

## Benzodiazepine Pharmacokinetics and Routes of Administration

### Introduction

1. Benzodiazepines are used for numerous acute states in the emergency department, especially seizures and agitation
2. IV access is often not available for patients with seizures or agitation and alternative routes must be considered; the drug of choice may change depending on the route of administration
3. This handout will focus on the pharmacokinetics of the two most utilized benzodiazepines in the emergency department, lorazepam and midazolam

Pharmacology					
	Lorazepam		Midazolam		
Administration	IV	IM	IV	IM	IN
Dose	Sedation: 0.5-2 mg  Seizure: 4mg	Sedation: 0.5-2mg  Seizure: 0.5 -2mg (not preferred)	Sedation: 0.5-2mg  Seizure: 0.2mg/kg (not preferred)	Sedation: 5mg  Seizure:10mg or 0.2mg/kg; max 10mg	Sedation: 0.1mg/kg  Seizure: 0.2mg/kg; max 10mg
Onset	2-10 min (longer for anticonvulsant)	20-30 min	3-5 min	15 min	10 min
Duration	3 – 6 hours for seizures, up to 8 hours for sedation	6 – 8 hours	< 2 hour	2-6 hour	20-30 min
Bioavailability	100%	83-100%	100%	90%	44%
Pros /Cons	<b>Pro:</b> Fastest onset	<b>Pro:</b> No IV access needed  <b>Con:</b> erratic absorption	<b>Con:</b> short duration, potential for recurrence of agitation/seizure	<b>Pro:</b> No IV access needed	<b>Pro:</b> Least invasive administration  <b>Con:</b> small volumes (max 1mL each nare), high concentration drug needed
Concentrations available (at GHS)	2mg/mL	2mg/mL	1mg/mL 5mg/mL	1mg/mL 5mg/mL	5mg/mL

# Overview of Evidence

Author, year	Design/ sample size	Intervention & Comparison	Outcome
Nobay 2004	Prospective, double-blind, randomized N=95	IM midazolam vs. IM haloperidol vs. IM lorazepam for agitation	Mean time to sedation (min) <b>Lorazepam: 32.3 (±20)</b> <b>Midazolam: 18.3 (±14)</b> Haloperidol: 28.3 (±25)  *lorazepam dropped from study due to significantly longer time to sedation and awakening
Silbergleit 2012	Prospective, double-blind, randomized, non-inferiority N= 893	IM midazolam versus IV lorazepam for seizure	Seizures absent at time of arrival to ED IM midazolam: 73.4% IV lorazepam: 63.4% Statistically significant for non-inferiority  Faster time to drug administration of IM midazolam was offset by the faster onset of IV lorazepam
Haut 2016	Systematic Review N=75 studies	Compared time to administration and time to seizure termination for multiple different benzodiazepines given by various routes	Median time to seizure termination IV: 0.3-5.7 min IM: 1.1-7.9 min IN: 2.3-7.5 min  10 studies showed faster <b>time to administration</b> with IM/IN administration over IV or rectal administration, 7 of which were statistically significant
Owusu 2019	Retrospective cohort N= 50	IV lorazepam vs. IN midazolam for seizure	Median time to seizure termination IV lorazepam (N=27): 3.3 min (IQR 1.2-62.4) IN midazolam (N=23): 3.2 min (IQR 0.1-28.5)  There was no difference in the number of repeat benzodiazepine doses required or time to administration

## Conclusions

1. The initial agent used does not have to be the definitive agent for treatment. Utilizing alternative routes in order to obtain IV access in agitation/convulsing patients is often the safest for both the patient and staff members. It may also allow therapy to be initiated faster than waiting to obtain IV access.
2. A lack of literature directly comparing all routes of administration for all benzodiazepines should not limit utilization. **Important differences exist in pharmacokinetics of each drug and route of administration that may be beneficial for specific populations and disease states.**

## References

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