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REVIEW ARTICLE

Intravenous and Intramuscular Formulations of Antiseizure Drugs in the Treatment of Epilepsy

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Abstract Intravenous and intramuscular antiseizure drugs (ASDs) are essential in the treatment of clinical seizure emergencies as well as in replacement therapy when oral administration is not possible. The parenteral formulations provide rapid delivery and complete (intravenous) or nearly complete (intramuscular) bioavailability. Controlled administration of the ASD is feasible with intravenous but not intramuscular formulations. This article reviews the literature and discusses the chemistry, pharmacology, pharmacokinetics, and clinical use of currently available intravenous and intramuscular ASD formulations as well as the development of new formulations and agents. Intravenous or intramuscular formulations of lorazepam, diazepam, midazolam, and clonazepam are typically used as the initial treatment agents in seizure emergencies. Recent studies also support the use of intramuscular midazolam as easier than the intravenous delivery of lorazepam in the pre-hospital setting. However, benzodiazepines may be associated with hypotension and respiratory depression. Although loading with intravenous phenytoin was an early approach to treatment, it is associated with cardiac arrhythmias, hypotension, and tissue injury at the injection site. This has made it less favored than fosphenytoin, a water-soluble, phosphorylated phenytoin molecule. Other drugs being used for acute seizure emergencies are intravenous formulations of valproic acid, levetiracetam, and lacosamide. However, the comparative effectiveness of these for status epilepticus (SE) has not been evaluated adequately. Consequently, guidelines for the medical management of SE continue to recommend lorazepam followed by fosphenytoin, or phenytoin if fosphenytoin is not available. Intravenous solutions for carbamazepine, lamotrigine, and topiramate have been developed but remain investigational. The current ASDs were not developed for use in emergency situations, but were adapted from ASDs approved for chronic oral use. New approaches for bringing drugs from experimental models to treatment of human SE are needed.

Key Points

The chemistry, pharmacology, pharmacokinetics, and clinical use of the currently available intravenous and intramuscular antiseizure drugs are reviewed.

The use of intravenous and intramuscular antiseizure drugs in the management of status epilepticus and as replacement therapy is discussed.

The development of intravenous carbamazepine, intravenous topiramate, and intravenous lamotrigine is reviewed.

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1 Introduction

Although many antiseizure drugs (ASDs) are available for oral use, few are formulated for intravenous delivery and even fewer are for intramuscular use. Most of the ASDs now available in intravenous or intramuscular formulations were initially developed as oral preparations for the long-term treatment of epilepsy, and parenteral formulations were developed much later. For example, parenteral phenytoin was approved by the US FDA in 1956, more than 15 years after the oral form had become widely used. On the other hand, fosphenytoin is a phenytoin prodrug developed for intravenous and intramuscular use to overcome the toxic properties of intravenous phenytoin. Intravenous formulations of valproic acid (VPA) and levetiracetam were developed many years after the oral formulations became available, even though they are more water soluble and less complicated than phenytoin to prepare as aqueous solutions. Lacosamide is the only ASD whose intravenous formulation was developed contemporaneously with the oral formulation. Lorazepam, midazolam, fosphenytoin, levetiracetam, and phenobarbital may be used both intravenously and intramuscularly. Although diazepam and phenytoin may be given intramuscularly, absorption is slow for both, and phenytoin crystallizes in muscle tissue.

The major use of parenteral ASDs is for the treatment of clinical emergencies such as status epilepticus (SE), prolonged seizures, and repetitive seizures. In addition to emergent clinical scenarios, intravenous and intramuscular ASDs are used for rapid correction of low ASD levels and are useful for maintenance when oral ingestion is not possible due to illness or surgery. The parenteral formulations provide rapid delivery, and intravenous delivery is 100 % bioavailable by definition. Although some of the newer oral ASDs have favorable physical/chemical properties potentially allowing parenteral preparation, a major barrier to developing them for clinical use is the limited market. Because the benzodiazepines and hydantoins are the agents with the most evidence for use in SE and are incorporated in the European Federation of Neurological Societies (EFNS) guidelines, they are discussed first [1]. This is followed by the ASDs that have less evidence but are often used. We also discuss new developments involving intravenous carbamazepine, topiramate, and lamotrigine as well as novel approaches to development of new parenteral agents for clinical use (Table 1).

In the treatment of SE, loading with an appropriate dose is important, and the volume of distribution (Vd) is the critical pharmacokinetic parameter in the acute treatment phase. It may be used to calculate a loading dose needed to attain the desired concentration. However, the reported Vd values vary somewhat from study to study. In replacement therapy, the bioavailability of the oral preparation is the most important factor to consider. Unfortunately, bioavailability may vary among preparations, such as 'instant', 'rapid', or 'delayed' release formulations. Thus, there is some imprecision in attaining the desired concentrations, and treatment will need to be monitored.

The ideal ASD for parenteral use would be an inexpensive agent with intravenous, intramuscular, and oral formulations in which the injectable products are highly effective in controlling all seizure types for a sufficient period of time with no adverse events. For SE, the ideal drug would have a rapid onset of action, an adequate but not overly prolonged duration of pharmacodynamic

Table 1 Parenteral formulations of antiseizure drugs

Drug	IV	IM	Comment
Phenytoin	Yes	No	IM use is unsafe
Fosphenytoin	Yes	Yes	IM safe
Valproic acid	Yes	No	IM use is unsafe
Levetiracetam	Yes	Yes	IM tested in dogs and humans
Lacosamide	Yes	No	IM not recommended
Pentobarbital	Yes	No	IM not used
Carbamazepine	Yes	No	Lundbeck seeking FDA approval for IV
Topiramate	Yes	No	CURx beginning human trials for IV
Lamotrigine	Yes	No	No sponsor
Diazepam	Yes	Yes	IM slow absorption
Midazolam	Yes	Yes	IM rapid absorption
Lorazepam	Yes	Yes	IM slow absorption

All drugs listed here have been administered via the intravenous route by clinicians, but may not have regulatory approval for this route or have had extensive testing in patients. The intramuscular route may not be recommended for many

FDA US Food and Drug Administration, *IM* intramuscular, *IV* intravenous

activity, and minimal side effects, especially those that may cause cardiopulmonary depression and impairment of the central nervous system (CNS). In addition, the ideal drug should be stable in a range of commonly used intravenous solutions, should not react with infusion apparatus, and should not precipitate or react with the other intravenous components. The oral formulation would be used for maintenance after the emergency situation has been controlled.

In this review, we discuss the chemistry, pharmacology, pharmacokinetics, and clinical use of the currently available intravenous and intramuscular formulations of ASDs. Development of intravenous carbamazepine, topiramate, and lamotrigine is also discussed. The search strategy used to identify relevant studies was a literature search of PubMed, Ovid, and the Cochrane databases. Several key phrases such as 'treatment of status epilepticus', 'parenteral formulation of antiepileptic drugs', 'pharmacokinetics of antiepileptic drugs', 'intravenous antiepileptic drugs', 'intramuscular antiepileptic drugs', and 'side effects of antiepileptic drugs' were used. In addition, we also searched bibliographies of review and original articles. Searches were restricted to those in English.

2 Chemistry, Pharmacokinetics, and Mechanisms of Action of Available Antiseizure Drugs (ASDs)

2.1 Benzodiazepines: Lorazepam, Diazepam, Midazolam, and Clonazepam

The benzodiazepines are a family of drugs whose core chemical structure is the fusion of a benzene ring to a seven-membered diazepam ring (5-aryl-1, 4-benzodiazepines). Of the approximately 35 benzodiazepines that have been synthesized, lorazepam, diazepam, midazolam, and clonazepam are of particular interest in the treatment of seizures. The benzodiazepines exert their primary anticonvulsant action by interacting with gamma-aminobutyric acid (GABA)-$_A$ receptors. The GABA receptor is a pentameric structure that forms a ligand-gated chloride channel [2]. Benzodiazepines enhance the inhibitory effects of GABA when bound to the $GABA_A$ receptor on neuronal membranes by increasing the frequency of gated chloride channel openings [3]. The molecular biology of this receptor is quite complex and continues to be explored.

Diazepam is poorly soluble in water. Injectable diazepam US Pharmacopeia (USP) contains diazepam 5 mg/ml with 40 % propylene glycol, 10 % alcohol, 5 % sodium benzoate, and benzoic acid as buffers. This makes intravenous or intramuscular injection very painful for a conscious patient. The primary metabolic pathway of diazepam is hepatic demethylation, hydroxylation, and glucuronidation to three active metabolites: *N*-desmethyldiazepam (its major metabolite), oxazepam, and 4-hydroxydiazepam [4]. Diazepam is very fat soluble; its volume of distribution is large (1.2 l/kg), its elimination half-life is long (40–60 h), and its clearance is low (0.5 ml/min/kg) after a dose of 0.15 mg/kg in healthy volunteers [5]. Its major metabolite also has a long half-life and low clearance. Following an initial intravenous dose, diazepam distributes rapidly from the vascular compartment into the CNS, but then quickly re-distributes into muscle and adipose tissue [6]. Consequently, its pharmacodynamic half-life is much shorter than its elimination half-life. Because of its long elimination half-life and that of its metabolites, repeated administration may lead to prolonged sedation. After intramuscular administration, absorption is slow, and reaches its maximum concentration 1 h after doses of 5, 10, or 15 mg [7].

