CLONazepam
Newborn use only

2022

Alert	Schedule 4 medication – High risk. May be subject to additional state-based regulations. May cause respiratory depression and hypotonia. Intravenous clonazepam contains benzyl alcohol which has been associated with severe adverse reactions such as gasping syndrome (gasping respiration, central nervous system (CNS) depression, metabolic acidosis, cardiovascular failure). Only use if no therapeutic alternative is available.
Indication	Seizures not controlled with primary anticonvulsant treatment. Hyperekplexia.
Action	Anticonvulsant: Clonazepam enhances the polysynaptic inhibitory process blocking spread of electrical activity from a focal lesion. Hyperekplexia: Clonazepam binds to gamma-aminobutyric acid (GABA) receptors and potentiates the inhibitory GABA. Clonazepam is a $GABA_A$ receptor α1 agonist, enhancing GABA-gated chloride channel function and presumably compensating for the defective glycine-gated chloride channel function in hyperekplexia.
Drug type	Benzodiazepine
Trade name	Rivotril
Presentation	IV: 1 mg/1 mL ampoule + 1 mL diluent (WFI). Oral: 2.5 mg/mL oral liquid; 500 microgram (0.5 mg) tablet (50 microgram/mL oral solution may be prepared using the tablet).
Dose	**Seizures** IV: 100 microgram/kg/dose DAILY.[1] **Hyperekplexia** Oral or IV: Commence at 10 to 20 microgram/kg DAILY and increase to 100 to 200 microgram/kg DAILY.[2,3]
Dose adjustment	Therapeutic hypothermia – No information to guide any dose adjustment. ECMO – No information to guide any dose adjustment. Renal impairment - Dose adjustment may be necessary. Discuss with paediatric neurologist. Hepatic impairment - Dose adjustment may be necessary. Discuss with paediatric neurologist.
Maximum dose	200 microgram/kg/day.[3]
Total cumulative dose	
Route	IV Oral
Preparation	**IV:** Add 1 mL of diluent to 1 mg/1 mL ampoule to make 1 mg/2 mL solution (500 microgram/mL). **FUTHER DILUTE:** Draw up 1 mL (500 micrograms) of the above solution and add to 4 mL of sodium chloride 0.9% to make a final concentration of 100 microgram/mL. **Oral:** **2.5 mg/mL oral liquid** For doses less than 100 microgram: Draw up 0.1 mL (250 microgram of clonazepam) and add 0.9 mL of water for injection to make a final volume of 1 mL with a concentration of 250 microgram/mL. **Solution using 500 microgram tablet:** Disperse ONE tablet in 10mL of water for injection to make 50 microgram/mL. The tablet will disperse within 1 to 2 minutes. Mix well to obtain an even dispersion. Measure the desired dose and administer immediately. Prepare a fresh solution for each dose.
Administration	**IV:** Administer over 5 minutes into a large vein (preferably a central line) due to risk of thrombophlebitis. **Oral:** Administer with or without feed.
Monitoring	Routine plasma drug monitoring is not necessary. Therapeutic range is 60-150 nmol/L (takes 1 week to reach steady state). Very low and very high levels were regarded as therapeutic failure in one study.[4] Cardio-respiratory monitoring. Seizure activity.
Contraindications	Hypersensitivity to clonazepam or other benzodiazepines. Acute narrow angle glaucoma. Severe hepatic impairment.
Precautions	
Drug interactions	Potentiates the sedative effects of central nervous system (CNS) depressants. Concomitant administration with phenobarbital (phenobarbitone) or phenytoin may enhance the metabolism of clonazepam.
Adverse reactions	Respiratory and CNS depression, hypotension, tachycardia, sedation, drowsiness, muscle relaxation, hypersalivation.
Compatibility	Fluid: Glucose 5%, glucose 10%, sodium chloride 0.9%, glucose 2.5% with sodium chloride 0.45%.

