Protocol for benzodiazepine poisoning management

**Category/Use:** Antianxiety agent; anticonvulsant; sedative

**Specific substances with range of toxicity**

<table>
<thead>
<tr>
<th>Name of the drug</th>
<th>Maximum tolerated exposure</th>
<th>Minimum lethal Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>Ingestion of 500 - 2000 mg developed minor symptoms</td>
<td>Not established</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>20 to 60 mg presented with mild lethargy and combativeness</td>
<td>Not established</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>900 milligrams</td>
<td>Not established</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>2.5-25mg of lorazepam developed minor symptoms</td>
<td>Not established</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>Not established</td>
<td>Not established</td>
</tr>
<tr>
<td>Clobazam</td>
<td>Not established</td>
<td>Not established</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>Not established</td>
<td>Not established</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>Not established</td>
<td>Not established</td>
</tr>
</tbody>
</table>

**Mortality rate/survival rate:** Not available

**Clinical presentation:**

**Ingestion:** Common signs and symptoms of overdose are a result of CNS and respiratory depression and may include sedation, dizziness, amnesia, ataxia, slurred speech, lethargy, and respiratory difficulties. Acute, single-drug ingestions are typically mild and exhibit reversible symptomatology. Severe toxicity, albeit uncommon and more often associated with coingestions, may result in coma, hypotension, hypothermia, and respiratory failure.

**Intra-arterial:** Inadvertent intra-arterial administration of benzodiazepines has resulted in ischemia, gangrene, compartment syndrome, and tissue necrosis of the extremity used for injection.

**Intranasal:** Intranasal administration of benzodiazepines has been reported in both mixed-drug and single-drug exposures; administration with other substances (eg, heroin, methamphetamine) in an attempt to decrease the adverse effects associated with the co administered agents has been previously described. The clinical presentation may be similar to that seen following ingestion.
and/or intravenous administration of benzodiazepines; however, the onset, duration, and severity of toxicity may differ secondary to differences in pharmacokinetics with intranasal administration.

**Intravenous:** The use of intravenously-administered benzodiazepines may result in a similar clinical presentation as described for ingestion. The onset, duration, and severity of toxicity may differ secondary to differences in pharmacokinetics with intravenous administration.

Therapeutic use of prolonged, high-dose infusions of lorazepam is associated with an increased risk of acute tubular necrosis, lactic acidosis, and/or hyperosmolar states secondary to the accumulation of polyethylene glycol and propylene glycol

**Population-dependent:**

**Neonates:** Neonates born of women who have received benzodiazepines shortly before delivery (chronic, therapeutic, or illicit use) may experience hypotonia upon delivery known as "floppy infant syndrome," respiratory depression, hypothermia, feeding difficulties, and/or withdrawal symptoms.

**Mechanism of toxicity**

Its effects are mediated via enhancement of the activity of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter.

**Pharmacokinetics**

<table>
<thead>
<tr>
<th>DRUGS</th>
<th>DISTRIBUTION</th>
<th>PROTEIN BINDING</th>
<th>METABOLISM</th>
<th>ELIMINATION</th>
<th>TIME TO PEAK</th>
<th>EXCRETION</th>
</tr>
</thead>
</table>
| Alprazolam | $V_d$: 0.8-1.2 L/kg | 80%; primarily to albumin | Hepatic via CYP3A4; forms two active metabolites (4-hydroxyalprazolam α-hydroxylprazolam) and one inactive metabolite (benzophenone metabolite) | Adults: 11.2 hours  
Elderly: Immediate release: 16.3 hours  
Alcoholic liver disease: Immediate release: 19.7 hours  
Obesity: | Immediate release: 1-2 hours | Urine (as unchanged drug and metabolites) |
<table>
<thead>
<tr>
<th>Drug</th>
<th>Vd:</th>
<th>%</th>
<th>Metabolism</th>
<th>Elimination Times</th>
<th>Serum Half Life</th>
<th>Urine Disposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromazepam</td>
<td>1 L/kg</td>
<td>70%</td>
<td>Hepatic via hydroxylation and glucoronidation to 3-hydroxy-bromazepam (active) and pyridine</td>
<td>17 hours (range: 11-22 hours)</td>
<td>Serum: 0.5-4 hours</td>
<td>Urine (69%; primarily as metabolites)</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>0.3-0.6 L/kg</td>
<td>94 to 98%</td>
<td>Hepatic to desmethylchlordiazepoxide (active), N-desmethyldiazepam (active) and oxazepam (active)</td>
<td>10 hours (range: 6-28 hours)</td>
<td>Serum: 1 to 4 hours</td>
<td>Urine (primarily as metabolites)</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>3 L/kg</td>
<td>85%</td>
<td>Hepatic via nitroreduction to 7-aminoclonazepam</td>
<td>~25 hours</td>
<td>Serum: 1-4 hours</td>
<td>Urine (&lt;2% as unchanged drug)</td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.8-1.0 L/kg</td>
<td>98%</td>
<td>Hepatic via CYP3A4 and CYP2C19 to N-desmethyl diazepam (active), oxazepam (active), temazepam (active)</td>
<td>31 hours (range: 14-61 hours); may be increased in neonates, elderly, and those with severe hepatic disorders</td>
<td>Serum: 1.25 hours (range: 0.25 to 2.5 hours)</td>
<td>Urine (primarily as metabolites)</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.8-1.6 L/kg</td>
<td>89% to 93%</td>
<td>Hepatic to lorazepam glucuronide (inactive)</td>
<td>13 hours (range: 8-25 hours);</td>
<td>Serum: IM: 3 hours</td>
<td>Urine</td>
</tr>
</tbody>
</table>
up to 40% in neonates; increased up to 50% in children