Lorazepam, like diazepam, is nearly insoluble in water, but is much less lipid soluble. Each milliliter of the parenteral solution contains 2.0 or 4.0 mg lorazepam and 18 % polyethylene 400 in propylene glycol with 2.0 % benzyl alcohol. The major metabolic pathway for lorazepam is conjugation to glucuronic acid at the 3-position, which is then excreted as an inactive glucuronide metabolite [8]. Lorazepam has a volume of distribution of 0.8–1.3 l/kg, a plasma clearance of 0.7–1.2 ml/kg/min, an elimination half-life of 15 h with a range of 8–25 h and is 90 % bound to plasma proteins [8]. After intramuscular administration, the time to the maximum concentration of lorazepam is 1.2 h, and it is 90 % bound to plasma protein [8]. The lower lipid solubility of lorazepam means that the drug re-distributes more slowly than diazepam to muscle and fat tissue. This results in a longer residence time in the CNS, which translates into more prolonged pharmacodynamic CNS effects than diazepam [9].

In contrast to diazepam and lorazepam, the injectable form of midazolam is water soluble, which is accomplished by ionizing the molecule in an acidic solution. Each milliliter of the parenteral solution contains either midazolam 1 or 5 mg in water with the pH adjusted to 2.5–3.7. Once the drug is injected into a vein, the pH of blood almost instantaneously causes a re-confirmation of midazolam into its un-ionized, highly lipid-soluble form. As a result, midazolam enters the CNS quickly. The bioavailability of intramuscular midazolam is 87 ± 18 % [10]. The primary metabolites of midazolam are 1-hydroxy midazolam and 4-hydroxy midazolam. Both are active metabolites, with 1-hydroxy midazolam being as potent as the parent compound. These active metabolites are further conjugated to inactive compounds with glucuronic acid [4]. Midazolam is 94–98 % protein bound [4]. It has an elimination half-life of 2.29 ± 0.42 h, its Vd at steady state is 50.2 ± 11.3 L, and its total clearance is 323 ± 86 ml/min

[10]. However, its Vd may vary from 4.2 to 6.6 l/kg, with the largest Vd being observed in obese subjects [11]. In contrast to other parenteral formulations of benzodiazepines, intramuscular midazolam is rapidly absorbed, with peak serum concentrations achieved at 17.5 ± 6.5 to 25 ± 23 min [12, 13].

Clonazepam is highly lipid soluble but insoluble in water. It is formulated as 1 mg/ml with ethanol, benzyl alcohol, acetic acid, and propylene glycol. After intravenous administration, its distribution follows a two-compartment model, with a distribution half-life ranging from 0.7 to 3.4 h and the Vd ranging from 1.5 to 4.4 l/kg [14]. Its protein binding is 86 %, lower than that of the other benzodiazepines. Clonazepam is extensively metabolized primarily by cytochrome P450 (CYP)-3A4, and its elimination half-life has been reported to range from 17 to 56 h and clearance from 94 to 125 ml/h/kg [14].

2.2 Hydantoins: Fosphenytoin and Phenytoin

Phenytoin is the generic name for 5,5-diphenylhydantoin [15]. It can be formulated as a free acid (molecular weight 252) or the sodium salt (molecular weight 274). The mechanism of action for phenytoin appears to be blockage of the Na+ currents that causes an interference with neuronal action potential [16, 17]. The sodium salt, a weak organic acid with an apparent disassociation constant (p*K*a) in the range of 8.3–9.2, is used in the parenteral formulation [15]. The parenteral phenytoin solution (phenytoin sodium injectable, USP) has a pH of 11.38–12.00 adjusted with sodium hydroxide and contains 40 % propylene glycol, 10 % alcohol, and 50 mg/ml phenytoin [18]. In a study of intravenous phenytoin for the treatment of acute seizures, the elimination half-life of phenytoin after an intravenous load of 18 mg/kg was 51.2 ± 31.6 h, Vd (l/kg) was 0.78 ± 0.11, and clearance (l/kg/h) was 0.0157 ± 0.0132 [19]. It should not be infused at a rate of more than 50 mg/min; this should be slower if hypotension develops. The half-life was considerably longer than reported for smaller oral doses due to the saturation of its major metabolic enzymes, 2C9 and 2C19. When administered intramuscularly, the parenteral formulation of phenytoin crystallizes in muscle tissue, causes tissue necrosis, is very poorly absorbed, and causes severe pain at the injection site [20–22].

Phenytoin is highly protein bound. In healthy adults, approximately 90 % is protein bound and 10 % is unbound ('free'). In patients who have low albumin, are using drugs that compete for binding sites, or are in renal failure, standard measurements of phenytoin may be misleading, and determination of the unbound level is necessary [23].

Fosphenytoin is a prodrug of phenytoin that was developed to overcome the unfavorable properties of phenytoin [24]. It is the sodium phosphate ester of phenytoin, which makes it much more soluble than phenytoin in aqueous solutions. The commercial formulation has a near physiological pH of 8.6–9.0 [25], allowing for faster infusion and fewer adverse events, especially at the injection site [26]. Fosphenytoin is metabolized to phenytoin by phosphatases found in the liver and red blood cells; the conversion half-life to phenytoin is 8–15 min [27]. Once fosphenytoin is converted to phenytoin, the pharmacokinetics of phenytoin are applicable. Unlike phenytoin, fosphenytoin can be administered intramuscularly; by this route, the time to maximum concentrations of the derived phenytoin is 36 min [28].

2.3 Valproic Acid

VPA is the generic name for 2-*n*-propylpentanoic acid, a simple branched chain fatty acid [29]. It has a molecular weight of 144 and is a weak acid (p*K*a = 4.8) that is water insoluble. VPA has multiple modes of action; it antagonizes *N*-methyl-D-aspartate (NMDA) receptor-mediated neuronal excitation, potentiates postsynaptic neuronal response to GABA, may reduce sodium conductance at the sodium channel, may block voltage-sensitive T-type calcium channels in thalamocortical neurons, and may decrease excitatory amino acid aspartate concentrations [30, 31]. VPA is metabolized by the liver and undergoes β-oxidation, oxidative metabolism, and glucuronidation [32]. An active metabolite of VPA is the trans isomer 2-ene-valproic acid (2-ene-VPA) [33]. Unlike the acid, the sodium salt of VPA is water-soluble [29]. Its intravenous preparation has a pH of 7.6 and consists of disodium edetate (0.4 mg/ml) with an equimolar amount of sodium hydroxide and valproate sodium [34].

Other than reaching its maximum concentration very rapidly, its elimination pharmacokinetics after intravenous administration are similar to those of oral VPA [35]. In a study of rapid infusion of the marketed intravenous preparation, the mean Vd was 0.21 ± 0.044 l/kg [36]. Using stable labeled intravenous VPA in individuals with epilepsy, the most accurate means by which to determine pharmacokinetic parameters, adults (mean age 36 years) had a Vd of 12.6 ± 2.6 L [37].

Serum VPA concentrations are significantly influenced by a patient's induction status and albumin concentration [36]. Unbound (free) VPA is approximately 10–15 % of total VPA serum concentrations in healthy adults when total VPA is 50–100 mg/l. When total serum VPA levels increase, the unbound VPA fraction also increases. The total concentration thus increases disproportionally less than the unbound. For studies of efficacy related to concentrations, obtaining both total and unbound levels may be helpful in interpreting results. The intravenous formulation

should never be administered into muscle as it causes necrosis at all doses [38].

2.4 Levetiracetam

Levetiracetam is the (S)-enantiomer of alpha-ethyl-2-oxo-1-pyrrolidine acetamide; the (R)-enantiomer has no antiepileptic activity [39]. Unlike most parenteral ASDs, it is extremely water soluble, as 104 gm can be dissolved in 100 ml of water [40]. The intravenous formulation contains 100 mg/ml buffered to an approximate pH of 5.5 with glacial acetic acid and sodium acetate trihydrate. It has a different profile than classic ASDs in animal models used to screen compounds for activity against seizures. It has high affinity for the synaptic vesicle membrane protein SV2A, but the molecular action of SV2A is not entirely clear [41, 42]. It also partially inhibits N-type high-voltage activated Ca2+ currents, opposes negative allosteric modulators of neuronal $GABA_A$ glycine-gated currents, and affects voltage-gated potassium channel conductance [39, 43–45]. Although a specific intramuscular formulation has not been developed for levetiracetam, it has been shown that the formulation developed for intravenous use can be given safely to dogs and humans with no muscle damage, minimal side effects, and complete bioavailability [46, 47]. In humans, the mean time to maximum concentration after intramuscular administration was 2 h, with a range of 0.75–4 h [46]. It does not yet have FDA approval to be administered by this route.

Levetiracetam has linear pharmacokinetics: its Vd is approximately 0.5–0.7 l/kg, and <10 % is protein bound [48, 49]. Animal studies show that, in spite of its water solubility, levetiracetam crosses the blood–brain barrier [50]. Levetiracetam is not dependent on hepatic CYP enzymes, epoxide hydrolase, or UDP-glucuronidation metabolism [51, 52]. In healthy adults, it is excreted predominately unchanged in the urine [51, 52]. Elderly patients or those with impaired renal function will have decreased clearance of levetiracetam and increased plasma half-life related to creatinine clearance. Levetiracetam clearance may be reduced by 40 % with creatinine clearance of 50–80 ml/min, by 50 % with clearance of 30–50 ml/min, and by 60 % with clearance of <30 ml/min [51, 52].

2.5 Lacosamide

Lacosamide is an (R)-enantiomer of 2-acetamido-*N*-benzyl-3-methoxypropionamide. It is sparingly water soluble, and the intravenous formulation consists of 10 mg/ml in water with sodium chloride and a pH adjusted to 3.5–5.0 with hydrochloric acid. Its mechanism of action involves enhancement of slow sodium channel inactivation, but it does not appear to have an effect on fast sodium channel inactivation [53]. It is also thought to block NMDA receptors [54]. Oral and intravenous formulations of lacosamide are bioequivalent [55]. Orally administered lacosamide has a half-life of approximately 13 h, and 95 % is excreted in the urine with <0.5 % in the feces. The protein binding of lacosamide has been reported to be <15 % in various reports and by in vitro equilibrium dialysis [56, 57] However, another study measuring unbound lacosamide in filtered serum and saliva from patients with epilepsy reported lacosamide binding of 91 ± 4 % [58]. From the literature, it is unclear whether lacosamide is not well bound or highly bound. Excreted lacosamide consists of the parent drug and its inactive metabolite, O-desmethyl [55]. Studies confirm that lacosamide does not have major interactions with other commonly used ASDs [55, 56].

2.6 Barbiturates

Barbiturates (phenobarbital and pentobarbital) are derivatives of barbituric acid and have similar mechanisms of action. Phenobarbital binds to the $GABA_A$ receptor and prolongs the open time of the chloride channel, as does pentobarbital [59]. They also block high-voltage activated calcium channels and exert an inhibitory effect on specific subtypes of glutamate receptors, reducing neuronal excitability [30]. After intravenous administration, the mean distribution half-life of phenobarbital is 0.18 h, and the mean elimination half-life is long: 5.8 days [60]. Its Vd ranges from 0.54 to 0.60 l/kg in adults and 1.0 l/kg in neonates [60–62]. Pentobarbital has a half-life of approximately 14 h, much shorter than phenobarbital [63]. Its shorter half-life makes it much easier to use in clinical settings. Both barbiturates are renally eliminated and are metabolized by hepatic oxidative enzymes.

2.7 Others

Paraldehyde is a cyclic polymer of acetaldehyde that was introduced into clinical practice in 1882 [64]. After intravenous injection, anesthesia occurs within 2–5 min, indicating rapid distribution to the brain. After intramuscular administration, blood levels peak in 20–60 min. Although 70–80 % is metabolized by hepatic enzymes, a significant route of elimination is exhalation through the lungs. Clearance of paraldehyde is approximately 0.1 l/kg/h and thus its elimination half-life is long [64].

Chlormethiazole edisylate is a sedative hypnotic, although it is structurally related to thiamine. Its primary mechanism of action appears to be related to its effect on $GABA_A$ receptors [65]. Its Vd is large, between 4 and 19 l/kg, and it is approximately 70 % protein bound. It is cleared very rapidly, and the rate of hepatic blood flow appears to be the determining factor [64].

3 Intravenous Drugs in Development

3.1 Carbamazepine

Carbamazepine is an iminodibenzyl derivative, with the most reactive site being the double bond between C-10 and C-11 [29]. It is virtually insoluble in water, but an intravenous preparation of 10 mg/ml carbamazepine solubilized in 22.5 % 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) has been developed [66–68] and is awaiting FDA approval. Nearly 40 % of carbamazepine is metabolized to carbamazepine-10, 11 epoxide (CBZ-E) via epoxidation of the 10, 11 double bond of the azepine ring catalyzed by the hepatic monooxygenases [69]. CBZ-E is further metabolized to 10, 11 dihydro-10, 11 dihydroxycarbamazepine by the microsomal epoxide hydrase trans-dihydrodiol [69, 70]. In a study using stable labeled carbamazepine, the Vd was expressed both as 89.78 ± 37.5 L and 1.11 ± 0.26 l/kg [67, 68]. The absolute bioavailability of carbamazepine (F) was determined in a subset of 42 subjects (12 receiving immediate-release and 30 receiving extended-release carbamazepine). The mean and median fraction absorbed in this study was 0.78 and 0.75, respectively, with almost a fourfold variability across subjects (0.38–1.44). No adverse effects on blood pressure or heart rate were observed after a single dose of intravenous carbamazepine 100 mg [66, 67].

3.2 Topiramate

Topiramate is a sulfamate-substituted derivative of D-fructose, originally developed for treatment of diabetes. However, in 'routine' screening for antiseizure properties, it was found to be effective against maximal electroshock seizures but not chemo-convulsants. It has a molecular weight of 339, is a white crystalline powder, and is poorly soluble in water, with only 9.8 mg/ml at room temperature [71]. An injectable topiramate formulation consisting of topiramate 10 mg/ml dissolved in 10 % sulfobutyl cyclodextrin has been formulated [72, 73]. A comparison of oral and intravenous topiramate 50 and 100 mg in healthy volunteers found that following an intravenous topiramate infusion over 15 min, the clearance was 1.33 ± 0.26 l/h, the Vd was 1.06 ± 0.29 l/kg, and the half-life was 42.3 ± 6.2 h. No statistically significant difference was observed in the pharmacokinetic parameters of intravenous and oral topiramate [72]. The bioequivalence of oral topiramate was 109 ± 10.8 % [72]. A commercial formulation is under development. With regards to the potential use of injectable topiramate in seizure emergencies, it is important to note that, in the healthy volunteer study, CNS symptoms were observed within 15 min after beginning drug infusion of 100 mg, suggesting rapid diffusion of topiramate into the CNS [72].

3.3 Lamotrigine

Lamotrigine [3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine] is a phenyltriazine molecule. Its mechanism of action is inhibition of voltage-gated sodium channels, presynaptic modulation of excitatory amino acids such as glutamate and aspartate, and stabilization of neuronal membranes [55]. Lamotrigine is metabolized by hepatic glucoronidation and then eliminated renally. Its clearance is 2.14 ± 0.82 l/h [73, 74]. The Vd ranges from 1.28 to 1.36 l/kg. An intravenous formulation of lamotrigine with stable labeled isotopes for human investigational use has been developed [75].

4 Clinical Use of Intravenous ASDs in Status Epilepticus

SE is a serious, life-threatening neurological emergency consisting of prolonged and/or frequent seizures. It is associated with some of the highest mortalities and morbidities of any neurological condition. It has been reported that 152,000 cases with 42,000 deaths (28 %) occur each year in the USA [76]. Although the cognitive outcome of SE is variable and mainly dependent on the cause, some individuals may have a significant decrease in their IQ [77]. Specific parenteral preparations, availabilities, brand names, dosing recommendations, formulations, and regulatory approval vary from country to country, and readers should review the specifications for products available in their country. In general, adverse events for the specific drugs are the same as for oral use, except that the CNS symptoms may occur more rapidly and be more severe with intravenous use. In addition, intravenous administration may be associated with cardiac and circulatory adverse events not seen with the oral preparations. At this time, there is no Class I evidence to choose among the major ASDs. A study funded by the National Institutes of Health (NIH), the ESETT (Established Status Epilepticus Treatment Trial) started enrolling subjects at the end of 2015 and will be a randomized, double-blind study comparing fosphenytoin, VPA, and levetiracetam for the treatment of SE. Until the results of this study are made public, there is no good evidence to choose one of these drugs as the treatment of choice for SE, and thus the following section gives only general information on the use of these ASDs.

4.1 Benzodiazepines

First-line medical treatment of SE is the use of the benzodiazepines. Multiple studies have shown that lorazepam is an effective initial treatment strategy for convulsive SE

[78–82]. The efficacy of four intravenous ASDs, phenytoin, lorazepam, diazepam, and diazepam followed by phenytoin, were compared in a double-blind, randomized study of 384 patients with generalized convulsive SE [81]. Lorazepam was the most successful for generalized SE, with a success rate of 64.9 % [81]. Lorazepam was the most effective, and phenytoin the least, but the differences were not statistically significant in the intent-to-treat analysis. However, the lengthy time required for administration of phenytoin may have contributed to its inferiority.

