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Review

Intramuscular and rectal therapies of acute seizures

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ABSTRACT

The intramuscular (IM) and rectal routes are alternative routes of delivery for antiepileptic drugs (AEDs) when the intravenous route is not practical or possible. For treatment of acute seizures, the AED used should have a short time to maximum concentration (T_{max}). Some AEDs have preparations that may be given intramuscularly. These include the benzodiazepines (diazepam, lorazepam, and midazolam) and others (fosphenytoin, levetiracetam). Although phenytoin and valproate have parenteral preparations, these should not be given intramuscularly. A recent study of prehospital treatment of status epilepticus evaluated a midazolam (MDZ) autoinjector delivering IM drug compared to IV lorazepam (LZP). Seizures were absent on arrival to the emergency department in 73.4% of the IM MDZ compared to a 63.4% response in LZP-treated subjects ($p < 0.001$ for superiority). Almost all AEDs have been evaluated for rectal administration as solutions, gels, and suppositories. In a placebo-controlled study, diazepam (DZP) was administered at home by caregivers in doses that ranged from 0.2 to 0.5 mg/kg. Diazepam was superior to placebo in reduced seizure frequency in children ($p < 0.001$) and in adults ($p = 0.02$) and time to recurrent seizures after an initial treatment ($p < 0.001$). Thus, at this time, only MZD given intramuscularly and DZP given rectally appear to have the properties required for rapid enough absorption to be useful when intravenous routes are not possible.

Some drugs cannot be administered rectally owing to factors such as poor absorption or poor solubility in aqueous solutions. The relative rectal bioavailability of gabapentin, oxcarbazepine, and phenytoin is so low that the current formulations are not considered to be suitable for administration by this route. When administered as a solution, diazepam is rapidly absorbed rectally, reaching the T_{max} within 5–20 min in children. By contrast, rectal administration of lorazepam is relatively slow, with a T_{max} of 1–2 h.

The dependence of gabapentin on an active transport system, and the much-reduced surface area of the rectum compared with the small intestine, may be responsible for its lack of absorption from the rectum.

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1. Introduction

There are many routes through which drugs may be delivered, including oral, intravenous (IV), intramuscular (IM), buccal, intranasal, rectal, intrathecal, subcutaneous, and dermal routes. Although all antiepileptic drugs (AEDs) have oral formulations, the number formulated for parenteral delivery is small. Some also have formulations that may be administered rectally, intranasally, and buccally. None have been developed to be delivered intrathecally, subcutaneously, or dermally. For acute seizures, the AED should have a short time to maximum concentration (T_{max}). Ideally, this would mean IV administration. Unfortunately, this is not always possible in settings that do not have trained personnel and the proper equipment. In these settings, IM, rectal, nasal, and buccal routes may be helpful. Nasal and buccal routes have been discussed elsewhere in this volume. The chemical properties and pharmacokinetic parameters of the various AEDs available for IM and rectal delivery and their usefulness for acute treatment of seizures will be discussed in this article.

Drugs administered intramuscularly are absorbed into the blood stream or lymphatic circulation. Absorption depends on a number of factors such as the chemical properties of the drug and its vehicle, the injection site, injection volume, blood flow, and the state of health of the patient. Because drugs given intramuscularly need to cross membranes, lipid molecules are generally more rapidly absorbed than water-soluble agents. Absorption of water-soluble drugs is also influenced by molecular size, with smaller compounds entering the circulation through capillaries, and much larger molecules entering the circulation through the lymphatic system [1]. The rate of blood flow is the rate-limiting factor in IM absorption. Vascular perfusion through muscle ranges from 0.02 to 0.07 mL/min/g [1]. The site of injection

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may be a factor. For example, lidocaine and insulin are absorbed more rapidly from IM injection into the arm muscle (deltoid) than from the gluteus maximus [1]. There is also a sex difference for some drugs, with men absorbing cefuroxime more rapidly than women after IM administration [2]. Age can also be a factor for bioavailability, as phenobarbital appears to be completely bioavailable in children and only 80% in adults [3]. Intramuscular administration may not be completely reliable for all AEDs, and some may be more appropriate than others. In general, parenteral AEDs were formulated to be given intravenously, and it is these formulations that are used intramuscularly. However, only some can be given through the intramuscular route. Administration of AEDs intramuscularly has advantages in emergency situations because it does not require the initiation of IV access. Initiating an IV infusion system can be challenging, requiring specially trained and competent personnel as well as various supplies. In comparison, IM injection can be done easily and quickly by persons with much less training than required for IV administration. Intramuscular injection can thus be performed in many settings, including nursing homes or other facilities lacking the supplies and trained staff.

The rectum is a body cavity into which drugs in various formulations can be inserted. Absorption from aqueous and alcoholic solutions may occur very rapidly, but absorption from suppositories is generally slower. The nature of the suppository base, the use of surfactants or other additives, and particle size of the active ingredient can influence the rate and extension of absorption [4]. Particle size of the drug will affect the rate of absorption and bioavailability of rectally administered drugs. A major advantage of the rectal route is that the hepatic first-pass elimination of high clearance drugs may be avoided after rectal administration. The upper part of the rectal blood drainage is connected with the portal system, while the lower part is connected with the systemic circulation. Thus, it is important to place the drug in the distal portion of the rectum. The size (diameter, length, and volume) of the rectum increases from infancy and reaches adult dimensions usually by the age of 10 [5]. This must be considered when designing delivery products. Influence of the formulation seems to be very critical. Very little water and sodium is absorbed in the rectum, and lipid solubility and ionization influence absorption [5]. In general, absorption of lipid-soluble compounds is better. As for oral drugs, issues of dissolution and disintegration can be problematic. The dependence of gabapentin on an active transport system and the much-reduced surface area of the rectum compared with the small intestine may be responsible for its lack of absorption from the rectum [6]. Movement of drug from the distal rectum into more proximal areas, in which absorption is into the portal vein system, makes rectal bioavailability more variable than IV or IM delivery. Drawbacks of rectal drug administration include the expulsion of the drug by defecation, potentially lower bioavailability, and lack of patient and caregiver acceptability.

