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Review Article

FACETS OF INHALATIONAL MIDAZOLAM IN STATUS EPILEPTICUS

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ABSTRACT

Status epilepticus (SE) is a medical emergency associated with significant morbidity and mortality. SE is defined as a continuous seizure lasting more than 30 minutes, or two or more seizures without full recovery of consciousness between any of them. Early treatment of SE with benzodiazepines, followed if necessary by fosphenytoin administration, is the most widely followed strategy. In developing countries where facilities for assisted ventilation are not readily available, it may be helpful to use inhalational midazolam in such settings. It is important to recognize SE and institute treatment as early as possible to avoid a refractory state. It is equally important to attend to the general condition of the patient and to ensure that the patient is hemodynamically stable.

Keywords: Epilepsy, Nasal route, Midazolam, Inhalational route, Facets.

INTRODUCTION

Status epilepticus (SE) was initially defined as "an enduring epileptic condition," without specifying exact durations [1].

Since then, the definition has undergone multiple revisions to include and then modify the required duration, shortening the required seizure duration from 30 to 5 minutes [1]. This shortening of time was based largely on data demonstrating that seizures that do not cease in 5-10 minutes are less likely to terminate without intervention [2].

MIDAZOLAM

Mechanism of action

The mechanism of midazolam involves: The positive allosteric modulation of aminobutyric acid Type A receptors (fast, chloride permeable, and ionotropic), which suppresses neuronal excitability. Midazolam is a fast-acting, water-soluble benzodiazepine with a half-life of 4-6 hrs.

It acts by binding to gamma aminobutyric acid (GABA)-A receptors. Midazolam is an alternative to propofol [3].

The drug undergoes hepatic transformation into an active metabolite. Midazolam is metabolized into the active metabolite alpha1-hydroxymidazolam that is cleared by the kidneys. Midazolam is hydroxylated in the liver, and the metabolite is excreted by the kidneys so that levels are affected by other medications metabolized by this isozyme and by hepatic or renal dysfunction. With more prolonged use, midazolam may accumulate, extending the terminal half-life, and tachyphylaxis may occur [4].

Midazolam is typically started after securing endotracheal intubation and ventilator assistance. It is usually started with a loading dose of 0.2 mg/kg, but increments of 0.2-0.4 mg/kg can be given every 5 minutes until the seizures stop, or a maximum of 2.9 mg/kg is reached. The maintenance dose is 0.1-0.2 mg/kg/h, given as an infusion to maintain electrographic suppression of seizures. For breakthrough seizures, an additional bolus dose can be given, and the continuous intravenous (IV) infusion rate can be increased by approximately 20%. The antiepileptic effect of midazolam lasts from minutes to hours.

The reported failure rate with midazolam is 14-18%.

PHARMACOKINETICS [5]

Absorption

Midazolam is rapidly absorbed. The oral area under the curve ratio of metabolite to midazolam is higher than IV. Mean Tmax is 0.17 to 2.65 h, and the absolute bioavailability is 36%.

DISTRIBUTION

Midazolam exhibits linear pharmacokinetics (dose 0.25-1 mg/kg). Approximately, 97% is protein bound (mainly to albumin). The mean steady-state Vd is 1.24-2.02 L/kg in children 6 month to younger than 16 years of age receiving 0.15 mg/kg IV.

Metabolism

Midazolam is subject to substantial intestinal and hepatic first-pass metabolism by CYP-450 3A4. The active metabolite is alpha-hydroxymidazolam.

ONSET

Onset is 10-20 minutes.

SPECIAL POPULATIONS

Hepatic function impairment

Following oral administration (15 mg), C_{max} and bioavailability were 43% and 100% higher, respectively. Cl was reduced 40%, and $t_{½}$ increased 90%. Doses should be titrated.

Congestive heart failure

Following oral administration (7.5 mg), $t_{½}$ increased 43%.

One of the major disadvantages of midazolam is tachyphylaxis, because of which the dose often has to be increased several fold to maintain seizure control. Furthermore, with prolonged infusion, midazolam accumulates in the body, which may result in a prolonged time to awakening [4].

CONTRAINDICATIONS

Hypersensitivity to benzodiazepines; uncontrolled pain; existing central nervous system depression; shock; acute narrow-angle glaucoma; acute alcohol intoxication; coma.

INHALATIONAL MIDAZOLAM

Midazolam as an inhalational benzodiazepine:

- Fast acting,
- Rapidly penetrates the blood-brain barrier (BBB),
- Exerts a short duration of action.

Advantages with inhalational midazolam delivery

The nasal cavity is covered by a thin mucosa which is well vascularized [6]. Therefore, a drug molecule can be transferred quickly across the single epithelial cell layer directly to the systemic blood circulation without first-pass hepatic and intestinal metabolism. The effect is often reached within 5 minutes for smaller drug molecules [7]. Nasal administration can therefore be used as an alternative to oral administration of for example tablets and capsules if a fast effect is desired or if the drug is extensively degraded in the gut or liver [8]. Drugs which show poor absorbtivity can be given by this route.

Limitations with inhalational midazolam delivery

Nasal administration is primarily suitable for potent drugs since only a limited volume can be sprayed into the nasal cavity. Drugs for continuous and frequent administration may be less suitable because of the risk of harmful long-term effects on the nasal epithelium [9]. The nasal administration has also been associated with a high variability in the amount of drug absorbed. Upper airway infections may increase the variability as may the extent of sensory irritation of the nasal mucosa, differences in the amount of liquid spray that is swallowed and not kept in the nasal cavity and differences in the spray actuation process [10]. However, the variability in the amount absorbed after nasal administration should be comparable to that after oral administration [11,12].

Olfactory transfer

The major part of the approximately 150 cm^2 surface in the human nasal cavity is covered by respiratory epithelium, across which systemic drug absorption can be achieved. The olfactory epithelium is situated in the upper posterior part and covers approximately 10 cm^2 of the human nasal cavity. The nerve cells of the olfactory epithelium project into the olfactory bulb of the brain, which provides a direct connection between the brain and the external environment. The transfer of drugs to the brain from the blood circulation is normally hindered by the BBB, which is virtually impermeable to passive diffusion of all but small, lipophilic substances. However, if drug substances can be transferred along the olfactory nerve cells, they can bypass the BBB and enter the brain directly [13,14].

The olfactory transfer of drugs into the brain is thought to occur by either slow transport inside the olfactory nerve cells to the olfactory bulb or by faster transfer along the perineural space surrounding the olfactory nerve cells into the cerebrospinal fluid surrounding the olfactory bulbs and the brain [8,9,15,16].

CONCLUSION

SE treatment should follow a logical sequence of interventions. Every institution dealing with this problem should design a plan that is based on current information derived from authoritative sources, as well as on recent reviews of the literature, and the protocol should be communicated to the medical staff. Review the protocol at least annually. Physicians should become familiar with the pharmacology of the drugs used to treat SE. Prudence calls for doses of these drugs to be placed in visible locations within emergency departments, pediatric units, and nursing stations [17].

Intranasal midazolam was found to be efficacious and reasonably safe for treatment of acute seizures in the pediatric population. Various studies have demonstrated a shorter time to seizure cessation with intranasal midazolam versus rectal diazepam in children.

A good safety profile supports the use of intranasal midazolam, with fewer patients experiencing respiratory depression and oxygen desaturation compared with rectal diazepam. Optimal dosing of intranasal midazolam for all patients, including those with rhinitis and other nasal abnormalities, needs to be defined, although the studies presented primarily used 0.2 mg/kg per dose [18].

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