



Clinical Pharmacology & Toxicology Pearl of the Week

“Benzos, Benzos, Benzos”

Case

- ✓ A 19 year-old female presents to the ED after ingesting an unknown amount of venlafaxine in a suicide attempt
- ✓ She presents three hours post-ingestion with a GCS of 15, HR 108, BP 142/79. QRS duration on ECG is 173 ms. No clonus or rigidity, 3+ reflexes to lower extremities
- ✓ During observation in the ED, the patient develops dilated pupils and spontaneous clonus to her legs
- ✓ You decide to use benzodiazepines to treat this patient. Which benzo would you use and why?
- ✓ Is there any benefit to switching benzos in the same patient?
- ✓ How would your management change if this patient was in ethanol withdrawal or liver failure? What if they didn't have IV access?

Background

- ✓ Benzodiazepines increase inhibitory GABAergic neurotransmission by binding to their site on the GABA-A receptor, which is a ligand-gated chloride channel (see Figure).
- ✓ While the most common benzos are often used interchangeably, they have different onsets, peak effects and kinetics that render some more beneficial than others for various conditions (see Table below).
- ✓ Knowledge of time to onset of action and duration of action of various benzodiazepines allows safe and rapid dosing titration without over-sedation (see Table below).

GABA-A receptor (from Goldfrank 11th ed.)

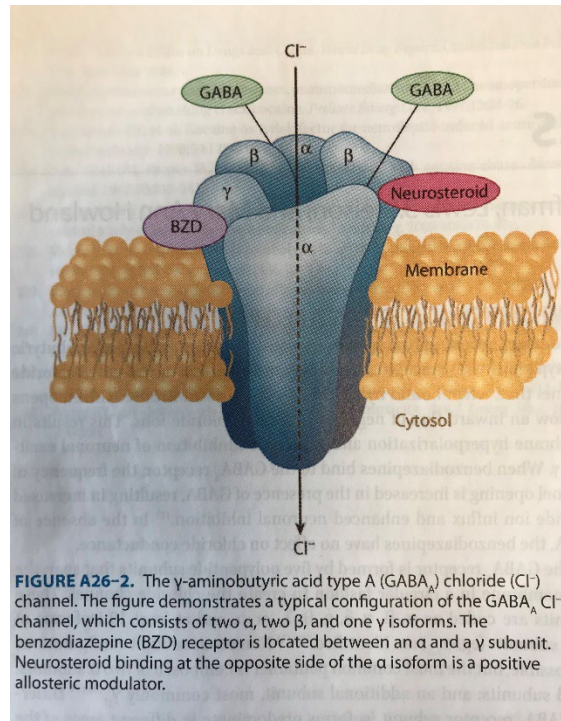


FIGURE A26-2. The γ -aminobutyric acid type A (GABA_A) chloride (Cl⁻) channel. The figure demonstrates a typical configuration of the GABA_A Cl⁻ channel, which consists of two α , two β , and one γ isoforms. The benzodiazepine (BZD) receptor is located between an α and a γ subunit. Neurosteroid binding at the opposite side of the α isoform is a positive allosteric modulator.

Kinetics

- ✓ Hepatic failure results in decreased clearance of benzos requiring hepatic metabolism (e.g. diazepam, midazolam).
- ✓ Active metabolites may prolong the clinical effect of some benzos (e.g. diazepam, midazolam), whereas others have no active metabolites (e.g. lorazepam).

Special considerations

- ✓ If IV access is not available, midazolam is the preferred benzodiazepine to use IM as it has the quickest onset of action (3 - 10 minutes) when given IM.

- ✓ Diazepam has erratic absorption when given IM and is therefore not preferred if the patient has no IV access.
- ✓ Lorazepam has a slower peak effect when used for sedation because of its decreased lipophilicity.
- ✓ Switching from one benzodiazepine to another is rarely indicated and increases the risk of an adverse drug event from unpredictable peak effects and different dosing intervals.
- ✓ Paradoxical reactions to benzos can occur, in which some patients become more agitated after benzodiazepine administration, particularly children.

Pharmacodynamic profile and typical dosing strategy for common IV benzodiazepines (from Goldfrank 11th ed.). Note that these dosing intervals are only suggestions.

	Diazepam IV	Midazolam IV	Lorazepam IV
Onset of action			
Anticonvulsant	Rapid (minutes)	Rapid (minutes)	Rapid (minutes)
Sedation	1-2 minutes	1-2 minutes	5 - 20 minutes
Duration of action			
Anticonvulsant	1 - 2 hours	30 - 80 minutes	Many hours
Sedation			
Single dose	Short	Short	Long
Repeat dose	Long (from active metabolites)	Intermediate (from active metabolites)	Long
Equivalency	5 mg	2 mg	1 mg
Typical starting dose	5 - 10 mg	2 - 5 mg	1 - 2 mg
Dosing interval	Q5 - 10 min	Q5 - 10 min	Q15 - 20 min
Conditions where this drug is preferred	Sedative-hypnotic/ethanol withdrawal, rapid control of agitation	Rapid control of agitation, seizure cessation	Seizure cessation, patient with hepatic failure

Treatment endpoints

- ✓ Agitation = the goal is rapid sedation equivalent to a Richmond Agitation Sedation Scale (RASS) of 0 to -2 (i.e. alert and calm to light sedation, briefly awakens to voice for less than 10 seconds)
- ✓ Seizure = termination of seizure
- ✓ Avoid benzodiazepine orders that are written only for treating a specific heart rate or specific beats of clonus as this may lead to oversedation and unnecessary treatment

Richmond Agitation and Sedation Scale (RASS)		
+4	Combative	violent, immediate danger to staff
+3	Very Agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious, apprehensive but movements not aggressive or vigorous
0	Alert & calm	
-1	Drowsy	Not fully alert, but has sustained awakening to voice (eye opening & contact \geq 10 sec)
-2	Light sedation	Briefly awakens to voice (eye opening & contact < 10 sec)
-3	Moderate sedation	Movement or eye-opening to voice (but no eye contact)
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Pbrainmd.wordpress.com

Case resolution

- ✓ The patient receives 250 mg of diazepam over several hours in the ED
- ✓ ICU is called to assess because of concerns about airway protection from oversedation
- ✓ ICU determines the patient is stable to admission to the medical ward. Patient is admitted to medicine and makes a full recovery

The Clinical Pharmacology physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. Clinical Pharmacology consultations are also available through the Netcare e-referral process and through Calgary Zone Specialist Link. Click [HERE](#) for more details.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK).