

The Situation of Suppression Seizures with Diazepam by Rectal Administration in China

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Abstract

Seizures are a manifestation of temporary brain dysfunction caused by abnormal discharge of brain neurons, Repeated; sustained seizures can cause irreversible brain damage. Rapid, reasonable choice on anticonvulsant drugs, Fast and effective measures on panic stop, Suppress of abnormal discharge, Prevention of convulsions again, All of which has an irreplaceable role on brain injury and recovery. In this paper, we have a brief overview on the place of diazepam rectally efficacy suppress seizures.

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Introduction

Epilepsy is a chronic, recurrent episode of illness. Epilepsy is super abnormal brain cells synchronized discharge caused by sudden and temporary brain dysfunctions. The main characteristic is no obvious cause of recurrent seizures. According to China's epidemiology survey data, the prevalence of epilepsy is about 7%. Currently, there are more than 9 million patients with epilepsy and each year about 400,000 new cases of the disease. In all patients with epilepsy, children under 18 account for about two-thirds^[1,2]. Neonatal or long-range development of recurrent seizures (the continuous state of epilepsy), 20% to 40% of them had retardation. It can cause mental retardation, affective disorder and other neurological sequelae in severe cases^[3].

Suppress seizure frequency, reduce the duration of seizures can reduce brain damage to varying degrees and relieve residual brain damage. Desired therapeutic drug seizures should have the following Properties: (1) High fat-soluble, rapid arrival to the peak of the brain; (2) Strong action without significantly inhibited respiration and blood pressure; (3) Long half-life which means it does not have to be administered repeatedly

It also can be intramuscular injection or enema and has a prompt treatment of seizures in emergency situations; (5) There is no adverse interactions with other drugs; (6) Patient wake up faster; (7) No contradictory reaction, that is to say, when we need to increase the dose of the drug because of ineffective or be replaced with similar drugs, but increased seizures; (8) Without unacceptable side effects. In summary, Diazepam has been recognized at home and abroad as status epilepticus rescue drug of choice and it can quickly enter the brain by intravenous or rectal administration, elevated blood density quickly, Inhibit abnormal EEG payment and prevent seizures again. Based on simple rectal medication, Foreign countries has regarded diazepam as the first choice outside the hospital when rescue seizure.

Diazepam pharmacological mechanism and characteristics

Diazepam is the Represented drug in benzodiazepine class. Diazepam has anticonvulsant, antiepileptic, anxiolytic, sedative, hypnotic and muscle relaxant central role. Radioligand binding assays proves that brain have high affinity for diazepam specific binding sites benzodiazepine receptor. Among its distribution, the densest system is the cortex, limbic system and the brain followed, the last is the brain stem and spinal cord. This distribution is consistent with the distribution of central inhibitory neurotransmitter γ -aminobutyric acid (GABA) of GABA_A receptor. Electrophysiological experiments proves that Benzodiazepine class

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can enhance GABA neurotransmission and synaptic function suppression effect As well as enhance GABA and GABA_A receptor binding effect. GABA_A receptors are gated chloride channel receptors. It is consisted of two α and two β subunits ($\alpha 2\beta 2$) constitute Cl⁻ channel. There is GABA by the point of the β -subunit. When GABA binds, Cl⁻ channel open, Cl⁻ flow, hyperpolarization of the nerve cells, resulting in suppression effect. On the α subunit, there are benzodiazepine receptors. When benzodiazepines combined with it, which does not make Cl⁻ channel opening. But it makes Cl⁻ channel opening frequency increases by facilitating GABA and GABA_A receptor binding leaving(Cl⁻ channel opening is not so prolonged or make Cl⁻ flow increases) More Cl⁻ flow inside, causing nerve cell membrane hyperpolarization^[5].

Diazepam has a strong antiepileptic effect, which is very effective to Status epilepticus, intravenous injection can make 70% to 80% of the seizures under control. But the efficacy to seizures and clonic seizures in children less than two Pan nitrate. Anxiolytic effects of diazepam is highly selective, which is five times chlordiazepoxide, which may be related to selectively acts on the limbic system, and combine central benzodiazepine receptors and promote γ -aminobutyric acid (GABA) release or facilitate synaptic transmission function. Larger doses can induce sleep, compared with barbiturates hypnotics, which has high therapeutic index and small breathing effect on REM sleep (REM) in particular affect and almost has no effect on hepatic drug metabolizing enzyme, large doses does not cause anesthesia. Zhuo central muscle relaxant effect is stronger than chlordiazepoxide, which is 10 times as chlordiazepoxide. oral absorption is fast, blood reached a peak of about 1 h, irregular and slow absorption after intramuscular, intravenous injection into the central nervous system take effect quickly, but then quickly distribution, and therefore short duration. Its plasma half-co period 20 ~ 50 h, a long-acting drug. Oxazepam metabolism by the liver is still biologically active, so there is accumulation of continuous use. Diazepam may enter through the placental barrier fetal Depend, children with mild respiratory center inhibition *in vivo*. Mainly from the kidneys, it can be excreted in the milk. Adverse reactions are drowsiness, allergic reactions, dependency, have liver drug enzyme induction.

Diazepam rectal administration controls status epilepticus and acute recurrent

Status epilepticus (SE) is traditionally defined as a seizure lasts longer than 30 min or frequent episodes of intermittent consciousness who has failed to fully returned to normal. In recent years, we found that as SE lasts longer than 2 h, the chance of permanent nerve damage twice in less than 2 h, we should select the powerful, quick, long duration of action, to maintain effective blood concentration of the respiratory and circulatory depression play the minimum role on circulatory depression, a sufficient amount of antiepileptic drugs to control seizures strong and timely sufficient amount of anti-epileptic drugs, fight for control of seizures in seizure within 30 ~ 90 min, particularly generalized tonic - clonic seizures continued state and the state of children's unilateral sustained, To avoid permanent brain damage, reduce morbidity and mortality. Diazepam is the first treatment choice of various types of status epilepticus effective drug, the advantage of it is quick action, to take effect within 1 ~ 3 min, sometimes draw only a few minutes. Especially status epilepticus occur outside hospital, venous access has not been able to establish a timely, diazepam rectal relatively safe and rapid onset, in case of emergency in the home, but the doctor must obtain the consent of patients or their families to apply, transferred into nearby emergency center for treatment as soon as possible after treatment^[6].

Fitzgerald BJ et al.^[7] in disability care institutions, patients in status epilepticus seizures were applied diazepam rectal gel and intravenous lorazepam to compare the efficacy and safety. The results shows that diazepam rectal gel administered more quickly and reliably, reducing overall rescue time, reducing potential nerve damage and other complications. Many adults in the formal taking antiepileptic drugs, there are still acute repetitive seizures at the same time. Acute recurrent is a predictable part of the seizures. According to patients with previous episodes, no seizure type, frequency, severity and duration, doctors and caregivers begin very easy to identify. The onset of a consistent predictable events (such as threatened or prodromal symptoms, which may be a non-convulsive seizures symptoms, or idiopathic unity or complex seizures), but it is short between its predictability and the subsequent seizure. Acute recurrent may include any type of seizure, and may occur at any age. Caregivers positive identification and timely treatment can avoid the onset or reduce seizure frequency, seizure degree^[8]. Therefore, in daily life we need backup rescue medication. Fakhoury T^[9] and other retroactive recurrent or persistent episodes of acute episodes, two episodes exist or exist and convulsions immediately applied diazepam rectal gel in the presence of 50 cases of patients with epilepsy in the past 18 months, collecting their diagnostic information, dosage, frequency of administration, drug reasons, safety and efficacy. It was found that immediately after the convulsions diazepam rectal gel applied effectively halt the onset of 45 cases (90%). In addition to drowsiness, there is no reports of other adverse events subject to the majority of patients after treatment. Diazepam rectal gel showed good effect on a variety of seizure types of seizures in the emergency rescue and can improve quality of life for patients with epilepsy. Cereghino JJ et al.^[10] evaluated diazepam rectal gel for adults with acute recurrent efficacy and tolerability in 96 over the age of 18 who has a history of repeated episodes of acute adult subjects, randomly selected from the group of 70 people, divided into two groups (active treatment group A n = 31, group B placebo n = 39), patients in group A receiving the first dose of 4 h received a second treatment, group B will only accept a second treatment. Observed in patients with first dose 12 hours after onset of the case. The results showed that compared with placebo, diazepam rectal gel group were significantly reduced seizure frequency. Diazepam rectal gel has a median of 0.00 episodes per hour, and 0.13 in the placebo group, there was a significant difference (P = 0.002) between the two. It is worth noting that the mainland 12 hours in observation of rectal diazepam gel seizure control rate of 71% (22/31) in the placebo group, 28% (11/39). Analysis using the Kaplan-Meier life table, diazepam rectal gel in the treatment group compared to the placebo treatment recurrence time was significantly prolonged (P < 001).

Similarly, we can see part of the patients who often have been regular anti-epileptic medication, usually no seizures in patients with epilepsy in some incentives, such as fever, vaccinations, stress, sleep deprivation, menstrual cramps, lower vomiting, surgery and so on, may lead to epileptic seizures cluster, while a few children who has no obvious cause, but also the performance of periodic cluster seizures. Cluster seizures can sometimes be transformed into status epilepticus, make physical and mental health of

children seriously affected. In response to these circumstances, some foreign authors suggest the use of a short oral or rectal infusion benzene benzodiazepine class of drugs can prevent relapse and treatment of epilepsy, without having to increase the type and dose in children other antiepileptic drugs, which can reduce the long-term or high-dose medication the risk of adverse effects^[11].

Application of intermittent rectal diazepam prevent further seizures febrile seizures

Febrile seizures are a common disease in children especially in 6 months to 3 years old infants. Prevention and treatment of children with febrile seizures effectively can prevent febrile seizures into epileptic. Patients with a history of febrile seizures, anticonvulsants usually do not advocate the application only when every risk of febrile illness. When he is fever, to prevent seizures happened, diazepam rectal solution can be used to inject or diazepam suppositories, if still hot after 8h, rectally applied again, in order to prevent diazepam accumulate in the body, no more than four times within 24 h. When Application of diazepam, we should promptly fever and treat the primary disease^[12]. Now that the intermittent short-term diazepam prophylaxis indications as follows: (1) after first relapse FS and have risk factors; (2) no recurrence risk factors FS recurrence but there can also be applied intermittent short-term preventive treatment. The prophylactic treatment method has been applied more than 20 years in Japan and Europe. Since FS occurred in the early stage of fever temperature swells, timely administration is a key to preventing relapse. Intermittent preventive treatment can reduce short-FS recurrence; there is no evidence of an impact on the long-term prognosis. But at least intermittent short-term preventive treatment can avoid continuous state which cause brain damage in children^[13,14].

Efterpi Pavlidou^[15] and other has long-term prospective controlled study, 139 children who had a history of febrile seizures (6 months to 3 years, 77 girls, 62 boys) were divided into two group (intermittent use of diazepam rectal intervention group n = 68, control group n = 71), all subjects had no history of seizures no heat, no history of epilepsy drug use, no brain developmental abnormalities. According to exist factors in Clinical data, the degree of risk of recurrence will be divided into high-risk, medium risk and low-risk group, and followed up for 3 years. The results showed that within three years, the control group of high-risk group recurrence rate of 83%, medium risk 55%, lower risk of 46%, while diazepam intervention seizure recurrence rate was significantly lower, high, medium and low-risk three groups relapse rates were 38 %, 35% and 33%. Studies have shown that intermittent use of diazepam rectal preventing seizures reduce the relapse rate in patients with high risk factors.