	Y-site (base fluid sodium chloride 0.9%): Cisatracurium besylate, clonidine hydrochloride, haloperidol lactate, heparin, insulin aspart, midazolam hydrochloride, morphine sulfate, valproate sodium. Y-site: At 40 microgram/mL and 1 mg/mL of clonazepam: Insulin (Novorapid).[5,6]
Incompatibility	Sodium bicarbonate
Stability	
Storage	Oral Liquid, Injection: Store below 25°C. Keep ampoules in the outer carton to protect from light. Tablet: Store below 30°C. Keep tablets in original packaging to protect from light and moisture.[5]
Excipients	Oral: Peach flavouring PHL-014725, saccharin sodium, brilliant blue FCF (E133, CI42090), glacial acetic acid, propylene glycol. Tablet: Lactose monohydrate, maize starch, pregelatinised potato starch, talc, magnesium stearate, iron oxide red, iron oxide yellow.[5] IV: Ethanol, benzyl alcohol, propylene glycol, glacial acetic acid, water for injections. **Use with caution in neonates.**
Special comments	Benzodiazepines are not generally suitable for long-term treatment of epilepsy because of their sedative effect and the development of tolerance in a high proportion of people. Stop treatment if clear and lasting therapeutic benefit cannot be demonstrated. Withdraw treatment slowly by gradually reducing the dose over several months. May cause respiratory depression. Antidote: Flumazenil.
Evidence	**Efficacy** **Seizures** An observational study in neonates (gestational age 28-41 weeks; postnatal age 4 hours to 23 days) found that a starting dose of 0.1 mg/kg **every 24 hours** (IV infusion over 5 minutes) was optimal in majority of cases. In this study, clonazepam treatment lasted from 48 to 263 hours and was generally discontinued after 48 hours without seizures. The therapeutic effect was noticed within 24-48 hours in most cases. Authors also observed that a dose of 0.1 mg/kg **every 12 hours** did not lead to any extra benefit and on the contrary, there was a possible paradoxical increase in seizures.[1] **Hyperekplexia** Hyperekplexia is clinically characterised by neonatal hypertonia and an exaggerated startle response to acoustic or tactile stimuli, and is often complicated by umbilical hernia, hip joint dislocation, epilepsy, or transient delayed motor development.[7,8] Mine et al reported clinical and genetic characteristics of 17 Japanese patients with hyperekplexia. Symptoms were noted in the neonatal period in all of them but diagnosis was not made for months to years in 11 of them (2 months to 45 years). A low dose of clonazepam was sufficient for treatment 0.01 to 0.1 mg/kg and 0.8 mg/day in children and adults respectively.[2] Shahar et al reported the clinical features of 39 neonates and young infants diagnosed with hyperekplexia. Nine of them had severe symptoms and they were treated with low oral doses of clonazepam up to 0.2 mg/kg, of whom 7 completely recovered and therapy was discontinued within 6 months.[3] **Safety** Study by Andre et al showed that both (0.1 mg/kg & 0.2 mg/kg) doses were well tolerated with only one case in each group showing marked hypotonia.[1] **Pharmacokinetics** The study by Andre et al which used IV clonazepam reported a variable plasma half-life between 20 and 40 hours.[4] At the end of the infusion period, plasma clonazepam ranged from 28 to 117 ng/mL in the 0.1 mg/kg group and from 99 to 380 ng/mL in the 0.2 mg/kg group. With 0.1 mg/kg, an immediate therapeutic response was observed in 7 out of 8 cases. Their data suggest that optimal therapeutic response might already have been achieved with the 0.1 mg/kg dose.
Practice points	Prior exposure to phenobarbital and/or phenytoin may decrease clonazepam levels due to liver enzyme induction.[8]
References	1. André M, Boutroy MJ, Bianchetti G, Vert P, Morselli PL. Clonazepam in neonatal seizures: dose regimens and therapeutic efficacy. Eur J Clin Pharmacol. 1991;40(2):193-5. 2. Mine J, Taketani T, Yoshida K, Yokochi F, Kobayashi J, Maruyama K, Nanishi E, Ono M, Yokoyama A, Arai H, Tamaura S. Clinical and genetic investigation of 17 Japanese patients with hyperekplexia. Developmental Medicine & Child Neurology. 2015 Apr;57(4):372-7. 3. Shahar E, Raviv R. Sporadic major hyperekplexia in neonates and infants: clinical manifestations and outcome. Pediatric neurology. 2004 Jul 1;31(1):30-4. 4. Andre M, Boutroy MJ, Dubruc C, et al. Clonazepam pharmacokinetics and therapeutic efficacy in neonatal seizures. Eur J Clin Pharmacol 1986;30:585-9.

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