Few randomized controlled trials address the question of which benzodiazepine has the best efficacy in the initial treatment of SE. Several studies have found that lorazepam and diazepam are either equally efficacious or that lorazepam is better as initial treatment for SE [78, 82]. In the first double-blind, randomized clinical trial in SE, lorazepam (4–8 mg) was compared with diazepam (10–20 mg) for the treatment of generalized and partial SE. Although 89 % had seizure cessation with lorazepam compared with 76 % with diazepam, the difference was not statistically significant [82]. Another study found that lorazepam was more efficacious than diazepam; lorazepam (2 mg) terminated SE in 59.1 % of patients who received it versus 42.6 % for diazepam (5 mg) and 21.1 % for placebo ($p < 0.001$) [78]. The pharmacokinetics of lorazepam also makes it more favorable than diazepam in the treatment of SE [5, 79, 82]. For acute treatment with benzodiazepines, the bolus should be injected slowly to avoid respiratory depression. For children, 1 mg per minute is appropriate; for adults, the bolus is often given over 5 min. Lorazepam may be initially given as an intravenous bolus of 0.05–0.1 mg/kg in adults and children and may be repeated after 10 min if needed [2]. The recommended dosing for intravenous diazepam for SE is 0.15–0.25 mg/kg in adults and 0.1–0.3 mg/kg in children. Clonazepam as intravenous injection has been used in children and adults with SE, and other than its longer duration of action, it is similar to diazepam [64]. Bolus doses of 0.25 mg repeated three times if needed or 250–750 μg/kg have been used in children [64]. Adults have usually been treated with doses of 1 mg, repeated if needed.

When intravenous access is not available, the benzodiazepines have been given intramuscularly. However, both intramuscular lorazepam and diazepam are absorbed very slowly [83]. In contrast, intramuscular midazolam exhibits rapid absorption, with peak serum concentrations attained at 17.5 ± 6.5 to 25 ± 23 min [12, 13]. A meta-analysis of six studies (total of 774 patients) also supports the use of intramuscular midazolam over intramuscular diazepam [84]. Midazolam at a dose of 0.2 mg/kg was studied in adults and children and found to achieve seizure cessation in 80–100 % of the subjects [85–87]. In a recent landmark multicenter double-blind study of pre-hospital treatment of seizures—RAMPART (Rapid Anticonvulsant Medication Prior to Arrival Trial)—intramuscular midazolam delivered via an auto-injector was compared with intravenous lorazepam. The study utilized the Neurological Emergencies Treatment Trials (NETT) network to recruit adults and children estimated to weigh ≥13 kg. Seizures were absent on arrival to the emergency department in 73.4 % of the intramuscular midazolam-treated subjects compared with 63.4 % of those assigned to intravenous lorazepam ($p < 0.001$ for noninferiority and $p < 0.001$ for superiority). Although intravenous lorazepam had a quicker onset of action after administration, intramuscular midazolam could be given without needing to start an intravenous line, and thus it had a shorter time to administration of the drug [88]. An additional limitation to the use of lorazepam in the non-hospital setting is that it needs to be refrigerated.

Adverse effects associated with the use of benzodiazepines are hypotension, decreased level of consciousness, and respiratory depression that may require cardiopulmonary supportive care [80, 82, 88–90]. In one study, 10.6 % of the patients treated with intravenous lorazepam, 10.3 % of the patients treated with intravenous diazepam, and 22.5 % of the patients given placebo ($p = 0.08$) experienced complications of hypotension, cardiac arrhythmia, or respiratory distress [78]. The high rate of complications with placebo was attributed to lack of seizure control. Regulatory approval varies from country to country, and not all parenteral ASDs commonly used for SE have specific regulatory approval for this indication in all countries.

4.2 Phenytoin and Fosphenytoin

Although the therapeutic effect of fosphenytoin is due to phenytoin, fosphenytoin is preferred because of safety issues [91]. Phenytoin and fosphenytoin are typically used after lorazepam or diazepam to provide a longer period of seizure control. A study of phenytoin in the treatment of SE in an emergency room setting found that 27 of 52 patients initially given diazepam alone had subsequent seizures within 4 h, and a loading dose of intravenous phenytoin was required [92]. This has led to the practice of using a longer-acting drug following a benzodiazepine even if seizures have been controlled initially [93]. Outcome of SE treatment is related to etiology; those with acute CNS lesions had a 57 % rate of recurrent seizures after intravenous phenytoin loading compared with 10 % of those with pre-existing epilepsy [93].

In the first study of escalating doses of intravenous phenytoin to determine its effective range for treating SE, a dose of 18 mg/kg administered at 50 mg/min was effective in maintaining phenytoin serum levels above 20 mg/l for 24 h in most patients [19]. In this cohort, hypotension was more

frequent among older patients, and the rate of infusion needed to be slowed [19, 94]. The initial study found that 18 mg/kg provided adequate levels; however, for ease of calculation, a loading dose of 20 mg/kg infused at a maximum rate of 50 mg/min (phenytoin) and 100–150 mg/min (fosphenytoin) is now used by some in the treatment of SE [95].

The most common adverse effects with intravenous phenytoin are hypotension, QT prolongation, and cardiac arrhythmias [19, 93]. Many of these can be seen in rodents given only the solvent system [94]. Purple glove syndrome is seen in up to 5.9 % of patients and has been attributed to extravasations of phenytoin's alkaline solution into soft tissue [96]. Purple glove syndrome causes pain, skin discoloration, and edema. If left untreated, it can progress to skin necrosis and ischemia, and some patients have needed limb amputation. Fosphenytoin has fewer side effects, but patients are still at risk for hypotension and cardiac arrhythmias. Purple glove syndrome has not been reported with fosphenytoin, since the solution has a neutral pH. Phenytoin is the only widely used intravenous drug with an extreme pH and high propylene glycol content. If monitoring of treatment is necessary in a patient, both free and total phenytoin concentrations may need to be measured after loading with either fosphenytoin or phenytoin [97].

4.3 Valproic Acid

Approximately one-third of patients do not respond to standard first- and second-line treatment for SE [81, 82, 93]. VPA may be considered in the treatment of SE in these cases, especially if there are concerns of cardiopulmonary or respiratory side effects as seen with phenytoin, barbiturates, and benzodiazepine [98–102]. Loading doses of 20–30 mg/kg with rates of up to 10 mg/kg/min have been shown to be safe, without significant adverse reactions in adult and pediatric populations [36, 103–107]. A study of the dose: concentration relationship of continuous infusion of intravenous VPA after a load of 28.5 mg/kg followed by a continuous infusion of 1.0 ± 0.2 mg/kg/h found steady state concentrations of 50–100 μg/ml were attained in 69 % of the patients [106]. In a series of 41 children with SE treated after failing standard initial treatment who were loaded with VPA 20–40 mg/kg over 1–5 min and maintained on an intravenous infusion of 5 mg/kg/h, SE stopped in 78 % with no significant adverse reactions [101]. At 1 h post intravenous VPA infusion, transient asymptomatic hyperammonemia may occur [108]. A number of studies have found VPA to be efficacious in aborting SE in 63.3–85.6 % of cases, with no significant adverse reactions in cardiopulmonary status and level of consciousness; doses ranged from initial bolus 300–900 mg or 20–40 mg/kg followed by infusion of 37.5–240 mg/h or 5 mg/kg/h [101, 105, 107, 109–111].

4.4 Levetiracetam

Several reports suggest levetiracetam may be an effective and well-tolerated treatment option to stop SE after standard treatments have failed [112–114]. One study randomized 79 patients to receive intravenous levetiracetam 20 mg/kg over 15 min or intravenous lorazepam 0.01 mg/kg over 2–4 min [115], and found that levetiracetam controlled SE in 76.3 % and lorazepam controlled SE in 75.6 % of patients, but lorazepam was associated with hypotension and respiratory depression [115]. The dose of intravenous levetiracetam that may be administered to adults is 500–3000 mg/day divided in two doses. Oral doses up to 5000 mg/kg (maximum tested dose) are not lethal in mice and rats [39]. Levetiracetam doses ≤4000 mg over 15 min and 2500 mg over 5 min were well tolerated and safe when studied in healthy adults [49]. Levetiracetam solution is available in a 100-mg/ml formulation. Adverse events after intravenous administration of levetiracetam are primarily CNS related and include dizziness (52.8 %), somnolence (33.3 %), fatigue (11.1 %), and headache (8.3 %) [49].

4.5 Lacosamide

Lacosamide has favorable features, including minimal drug interaction, few adverse reactions, renal excretion, and an available intravenous formulation, making it an attractive option in the treatment of SE. To date, no randomized controlled trials have investigated the efficacy of lacosamide in SE. Several reports have illustrated the efficacy of lacosamide in treating SE after initial standard treatments have failed [116–119]. A retrospective analysis of 39 patients with SE who received one dose of lacosamide (200–400 mg bolus) after standard therapy failed [118] showed that SE was controlled in 44 % (17 of 39) of patients with no adverse side effects [118]. A review of the literature found that 58 of 103 (56 %) reported cases of SE were terminated with lacosamide [120]. These descriptive reports provide encouraging results that lacosamide may be a potential medication for SE, but controlled studies are needed [121].

4.6 Paraldehyde and Chlormethiazole

Although paraldehyde has been available for over 100 years, there are few studies of its use in SE. It may be given by deep injection intramuscularly or rectally in doses of 5–10 ml [64]. It may be used early in SE when intravenous access is limited [64]. However, it has a tendency to decompose and has lost favor in many settings because of adverse effects probably related to decomposition products [64].