2. Chemistry and pharmacokinetics of available AEDs

2.1. Benzodiazepines: lorazepam, diazepam, midazolam, and clonazepam

The benzodiazepines (BZDs) are a large family of drugs whose core chemical structure is the fusion of a benzene ring to a seven-membered DZP ring (5-aryl-1, 4-benzodiazepines). Lorazepam (LZP), diazepam (DZP), midazolam (MDZ), and clonazepam (CLZ) are of particular interest in the treatment of seizures.

Diazepam is poorly soluble in water. Injectable diazepam USP contains 5 mg/mL DZP with 40% propylene glycol, 10% alcohol, 5% sodium benzoate, and benzoic acid as buffers. The primary metabolic pathway of DZP is hepatic demethylation, hydroxylation, and glucuronidation to three active metabolites: N-desmethyldiazepam (its major metabolite), oxazepam, and 4-hydroxydiazepam. 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 given to healthy volunteers [7]. Its major metabolite also has a long half-life and low clearance. Following an initial IV dose, DZP distributes rapidly from the vascular compartment into the central nervous system (CNS) but then quickly redistributes into muscle and adipose tissue [8]. 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 IM administration, absorption is slow, reaching its maximum concentration 1 h after doses of 5, 10, or 15 mg [9].

Lorazepam, like DZP, is nearly insoluble in water but is much less lipid-soluble. Each milliliter of the parenteral solution contains 2.0 or 4.0 mg LZP, and 18% polyethylene 400 in propylene glycol with 2.0% benzyl alcohol. The major metabolic pathway for LZP is conjugation to glucuronic acid at the 3-position, which is then excreted as an inactive glucuronide metabolite [10]. 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 [10]. After IM administration, the time to the maximum concentration of LZP is 1.2 h, and it is 90% bound to plasma protein [10]. The lower lipid solubility of LZP means that the drug redistributes more slowly than DZP to muscle and fat tissue. This results in a longer residence time in the CNS, which translates into more prolonged pharmacodynamic CNS effects than DZP [11]. In contrast to DZP and LZP, the injectable form of MDZ is water-soluble, which is accomplished by ionizing the molecule in an acidic solution. Each milliliter of the parenteral solution contains either 1 mg or 5 mg of MDZ in water with the pH adjusted to 2.5–3.7. Once the drug is injected into a vein, pH of blood almost instantaneously causes a reconfirmation of MDZ into its un-ionized, highly lipid-soluble form. As a result, MDZ enters the CNS quickly. The bioavailability of IM MDZ is 87 $\pm$ 18% [12]. The primary metabolites of MDZ are 1-hydroxy MDZ and 4-hydroxy MDZ. Both are active metabolites, with 1-hydroxy MDZ being as potent as the parent compound. These active metabolites are further conjugated to inactive compounds with glucuronic acid. Midazolam is 94–98% protein bound. It has an elimination half-life of 2.29 $\pm$ 0.42 h, its Vd at steady state is 50.2 $\pm$ 11.3 L, and its total clearance is 323 $\pm$ 86 mL/min [12]. However, its Vd may vary from 4.2 to 6.6 L/kg, with the largest Vd being observed in obese subjects [13]. In contrast to other parenteral formulations of BZDs, IM MDZ is rapidly absorbed, with peak serum concentrations achieved at 17.5 $\pm$ 6.5 min to 25 $\pm$ 23 min [14,15].

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 IV administration, its distribution follows a two compartment model, with distribution half-life ranging from 0.7 to 3.4 h and the Vd ranging from 1.5 to 4.4 L/kg [16]. Its protein binding is 86%, lower than that of the other BZDs. Clonazepam is extensively metabolized primarily by CYP3A4, and its elimination half-life has been reported to range from 17 to 56 h and clearance from 94 to 125 mL/h/kg [16]. Interestingly, the absorption rate of CLZ after IM administration is slower than the uptake after an oral dose. The T_{max} after an IM dose is 3.1 h compared to 1.7 h for the oral route [17].

2.2. Hydantoins: fosphenytoin and phenytoin

Phenytoin (PHT) is the generic name for 5,5-diphenylhydantoin [18]. It can be formulated as a free acid (molecular weight 252) or the sodium salt (molecular weight 274). The sodium salt, a weak organic acid with an apparent disassociation constant (pKa) in the range of 8.3 to 9.2, is used in the parenteral formulation [18]. The parenteral PHT solution (phenytoin sodium injectable, USP) has a pH of 11.38 to 12.00 adjusted with sodium hydroxide and contains 40% propylene glycol, 10% alcohol, and 50 mg/mL PHT [19].

Fosphenytoin (FOS) is a prodrug of PHT that was developed to overcome the unfavorable properties of PHT [20]. It is the sodium phosphate ester of PHT, which makes it much more soluble in aqueous solutions than PHT. The commercial formulation has a near physiological pH of 8.6–9.0 [21] allowing for faster infusion and fewer adverse events,