Taghdiri MM^[16] randomly divided The 80 cases of febrile seizure patients (September -5 years old) into two groups (treatment group, n = 40, control group n = 40), treatment group at each time not only use heating acetaminophen fever, the rectal diazepam gel injection (0.5 mg / kg), the control group, only fever treatment, rectal injection the same dose placebo followed for 1 year. The results showed that the treatment group, the recurrence of febrile seizures was 27.5% vs 37.5%, and the treatment group seizures shorter duration than the control group. it indicate when heat the use of diazepam rectal medication can reduce the risk of recurrence of simple febrile seizures.

Application of diazepam rectal administration in non-medical institutions

Pellock JM^[17] Investigate the report of diazepam rectal gel respiratory-related adverse events and deaths spontaneity. More than 2 million cases of drug use, was identified, identified nine adverse respiratory events, three deaths. A persistent episode of respiratory drug appears to inhibit the prognosis which was good. Death occurs due to persistent seizures edge, but the main cause of death in non-respiratory depression. It shows diazepam rectal gel has a lower morbidity or mortality.

Chiang LM et al.^[18] To investigate diazepam intravenous and rectal administration in the treatment of children with intractable epilepsy efficacy and safety. 24 cases of subjects aged 2 - 18 years, mean age of 9.1 years. Generalized seizure types and myoclonic grand mal seizures, seizure frequency 1 / week to 20 times / day range, 21 (87.5%) had mental retardation and / or developmental delays. Intravenous administration of 127 cases of seizure, including 103 cases (81.1%) in the control of seizures within 10 minutes, rectally 103 cases, of which 90 cases (87.3%) in the control of seizures within 10 minutes. First administration failed to control seizures, again the same method and the same dose after administration, intravenous and rectal administration group were 21 cases, 12 cases of termination of seizures within 10 minutes. 4 cases (three cases of intravenous administration, one case of rectal) attack more than 20 minutes after intravenous administration and rescue seizures stopped. 17% of patients (8% of intravenous administration, rectal 9%) drowsiness. No respiratory depression. The results show that diazepam rectal vein and have no significant difference in efficacy and safety.

What Above shows that diazepam rectal administration is equivalent to the intravenous drug , but in a home environment or special care facility and cannot establish intravenous access when epilepsy seizures, diazepam rectal relatively safe and rapid onset, used in care facilities reduce seizures emergency rate, and improve the quality of life in patients with epilepsy and their families.^[18]

O'Dell C et al.^[19] study the effectiveness of diazepam rectal gel in home management of patients with epilepsy. 38 cases of seizures in patients with a history are in the test group, which includes 14 complex seizures, 24 patients with epilepsy (including two cases of simple seizures). Including 23 (61%) continued seizures and 15 (39%) recurrent. During the six-month follow-up treatment, 12 children experienced 26 episodes, in line with diazepam rectal administration standards. 8 children applied with diazepam rectal gel application management total attack 19 times, 16 times (84%) seizures are controlled without the need for emergency treatment. Parental pressure drop to the overall group at baseline and six months and in all subgroups which shows home use of diazepam rectal gel can effectively control the seizures, often avoid hospital emergency treatment. Its use reduces the incidence of epilepsy and the related hospital costs, provides long-term or family members of patients with epilepsy recurrent home treatment selectivity.

Terry D et al.^[20] study in the form of a questionnaire survey about 64 parents of children with epilepsy, asking them to understand the school in the daily management of diazepam gel application, the visits, 43 parents (68%) and the school discuss management applications diazepam rectal gels, including 35 (81%) return requires signed agreement, eight (19%) consider the legal

considerations and impact on family life, rejected the school applications. That most children with epilepsy in the family agreed to school or day care application diazepam rectal gel, and barriers to the use of psychological disorder mostly based on the legal issues and the impact on family life.

In summary, diazepam rectal administration, because of its simplicity, feasibility, safety and efficacy of the high regard in controlling seizures increasingly popular. The aqueous solvent diazepam enema operation is relatively complex, diazepam gel save and use conditions exist, the old haunt of diazepam suppositories^[21,22] advent will significantly increase the effectiveness of family and community management in patients with recurrent seizures, increased patient quality of life and their families.

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