In the treatment of SE, an initial infusion of chlormethiazole 40–80 ml of an 0.8 % solution may be given at a rate of 5–15 ml/min [64]. Too rapid infusion may be associated with respiratory depression, hypotension, or cardiac arrhythmias. Infusion is continued until seizures are controlled [64]. Subsequent infusion may be necessary, and its advantage is that the dose can be titrated for moment-to moment control of seizures [64].

5 Refractory Status Epilepticus

Refractory status epilepticus (RSE) may be defined as SE that does not respond to first- or second-line treatment or treatment failure after 60 min [122]. Animal studies have shown that, in prolonged SE, the concentration of $GABA_A$ receptors is reduced and NMDA receptors are increased at the synaptic membranes [123–125]. This may explain why the $GABA_A$ agonists are less effective in RSE. At the present time, the treatment of RSE suffers from a lack of good, controlled studies, and almost all ASDs have been tried, with mixed results. This short section is not intended to be a comprehensive review of all of the published studies. Intravenous propofol, thiopental, pentobarbital, and midazolam are commonly used to treat RSE and induce clinical and electrographic coma. The major use of these intravenous medications is for RSE, administered only after the patient has been intubated. The recommended loading dose is 10–30 mg/kg, with an administration rate of 100 mg/min (2 mg/kg/min in children weighing <40 kg). Maintenance therapy in adults is 1.5–4 mg/kg and in children is 2–8 mg/kg. A multicenter randomized trial comparing propofol with barbiturates in 24 patients found the two drugs to be equally effective, but the propofol onset of action was more rapid [126]. Mechanical ventilation time was longer with barbiturates (4 vs. 13.5 days, $p = 0.03$), but there was no difference in mortality between propofol and barbiturates (43 vs. 34 %) [126]. A systematic review comparing propofol, pentobarbital, and midazolam in a total of 193 patients in 28 studies found that pentobarbital compared with midazolam or propofol had fewer treatment failures (8 vs. 23 %, $p < 0.01$), fewer breakthrough seizures (4 vs. 53 %, $p < 0.001$), and more hypotension, with no significant difference in mortality [122]. Barbiturate anesthetics, pentobarbital in the USA and thiopental sodium in Europe and Australia, are highly effective for refractory RSE both in children and in adults [127]. The advantage of propofol is that it has a short duration of action that permits clinical evaluation shortly after its reduction. However, it may cause a potentially fatal syndrome—propofol infusion syndrome—which comprises cardiac failure, renal failure, lactic acidosis, hypertriglyceridemia, and rhabdomyolysis [128].

Levetiracetam, lacosamide and VPA given intravenously and topiramate, oxcarbazepine and perampanel given orally by nasogastric tube have been used as adjunctive options for RSE with some positive results [116, 117, 119, 129–132]. Ketamine has been reported to be effective in stopping RSE when other drugs have failed [133]. At the present time, there is no consensus regarding the treatment of RSE, and randomized, controlled studies are needed to elucidate the best approach [127]. One new drug that may modulate extrasynaptic $GABA_A$ receptors—allopregnanolone (SAGE 547)—is in a phase III study in the USA.

6 Replacement Therapy

One of the significant difficulties faced by individuals with epilepsy is that most of their ASDs do not have an intravenous or intramuscular formulation. Thus, a patient who is unable to take medications orally because of an illness or surgical procedure is at risk for having seizures. In these situations, the physicians must temporize with a different ASD available via the parenteral route. The risks of exposing a patient to a different ASD that may be ineffective in this critical situation would be unnecessary if all of the ASDs were available in a parenteral preparation. Theoretically, there is no reason for parenteral formulations not to be available for all ASDs. Those that are soluble in aqueous solutions can be easily formulated. Those that are not water soluble can be formulated with solvent systems such as cyclodextrins. This has been demonstrated by the development of intravenous carbamazepine, topiramate, and lamotrigine for investigational use with FDA-issued investigational new drug status. These have been used safely in volunteers and individuals with epilepsy [66, 72, 134]. However, the small market for parenteral formulations coupled with the large cost of clinical trials for registration has discouraged the development of these. Replacement therapy may be implemented using intravenous or intramuscular ASDs. Intravenous replacement therapy is possible for phenytoin (fosphenytoin), VPA, levetiracetam, and lacosamide. However, bioavailability may vary among patients and among various formulations, and the parenteral replacement dose may need to be monitored and adjusted. An intravenous carbamazepine as replacement for oral administration has completed a phase III trial and is awaiting FDA approval [135].

If intravenous access is not available, fosphenytoin or levetiracetam may be given intramuscularly [46]. Phenytoin should not be administered via nasogastric tube or percutaneous gastric tube to critically ill patients, as absorption of the tablets or suspension is variable in these situations [136].

7 Conclusions and Future Directions

The major use of parenteral formulations of ASDs is in the treatment of SE. Unfortunately, there are very few controlled, randomized studies regarding the treatment of this critical condition [81, 82, 88]. Success rates vary greatly among studies because outcomes are related to the populations studied and the rigor of the design. The current guidelines involving use of benzodiazepines, phenytoin, or fosphenytoin are based on studies initiated more than 2 decades ago with drugs developed 30–70 or more years ago for the long-term treatment of epilepsy, not for the treatment of SE [1, 91]. Interest in using VPA, levetiracetam, and lacosamide for SE evolved from consideration that they may be safer. However, concerns also exist that the newer drugs may not be as effective [137]. To address this issue, ESETT is performing a randomized, controlled study of fosphenytoin, VPA, and levetiracetam [137]. The neurosteroid allopregnanolone acts as a positive allosteric modulator of synaptic and extrasynaptic $GABA_A$ receptors and has been used successfully in two pediatric patients with super-refractory SE [138]. Promising top-line data have also recently been reported for a phase I/II trial in 17 patients with super-refractory SE but have not yet been published in full.

In addition to the clinically available agents, a number of novel drugs have been shown to be more effective in animal models of SE than those currently used to treat human SE. These include valnoctamide and sec-butylpropylacetamide (SPD) [139].

Because of the high barriers, both ethical and financial, to bringing drugs tested only in rodent models to human use, a translational platform would be useful. One approach would be to study safety and efficacy in naturally occurring canine SE (CSE), a common condition in this species that is similar to that in humans [140, 141]. Drugs identified as safe and effective for CSE may then be investigated in the NETT that evaluated intramuscular midazolam compared with intravenous lorazepam [88]. The pathway to new and better parenteral drugs may well be identification of agents using small animal models, obtaining further safety and efficacy information from species closer to humans, and then using these in large, multicenter, controlled human trials. This rational approach may help alleviate much of the current lack of a scientific approach to SE.

Therefore, new treatment options are urgently needed. The ideal new drug for refractory generalized convulsive SE (GCSE) would be one that has the ability to stop seizures more effectively and safely than current drugs, and that has neuroprotective properties to prevent the brain damage and neurological morbidity caused by GCSE.

Compliance with Ethical Standards

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References

1. Meierkord H, Boon P, Engelsen B, Gocke K, Shorvon S, Tinuper P, et al. EFNS guideline on the management of status epilepticus in adults. Eur J Neurol. 2010;17(3):348–55.
2. Riss J, Cloyd J, Gates J, Collins S. Benzodiazepines in epilepsy: pharmacology and pharmacokinetics. Acta Neurol Scand. 2008;118(2):69–86.
3. Campo-Soria C, Chang Y, Weiss DS. Mechanism of action of benzodiazepines on GABAA receptors. Br J Pharmacol. 2006;148(7):984–90.
4. Olkkola KT, Ahonen J. Midazolam and other benzodiazepines. Springer-Verlag Berlin Heidelberg; 2008.
5. Greenblatt DJ, Divoll M. Diazepam versus lorazepam: relationship of drug distribution to duration of clinical action. Adv Neurol. 1983;34:487–91.
6. Celesia GGBH, Sato S. Brain and serum concentrations of diazepam in experimental epilepsy. Epilepsia. 1974;15:417–25.
7. Lamson MJ, Sitki-Green D, Wannarka GL, Mesa M, Andrews P, Pellock J. Pharmacokinetics of diazepam administered intramuscularly by autoinjector versus rectal gel in healthy subjects: a phase I, randomized, open-label, single-dose, crossover, single-centre study. Clin Drug Investig. 2011;31(8):585–97.
8. Greenblatt DJ, Shader RI, Franke K, MacLaughlin DS, Harmatz JS, Allen MD, et al. Pharmacokinetics and bioavailability of intravenous, intramuscular, and oral lorazepam in humans. J Pharm Sci. 1979;68(1):57–63.
9. Rey ETJ, Pons G. Pharmacokinetic optimization of benzodiazepine therapy for acute seizures. Focus on delivery routes. Clin Pharmacokinet. 1999;36:409–24.
10. Heizmann P, Eckert M, Ziegler WH. Pharmacokinetics and bioavailability of midazolam in man. Br J Clin Pharmacol. 1983;16(Suppl 1):43S–9S.
11. Wills RJ, Khoo KC, Soni PP, Patel IH. Increased volume of distribution prolongs midazolam half-life. Br J Clin Pharmacol. 1990;29:269–72.
12. Hung OR, Dyck JB, Varvel J, Shafer SL, Stanski DR. Comparative absorption kinetics of intramuscular midazolam and diazepam. Can J Anaesth. 1966;43:450–5.
13. Bell DM, Richards G, Dhillon S, Oxley JR, Cromarty J, Sander JW, et al. A comparative pharmacokinetic study of intravenous and intramuscular midazolam in patients with epilepsy. Epilepsy Res. 1991;10(2–3):183–90.
14. Anderson GD, Miller JW. Benzodiazepines: chemistry, biotransformation, and pahrmacokinetics. In: Levy RH, Mattson RH, Meldrum BS, Perucca E, editors. Antiepileptic drugs, 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 187–205.
15. Dill WA, Glazko AJ, Kazenko A, Wolf LM. Studies on 5, 5′-diphenylhydantoin (dilantin) in animals and man. J Pharmacol Exp Ther. 1956;118(3):270–9.
16. Yaari Y, Selzer ME, Pincus JH. Phenytoin: mechanisms of its anticonvulsant action. Ann Neurol. 1986;20(2):171–84.

