized by choosing the correct sequence of drug.

OVERARCHING SUPPORT STRATEGIES

Adequate ventilation, circulation, and airway management should be the main goals of the initial SE strategy. Protecting patients from injuries brought on by uncontrollable movement is crucial. In order to prevent inhalation, it is also crucial to position a peripheral venous catheter and place the patient in a lateral position. To assess the progression of SE, vital signs (heart rate, blood pressure, oxygen saturation, and temperature) must be monitored. To identify hypoglycemia poisoning, a quick blood test should be performed.[63] New Methods of Administration and Additional Benzodiazepines for the treatment of epilepsy and other conditions, novel drug delivery methods like the intrapulmonary route are presently being studied.[61,62] Because of a significant mechanism of action of Benzodiazepines.



Despite the structural similarity and close relationship between the benzodiazepines, their distinct pharmacological and pharmacokinetic characteristics produce pertinent differences that are especially significant when taking into account different delivery routes.

Intramuscular deliver,

Patients and nonmedical staff can easily administer medications with IM autoinjector devices. Research on the intramuscular administration of lorazepam, midazolam, and diazepamthe former two are absorbed faster than lorazepam. The effectiveness and safety of intravenous midazolam (5-10 mg) versus intravenous lorazepam (2-4 mg) in children and adults with status epilepticus treated by paramedics were compared in a controlled clinical trial supported by the National Institutes of Health and the Biomedical Advanced Research and Development Authority. The study's findings demonstrated that IM midazolam was more effective than IV lorazepam at stopping seizures[75] Regarding the need for endotracheal intubation and seizure recurrence, both treatment groups were comparable. The median time to start treatment was 1.2 minutes for midazolam and 4.8 minutes for IV lorazepam because the IM route does not require setting up an IV line.

Additionally, the median time from starting treatment to stopping convulsions was only marginally longer for midazolam than for lorazepam, at 3.3 and 1.6 minutes, respectively. On the other hand, autoinjector IM diazepam absorbs a little more slowly, about the same as rectal diazepam.[76] A randomized, placebo-controlled study of the IM diazepam autoinjector for the treatment of acute repetitive seizures was recently published by Abou-Khalil et al.[77] The results showed that the medication was significantly more effective than a placebo at preventing seizure recurrence.

Intranasal delivery

Intranasal administration is easy and convenient, doesn't require cooperation from the patient, and generally provides quick absorption of some medications, leading to a quick onset of action. Overcoming the limitations of small dose volumes (less than 200 µL per nostril) and variable absorption are challenges in the development of nasal formulations. The investigational diazepam and midazolam products under development seemed to have mostly overcome these difficulties. Other cautions

include minimizing the irritation of nasal tissues caused by organic solvents used in the formulations and assessing whether seizures impact nasal absorption. An open-label study comparing the safety and effectiveness of midazolam was carried out in children experiencing febrile seizures that lasted longer than ten minutes. The potential of IN therapy was shown by administering an injectable solution (0.2 mg/kg) intranasally along with IV diazepam (0.3 mg/kg). According to the study's findings, IN midazolam was just as effective as IV diazepam, but because IN therapy was started quickly, seizures stopped earlier.[78] Although bioavailability varies greatly, pharmacokinetics in healthy volunteers indicate that absorption after IN administration may be a little quicker than rectal diazepam. Commercial formulations of midazolam and diazepam are being developed in the United States. These formulations can be administered in small dose volumes without showing any signs of second peaks in plasma concentration-time profiles because of delayed absorption from swallowing a portion of a dose.[79-80] According to recent research, average and bioavailability of a cyclodextrin (CD)-based IN midazolam formulation containing the absorption enhancer chitosan in healthy volunteers were less than 10 minutes (range 5-30 minutes) and approximately 80% (range 41%-102%), respectively.[81.82] As a result, absorption from CD-based IN midazolam seems to happen more quickly than from IN diazepam; however, there was a lot of variation in the bioavailability of both diazepam and midazolam formulations. With one exception (Agarwal et al[79]). the majority of studies reported nasal irritation after drug administration. When combined, these studies show that IN benzodiazepine formulations under development have pharmacokinetic and safety profiles that support their use for managing seizure emergencies, despite certain limitations.

Table 1 Physicochemical properties and pharmacokinetic parameters of diazepam, midazolam, and lorazepam[14,15]

Drug	Lipid solubility[a]	Oral bioavailability, %	Protein binding, % bound	Elimination half-life, h[b]
Diazepam	309	100	96-99	21-70
Lorazepam	73	99	93.2	7-26
Midazolam	34 at pH 3, 475 at pH 7.4	40	96	1-4

[a] Measured as octanol/water partition ratio.
[b] Half-lives of benzodiazepines are shorter in patients with concomitant enzyme-inducing drug therapy.

Based on literature research, Below Fig shows the mean time in minutes from drug administration to the cessation of status epilepticus (SE) for various delivery routes (n.a. not available). With a latency of less than three minutes, intravenous (v.) administration exhibited the quickest onset of action, followed by intramuscular (i.m.), intra-nasal (i.nbuccal,ccal and rectal delivery. The displayed values should only be used as a basic guide due to the diverse patient populations and study settings.[83,84,85,86, 87-91] LZP lorazepam, DZP diazepam, CZP clonazepam, and MDZ midazolam.

Alprazolam and its metabolites are excreted primarily in the urine.[92] In a phase lla study, five patients with a diagnosis of photoparoxysmal response on EEG received alprazolam intrapulmonarily via the Staccato system in 0.5-2 mg doses after intermittent photic stimulation.[93] Following inhalation, the number of photic stimulation frequencies that resulted in a photoepileptiform response was counted. When compared to a placebo, staccato alprazolam decreased the frequency of photic stimulation at 2 minutes. The effect ceased 4 hours after the 0.5 mg dose and 6 hours after the 1 and 2 mg doses. Alprazolam plasma concentrations were dose related and reached 31.5 ± 3.14 ng/ml within 2 mins after the inhalation of 2 mg.[93] The patient's compliance, inadequate spontaneous breathing during seizures, or decreased transpulmonary diffusion capacity are possible drawbacks the outcomes of a double-blind, randomized phase Ilb study. Phase III and inpatient research examining the safety and effectiveness of Staccato. There are currently no approved alprazolam treatments for the acute cessation of a predictable seizure pattern.

DISCUSSION

Systematic research on the behavioral aspects of childhood epilepsy syndromes is remarkably lacking, even though seasoned epileptologists generally agree that behavioral issues present significant management challenges and can have a significant impact on social outcomes. The complexity of assessment is increased by the variability of each syndrome, both among individuals and within an individual over time. Additionally, a variety of conditions may be secondary to the

symptomatic syndromes, and the underlying condition may either directly affect the behavior or modify the impact of the epilepsy on the behavior. For instance, children with West syndrome who also have tuberous sclerosis appear to have a different prognosis than children without this underlying condition.

There is growing recognition of the significance of epileptiform discharges that do not manifest as overt seizures. Surgery or medication therapy may either make behavior better or worse. There have been concerns raised about the quality of the available data on how drugs affect behavior. When evaluating an individual's behavior, it is important to take into account the various causes of behavioral difficulties in epilepsy, including environmental effects. The literature already contains some helpful information on the behavioral aspects of childhood epilepsy syndromes, but more meticulously carried out research utilizing reliable behavioral measures and accounting for the different confounding factors could be extremely beneficial in the treatment of children with epilepsy and behavioral issues.

This study found differences in presurgical and post-surgical clinical variables between the first 11 years (pre-1997) and the second 11 years (post-1997) of our program, despite similarities in age at seizure onset, age at surgery, duration of epilepsy, and other presurgical clinical variables. In comparison to the pre-1997 group, the post-1997 series had fewer extra temporal and multilobar resections, more lobar/focal resections, fewer extra temporal and multilobar resections, more patients with TSC, fewer cases of nonspecific gliosis, fewer patients with diagnostic intracranial electrode studies, a higher rate of seizure-free patients at all measured time points after surgery, a lower percentage of seizure-free patients not taking AEDs at 0.5, 1, 2, and 5 years after surgery, as well as fewer operative complications and reoperations. The period of surgery (before vs. after 1997) and the use of an AED following surgery were found to be the most significant predictors of becoming seizure-free using logistic regression. When combined, these findings show that pediatric epilepsy surgery patients at the UCLA program showed long-term improvements. Multiple overlapping and interacting factors, rather than a single region, were probably responsible for the improvement in surgical outcome for pediatric patients with epilepsy. Better preoperative noninvasive technology to detect epileptogenic lesions, better surgical candidate selection, and our deliberate choice to remove the lesion entirely during surgery and modify postoperative AED management after 1997 are some of these factors. For instance, the identification of the epileptogenic zone and significant functional cortex was probably enhanced by the use of stronger MRI magnets with improved software, thinner slice FDG-PET scans, and the integration of FDG-PET/MRI coregistration, MSI, and fMRI into the presurgical evaluation process.

The rise in the percentage of patients undergoing focal/lobar procedures as opposed to multilobar resections after 1997 is likely also due to improved neuroimaging. Better results were also linked to modifications in practice, such as delaying the reduction of AEDDs in seizure-free patients following surgery, better outcomes, fewer complications, and fewer operations were probably associated with better surgical techniques, such as cerebral hemispherectomy, in the post-1997 group.

Over time, we also learned how crucial it is to perform full resections on children undergoing epilepsy surgery. Prior to 1997, we frequently limited cortical excisions to avoid neurologic impairments.

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