17. Rogawski MALW. The neurobiology of antiepileptic drugs. Nat Rev Neurosci. 2004;5:553–64.
18. Markowsky SJ, Kohls PR, Ehresman D, Leppik I. Compatibility and pH variability of four injectable phenytoin sodium products. Am J Hosp Pharm. 1991;48(3):510–4.
19. Cranford RE, Leppik IE, Patrick B, Anderson CB, Kostick B. Intravenous phenytoin: clinical and pharmacokinetic aspects. Neurology. 1978;28(9 Pt 1):874–80.
20. Boucher BA, Feler CA, Dean JC, Michie DD, Tipton BK, Smith KR Jr, et al. The safety, tolerability, and pharmacokinetics of fosphenytoin after intramuscular and intravenous administration in neurosurgery patients. Pharmacotherapy. 1996;16(4):638–45.
21. Ramsay RE, Wilder BJ, Uthman BM, Garnett WR, Pellock JM, Barkley GL, et al. Intramuscular fosphenytoin (Cerebyx) in patients requiring a loading dose of phenytoin. Epilepsy Res. 1997;28(3):181–7.
22. Pryor FM, Gidal B, Ramsay RE, DeToledo J, Morgan RO. Fosphenytoin: pharmacokinetics and tolerance of intramuscular loading doses. Epilepsia. 2001;42(2):245–50.
23. Patsalos PNBD, Bourgeois BFD, Cloyd JC, Glauser TA, Johannessen SI, Leppik IE, Tomson T, Perucca E. Antiepileptic drugs–best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia. 2008;49:1239–76.
24. Leppik IE, Boucher BA, Wilder BJ, Murthy VS, Watridge C, Graves NM, et al. Pharmacokinetics and safety of a phenytoin prodrug given i.v. or i.m. in patients. Neurology. 1990;40(3 Pt 1):456–60.
25. Gerber N, Mays DC, Donn KH, Laddu A, Guthrie RM, Turlapaty P, et al. Safety, tolerance and pharmacokinetics of intravenous doses of the phosphate ester of 3-hydroxymethyl-5,5-diphenylhydantoin: a new prodrug of phenytoin. J Clin Pharmacol. 1988;28(11):1023–32.
26. Eriksson K, Keranen T, Kalviainen R. Fosphenytoin. Expert Opin Drug Metab Toxicol. 2009;5(6):695–701.
27. Browne TRKA, Eldon MA. Pharmacology and pharmacokinetics of fosphenytoin. Neurology. 1996;46(6 Suppl 1):S3–7.
28. Leppik IE, Boucher R, Wilder BJ, Murthy VS, Rask CA, Watridge C, et al. Phenytoin prodrug: preclinical and clinical studies. Epilepsia. 1989;30(Suppl 2):S22–6.
29. Bialer M. Chemical properties of antiepileptic drugs (AEDs). Adv Drug Deliv Rev. 2012;64(10):887–95.
30. Sills GJ, Brodie MJ. Update on the mechanisms of action of antiepileptic drugs. Epileptic Disord. 2001;3(4):165–72.
31. Loscher W. Basic pharmacology of valproate: a review after 35 years of clinical use for the treatment of epilepsy. CNS Drugs. 2002;16(10):669–94.
32. Hussein Z, Patterson KJ, Lamm JE, Cavanaugh JH, Granneman GR. Effect of infusion duration on valproate pharmacokinetics. Biopharm Drug Dispos. 1993;14(5):389–99.
33. Perucca E, Gatti G, Frigo GM, Crema A, Calzetti S, Visintini D. Disposition of sodium valproate in epileptic patients. Br J Clin Pharmacol. 1978;5(6):495–9.
34. Ramsay RE, Uthman B, Leppik IE, Pellock JM, Wilder BJ, Morris D, Cloyd JC. The tolerablility and safety of valproate sodium injection given as an intravenous infusion. J Epilepsy. 1997;10:187–93.
35. Bryson SM, Verma N, Scott PJ, Rubin PC. Pharmacokinetics of valproic acid in young and elderly subjects. Br J Clin Pharmacol. 1983;16(1):104–5.
36. Cloyd JC, Dutta S, Cao G, Walch JK, Collins SD, Granneman GR, et al. Valproate unbound fraction and distribution volume following rapid infusions in patients with epilepsy. Epilepsy Res. 2003;53(1–2):19–27.
37. Remmel RP, Conway JM, Leppik IE, Beattie J, Ramsay RE, Rarick JO, et al. Valproic acid pharmacokinetics and bioavailability determined by a stable isotope technique. Neurology. 2007;68(12):A266.
38. Gallo BV, Slater JD, Toledo C, DeToledo J, Ramsay RE. Pharmacokinetics and muscle histopathology of intramuscular valproate. Epilepsy Res. 1997;28(1):11–5.
39. Shorvon SD, van Rijckevorsel K. A new antiepileptic drug. J Neurol Neurosurg Psychiatry. 2002;72(4):426–9.
40. Patsalos PN. Levetiracetam: chemistry, biotransformation, pharmacokinetics, and drug interactions. In: Levy RH, Mattson RH, Meddrum BS, Perucca E, editors. Antiepileptic drugs, 5th edn. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 428–32.
41. Lynch BA, Lambeng N, Nocka K, Kensel-Hammes P, Bajjalieh SM, Matagne A, et al. The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. Proc Natl Acad Sci USA. 2004;101(26):9861–6.
42. Vogl C, Mochida S, Wolff C, Whalley BJ, Stephens GJ. The synaptic vesicle glycoprotein 2A ligand levetiracetam inhibits presynaptic Ca2+ channels through an intracellular pathway. Mol Pharmacol. 2012;82(2):199–208.
43. Rigo JM, Hans G, Nguyen L, Rocher V, Belachew S, Malgrange B, et al. The anti-epileptic drug levetiracetam reverses the inhibition by negative allosteric modulators of neuronal GABA- and glycine-gated currents. Br J Pharmacol. 2002;136(5):659–72.
44. Niespodziany I, Klitgaard H, Margineanu DG. Levetiracetam inhibits the high-voltage-activated Ca(2+) current in pyramidal neurones of rat hippocampal slices. Neurosci Lett. 2001;306(1–2):5–8.
45. Huang CW, Tsai JJ, Huang CC, Wu SN. Experimental and simulation studies on the mechanisms of levetiracetam-mediated inhibition of delayed-rectifier potassium current (KV3.1): contribution to the firing of action potentials. J Physiol Pharmacol. 2009;60(4):37–47.
46. Leppik IE, Goel V, Rarick J, Nixdorf DR, Cloyd JC. Intramuscular and intravenous levetiracetam in humans: safety and pharmacokinetics. Epilepsy Res. 2010;91(2–3):289–92.
47. Patterson EE, Goel V, Cloyd JC, O'Brien TD, Fisher JE, Dunn AW, et al. Intramuscular, intravenous and oral levetiracetam in dogs: safety and pharmacokinetics. J Vet Pharmacol Ther. 2008;31(3):253–8.
48. Patsalos PN. Pharmacokinetic profile of levetiracetam: toward ideal characteristics. Pharmacol Ther. 2000;85(2):77–85.
49. Ramael S, Daoust A, Otoul C, Toublanc N, Troenaru M, Lu ZS, et al. Levetiracetam intravenous infusion: a randomized, placebo-controlled safety and pharmacokinetic study. Epilepsia. 2006;47(7):1128–35.
50. Doheny HC, Ratnaraj N, Whittington MA, Jefferys JG, Patsalos PN. Blood and cerebrospinal fluid pharmacokinetics of the novel anticonvulsant levetiracetam (ucb L059) in the rat. Epilepsy Res. 1999;34(2–3):161–8.
51. Patsalos PN. Clinical pharmacokinetics of levetiracetam. Clin Pharmacokinet. 2004;43(11):707–24.
52. Radtke RA. Pharmacokinetics of levetiracetam. Epilepsia. 2001;42(Suppl 4):24–7.
53. Errington AC, Coyne L, Stohr T, Selve N, Lees G. Seeking a mechanism of action for the novel anticonvulsant lacosamide. Neuropharmacology. 2006;50(8):1016–29.
54. Luszczki JJ. Third-generation antiepileptic drugs: mechanisms of action, pharmacokinetics and interactions. Pharmacol Rep. 2009;61(2):197–216.
55. Bialer M, Johannessen SI, Kupferberg HJ, Levy RH, Perucca E, Tomson T. Progress report on new antiepileptic drugs: a

summary of the Eigth Eilat Conference (EILAT VIII). Epilepsy Res. 2007;73(1):1–52.
56. Ben-Menachem E. Lacosamide: an investigational drug for adjunctive treatment of partial-onset seizures. Drugs Today (Barc). 2008;44(1):35–40.
57. Fountain NSL, Tytgat D, Rudd GD, Jaques P. Cawello. Low lacosamide plasma protein binding in lacosamide-naive patients. Neurology. 2012;78(PO1):077.
58. Greenway CRN, Sander JW, Patsalos PN. Saliva snd serum lacosamide concentrations in patients with epilepsy. Epilepsia. 2011;52:258–63.
59. Davies JA. Mechanisms of action of antiepileptic drugs. Seizure. 1995;4(4):267–71.
60. Nelson E, Powell JR, Conrad K, Likes K, Byers J, Baker S, et al. Phenobarbital pharmacokinetics and bioavailability in adults. J Clin Pharmacol. 1982;22(2–3):141–8.
61. Wyllie E, Gupta A, Lachhwani D. The treatment of epilepsy. Principles and practice. 4th ed. Gupta A, Lachhwani D, editors. Philadelphia: Lippincott Williams and Wilkins; 2006.
62. Pitlick W, Painter M, Pippenger C. Phenobarbital pharmacokinetics in neonates. Clin Pharmacol Ther. 1978;23(3):346–50.
63. Cordato D, Mather LE, Gross AS, Herkes GK. Pharmacokinetics of thiopental enantiomers during and following prolonged high-dose therapy. Anesthesiology. 1999;91:1693–702.
64. Shorvon S. Status Epilepticus: Its clinical features and treatment in children and adults. Cambridge: Cambridge University Press; 1994 **382 p**.
65. Usala M, Thompson SA, Whiting PJ, Wafford KA. Activity of chlormethiazole at human recombinant GABA(A) and NMDA receptors. Br J Pharmacol. 2003;140:1045–50.
66. Conway JM, White JR, Birnbaum AK, Eugene Ramsay R, Pennell PB, Rarick JO, et al. Safety of an IV formulation of carbamazepine. Epilepsy Res. 2009;84(2–3):242–4.
67. Tolbert D, Cloyd J, Biton V, Bekersky I, Walzer M, Wesche D, Drummond R, Lee D. Bioequivalence of oral and intravenous carbamazepine formulations in adult patients with epilepsy. Epilepsia. 2015;56(6):915–23.
68. Marino SE, Birnbaum AK, Leppik IE, Conway JM, Musib LC, Brundage RC, Ramsay RE, Pennell PB, White JR, Gross CR, Rarick JO, Mishra U, Cloyd JC. Steady-state carbamazepine pharmacokinetics following oral and stable-labeled intravenous administration in epilepsy patients: effects of race and sex. Clin Pharmacol Ther. 2012;91:483–8
69. Leppik IE. Metabolism of antiepileptic medication: newborn to elderly. Epilepsia. 1992;33(Suppl 4):S32–40.
70. Bellucci GBG, Chiappe C, Lippi A, Marioni F. The metabolism of carbamazepine in humans: steric course of the enzymatic hydrolysis of the 10,11-epoxide. J Med Chem. 1987;30(5):768–73.
71. Doose DR, Streeter, AJ. Topiramate: chemistry, biotransformation and pharmacokinetics. In: Levy RH, Mattson RH, Meldrum BS, Perucca E, editors. Antiepileptic drugs. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 727–34.
72. Clark AM, Kriel RL, Leppik IE, White JR, Henry TR, Brundage RC, Cloyd JC. Intravenous topiramate: safety and pharmacokinetics following a single dose in patients with epilepsy or migraines taking oral topiramate. Epilepsia. 2013;54(6):1106–11.
73. Chan V, Morris RG, Ilett KF, Tett SE. Population pharmacokinetics of lamotrigine. Ther Drug Monit. 2001;23(6):630–5.
74. Wootton R, Soul-Lawton J, Rolan PE, Sheung CT, Cooper JD, Posner J. Comparison of the pharmacokinetics of lamotrigine in patients with chronic renal failure and healthy volunteers. Br J Clin Pharmacol. 1997;43(1):23–7.
75. Remmel RP, Conway JM, Rarick JO, Birnbaum AK, Pennell PB, White JR, et al. The safety of an intrvenous formulation of lamotrigine in patients. Epilepsia. 2006;47(Suppl 4):171.
76. DeLorenzo R. Incidence and cases of status epilepticus. In: Wasterlain CG, Treiman DM, editors. Status epilepticus: mechanisms and management. Cambridge: The MIT Press; 2006. p. 17–32.
77. Dodrill CB, Wilensky AJ. Intellectual impairment as an outcome of status epilepticus. Neurology. 1990;40(5 Suppl 2):23–7.
78. Alldredge BK, Gelb AM, Isaacs SM, Corry MD, Allen F, Ulrich S, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med. 2001;345(9):631–7.
79. Dundee JW, McGowan WA, Lilburn JK, McKay AC, Hegarty JE. Comparison of the actions of diazepam and lorazepam. Br J Anaesth. 1979;51(5):439–46.
80. Levy RJ, Krall RL. Treatment of status epilepticus with lorazepam. Arch Neurol. 1984;41(6):605–11.
81. Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med. 1998;339(12):792–8.
82. Leppik IE, Derivan AT, Homan RW, Walker J, Ramsay RE, Patrick B. Double-blind study of lorazepam and diazepam in status epilepticus. JAMA. 1983;249(11):1452–4.
83. Lamson MJ, Sitki-Green D, Wannarka GL, Mesa M, Andrews P, Pellock J. Pharmacokinetics of diazepam administered intramuscularly by autoinjector versus rectal gel in healthy subjects: a phase I, randomized, open-label, single-dose, crossover, single-centre study. Clin Drug Investig. 2011;31:585–97.
84. McMullan J, Sasson C, Pancioli A, Silbergleit R. Midazolam versus diazepam for the treatment of status epilepticus in children and young adults: a meta-analysis. Acad Emerg Med. 2010;17(6):575–82.
85. Galvin GM, Jelinek GA. Midazolam: an effective intravenous agent for seizure control. Arch Emerg Med. 1987;4(3):169–72.
86. Ghilain S, van Rijckevorsel-Harmant K, Harmant J, de Barsy TH. Midazolam in the treatment of epileptic seizures. J Neurol Neurosurg Psychiatry. 1988;51(5):732.
87. Rivera R, Segnini M, Baltodano A, Perez V. Midazolam in the treatment of status epilepticus in children. Crit Care Med. 1993;21(7):991–4.
88. Silbergleit R, Durkalski V, Lowenstein D, Conwit R, Pancioli A, Palesch Y, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. N Engl J Med. 2012;366(7):591–600.
89. Bell DS. Dangers of treatment of status epilepticus with diazepam. Br Med J. 1969;1(5637):159–61.
90. Cormack RS, Milledge JS, Hanning CD. Respiratory effects and amnesia after premedication with morphine or lorazepam. Br J Anaesth. 1977;49(4):351–61.
91. Kalviainen R. Status epilepticus treatment guidelines. Epilepsia. 2007;48(Suppl 8):99–102.
92. Cranford RE, Leppik IE, Patrick B, Anderson CB, Kostick B. Intravenous phenytoin in acute treatment of seizures. Neurology. 1979;29(11):1474–9.
93. Leppik IE, Patrick BK, Cranford RE. Treatment of acute seizures and status epilepticus with intravenous phenytoin. Adv Neurol. 1983;34:447–51.
94. Phenytoin Leppik I. In: Resor SR, Kutt H, editors. The medical treatment of epilepsy: neurological disease and therapy. New York: Marcel Dekker; 1992. p. 279–92.
95. Lowenstein DH, Alldredge BK, Allen F, Neuhaus J, Corry M, Gottwald M, et al. The prehospital treatment of status epilepticus (PHTSE) study: design and methodology. Control Clin Trials. 2001;22(3):290–309.
96. O'Brien TJ, Cascino GD, So EL, Hanna DR. Incidence and clinical consequence of the purple glove syndrome in patients

receiving intravenous phenytoin. Neurology. 1998;51(4): 1034–9.
97. Peterson GM, Khoo BH, von Witt RJ. Clinical response in epilepsy in relation to total and free serum levels of phenytoin. Ther Drug Monit. 1991;13(5):415–9.
98. Chez MG, Hammer MS, Loeffel M, Nowinski C, Bagan BT. Clinical experience of three pediatric and one adult case of spike-and-wave status epilepticus treated with injectable valproic acid. J Child Neurol. 1999;14(4):239–42.
99. Hovinga CA, Chicella MF, Rose DF, Eades SK, Dalton JT, Phelps SJ. Use of intravenous valproate in three pediatric patients with nonconvulsive or convulsive status epilepticus. Ann Pharmacother. 1999;33(5):579–84.
100. Sheth RD, Gidal BE. Intravenous valproic acid for myoclonic status epilepticus. Neurology. 2000;54(5):1201.
101. Uberall MA, Trollmann R, Wunsiedler U, Wenzel D. Intravenous valproate in pediatric epilepsy patients with refractory status epilepticus. Neurology. 2000;54(11):2188–9.
102. Yu KT, Mills S, Thompson N, Cunanan C. Safety and efficacy of intravenous valproate in pediatric status epilepticus and acute repetitive seizures. Epilepsia. 2003;44(5):724–6.
103. Venkataraman V, Wheless JW. Safety of rapid intravenous infusion of valproate loading doses in epilepsy patients. Epilepsy Res. 1999;35(2):147–53.
104. Limdi NA, Knowlton RK, Cofield SS, Ver Hoef LW, Paige AL, Dutta S, et al. Safety of rapid intravenous loading of valproate. Epilepsia. 2007;48(3):478–83.
105. Devinsky O, Leppik I, Willmore LJ, Pellock JM, Dean C, Gates J, et al. Safety of intravenous valproate. Ann Neurol. 1995;38(4):670–4.
106. Taylor LM, Farzam F, Cook AM, Lewis DA, Baumann RJ, Kuhn RJ. Clinical utility of a continuous intravenous infusion of valproic acid in pediatric patients. Pharmacotherapy. 2007;27(4):519–25.
107. Ramsay RE, Cantrell D, Collins SD, Walch JK, Naritoku DK, Cloyd JC, et al. Safety and tolerance of rapidly infused Depacon. A randomized trial in subjects with epilepsy. Epilepsy Res. 2003;52(3):189–201.
108. DeWolfe JL, Knowlton RC, Beasley MT, Cofield S, Faught E, Limdi NA. Hyperammonemia following intravenous valproate loading. Epilepsy Res. 2009;85(1):65–71.
109. Birnbaum AK, Kriel RL, Norberg SK, Wical BS, Le DN, Leppik IE, et al. Rapid infusion of sodium valproate in acutely ill children. Pediatr Neurol. 2003;28(4):300–3.
110. Peters CN, Pohlmann-Eden B. Intravenous valproate as an innovative therapy in seizure emergency situations including status epilepticus—experience in 102 adult patients. Seizure. 2005;14(3):164–9.
111. Olsen KB, Tauboll E, Gjerstad L. Valproate is an effective, well-tolerated drug for treatment of status epilepticus/serial attacks in adults. Acta Neurol Scand Suppl. 2007;187:51–4.
112. Farooq MU, Naravetla B, Majid A, Gupta R, Pysh JJ, Kassab MY. IV levetiracetam in the management of non-convulsive status epilepticus. Neurocrit Care. 2007;7(1):36–9.
113. Rossetti AO, Bromfield EB. Levetiracetam in the treatment of status epilepticus in adults: a study of 13 episodes. Eur Neurol. 2005;54(1):34–8.
114. Rupprecht S, Franke K, Fitzek S, Witte OW, Hagemann G. Levetiracetam as a treatment option in non-convulsive status epilepticus. Epilepsy Res. 2007;73(3):238–44.
115. Misra UK, Kalita J, Maurya PK. Levetiracetam versus lorazepam in status epilepticus: a randomized, open labeled pilot study. J Neurol. 2012;259:645–8.
116. Albers JM, Moddel G, Dittrich R, Steidl C, Suntrup S, Ringelstein EB, et al. Intravenous lacosamide—an effective add-on treatment of refractory status epilepticus. Seizure. 2011;20(5):428–30.
117. Kellinghaus C, Berning S, Besselmann M. Intravenous lacosamide as successful treatment for nonconvulsive status epilepticus after failure of first-line therapy. Epilepsy Behav. 2009;14(2):429–31.
118. Kellinghaus C, Berning S, Immisch I, Larch J, Rosenow F, Rossetti AO, et al. Intravenous lacosamide for treatment of status epilepticus. Acta Neurol Scand. 2011;123(2):137–41.
119. Shiloh-Malawsky Y, Fan Z, Greenwood R, Tennison M. Successful treatment of childhood prolonged refractory status epilepticus with lacosamide. Seizure. 2011;20(7):586–8.
120. Fernandez EM, Franck AJ. Lacosamide for the treatment of refractory status epilepticus. Ann Pharmacother. 2011;45(11):1445–9.
121. Höfler J, Trinka E. Lacosamide as a new treatment option in status epilepticus. Epilepsia. 2013;54:393–404.
122. Claassen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. Epilepsia. 2002;43(2):146–53.
123. Borris DJ, Bertram EH, Kapur J. Ketamine controls prolonged status epilepticus. Epilepsy Res. 2000;42(2–3):117–22.
124. Goodkin HP, Yeh JL, Kapur J. Status epilepticus increases the intracellular accumulation of GABAA receptors. J Neurosci. 2005;25(23):5511–20.
125. Mazarati AM, Wasterlain CG. *N*-methyl-D-asparate receptor antagonists abolish the maintenance phase of self-sustaining status epilepticus in rat. Neurosci Lett. 1999;265(3):187–90.
126. Rossetti AO, Milligan TA, Vulliemoz S, Michaelides C, Bertschi M, Lee JW. A randomized trial for the treatment of refractory status epilepticus. Neurocrit Care. 2011;14(1):4–10.
127. Kälviäinen R, Eriksson K, Parviainen I. Refractory generalised convulsive status epilepticus : a guide to treatment. CNS Drugs. 2005;19:759–68.
128. Vasile B, Rasulo F, Candiani A, Latronico N. The pathophysiology of propofol infusion syndrome: a simple name for a complex syndrome. Intensive Care Med. 2003;29(9):1417–25.
129. Patel NC, Landan IR, Levin J, Szaflarski J, Wilner AN. The use of levetiracetam in refractory status epilepticus. Seizure. 2006;15(3):137–41.
130. Ruegg S, Naegelin Y, Hardmeier M, Winkler DT, Marsch S, Fuhr P. Intravenous levetiracetam: treatment experience with the first 50 critically ill patients. Epilepsy Behav. 2008;12(3):477–80.
131. Tripathi M, Vibha D, Choudhary N, Prasad K, Srivastava MV, Bhatia R, et al. Management of refractory status epilepticus at a tertiary care centre in a developing country. Seizure. 2010;19(2):109–11.
132. Sutter R, Marsch S, Rüegg S. Safety and efficacy of intravenous lacosamide for adjunctive treatment of refractory status epilepticus: a comparative cohort study. CNS Drugs. 2013;27:321–9.
133. Gaspard N, Foreman B, Judd LM, Brenton JN, Nathan BR, McCoy BM, Al-Otaibi A, Kilbride R, Fernández IS, Mendoza L, Samuel S, Zakaria A, Kalamangalam GP, Legros B, Szaflarski JP, Loddenkemper T, Hahn CD, Goodkin HP, Claassen J, Hirsch LJ, Laroche SM. Intravenous ketamine for the treatment of refractory status epilepticus: a retrospective multicenter study. Epilepsia. 2013;54:1498–503.
134. Remmel RPCJ, Rarick JO, Birnbaum AK, Pennell PB, White JR, Leppik IE. The safety of an intravenous formulation of lamotrigine in patients. Epilepsia. 2006;47(Suppl 4):73.
135. Lee DKU, Halford JJ, Biton V, Cloyd J, Klein P, Bekersky I, Peng G, Dheerendra S, Tolbert D. Intravenous carbamazepine as short-term replacement therapy for oral carbamazepine in adults with epilepsy: pooled tolerability results from two open-label trials. Epilepsia. 2015;56:906–14.

136. Yeung S, Ensom MH. Phenytoin and enteral feedings: does evidence support an interaction? Ann Pharmacother. 2000;34:896–905.
137. Cock HREG. Established status epilepticus treatment trial (ESETT). Epilepsia. 2011;52:50–2.
138. Broomall E, Natale JE, Grimason M, Goldstein J, Smith CM, Chang C, Kanes S, Rogawski MA, Wainwright MS. Pediatric super-refractory status epilepticus treated with allopregnanolone. Ann Neurol. 2014;76:911–5.
139. Shekh-Ahmad T, Mawasi H, McDonough JH, Yagen B, Bialer M. The potential of sec-butylpropylacetamide (SPD) and valnoctamide and their individual stereoisomers in status epilepticus. Epilepsy Behav. 2015;49:298–302.
140. Leppik IE, Patterson EN, Coles LD, Craft EM, Cloyd JC. Canine status epilepticus: a translational platform for human therapeutic trials. Epilepsia. 2011;52(Suppl 8):31–4.
141. Patterson EELI, Coles LD, Podell M, Vite CH, Bush W, Cloyd JC. Canine status epilepticus treated with fosphenytoin: a proof of principle study. Epilepsia. 2015;56:882–7.