<table>
<thead>
<tr>
<th>Drug</th>
<th>Vd:</th>
<th>Clearance</th>
<th>Half-life</th>
<th>Serum</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrazepam</td>
<td>2.4l/kg (range: 1.6-3.2L/kg); elderly: 4.8 L/kg (3.1-6.5 L/kg)</td>
<td>87%</td>
<td>Hepatic via nitroreduction and acetylation to inactive metabolites</td>
<td>30 hours (range: 18-57 hours); elderly, ill patients: 40 hours</td>
<td>Serum: 2-3 hours</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>0.5-2.0 L/kg</td>
<td>&gt;95%</td>
<td>Hepatic via glucuronidation to an inactive metabolite</td>
<td>8.2 hours (range: 5.7 - 10.9 hours)</td>
<td>Serum: 3 hours</td>
</tr>
</tbody>
</table>

**Criteria for hospital admission:**

Patients with severe and persistent CNS depression, hemodynamic instability, and/or respiratory depression require hospital admission and intensive care support.

**Monitoring parameters**

A) Benzodiazepine plasma levels are not usually clinically useful.

B) No specific lab work (CBC, electrolytes, urinalysis) is needed unless otherwise indicated.

**First aid measures:** Same as decontamination method explained in the treatment part.

**Treatment**

**Oral exposure:**

**Stabilization**

Initially, evaluate and correct immediate life-threatening complications (eg, airway, breathing, and circulation). The most serious complications include CNS and respiratory depression. Supportive care with an emphasis on respiratory support, supplemental oxygen administration, and aspiration prevention is the primary treatment.

**Decontamination method**

**Emesis:** Ipecac-induced emesis is not recommended because of the potential for CNS depression.
If the patient presents within 1 hour of ingestion, consider the following decontamination procedure(s):

**Activated charcoal:** Use a minimum of 240 milliliters of water per 30 grams charcoal

- Adults and adolescents: usual dose is 25 to 100 grams
- Children aged 1 to 12 years: 25 to 50 grams (or 0.5 to 1 gram/kilogram body weight)
- Infants up to 1 year old: 0.5 to 1 gram/kilogram

**Gastric lavage:** Gastric lavage is recommended

**Specific treatment/Antidote**

**Flumazenil:**

**Indication for use:** Severe CNS and/or respiratory depression following overdose with a benzodiazepine. **Mechanism of action:** Flumazenil competitively and reversibly binds to BZ receptor sites in the CNS (BZ$_1$ and BZ$_2$) and inhibits the effects of benzodiazepines on the GABAnergic pathway.

**Adult dose:** 0.2 to 3 milligrams flumazenil in the case of benzodiazepine overdose.

**For higher doses ingestion:** 1 to 10 milligrams in an adult, may be necessary to treat the profound coma in some overdose cases

**Pediatrics:** In children 1 year or older: 0.01 milligram/kilogram (up to 0.2 milligram) administered intravenously over 15 seconds. If adequate anesthesia reversal does not occur after waiting an additional 45 seconds, further injections of 0.01 milligram/kilogram (up to 0.2 milligram) may be repeated at 1-minute intervals as needed, up to 4 times. The maximum total dose is 0.05 milligram/kilogram or 1 milligram.

**In children Less than 1 year:** The safety and efficacy have not been established.

**Duration** - The duration of effect depends on the type and dose of benzodiazepine ingested, the dose of flumazenil, and the time interval between ingestion of the benzodiazepine and administration of flumazenil; usually 1 to 4 hours.

**Contraindications:** Flumazenil should not be used in patients with serious cyclic antidepressant poisoning, as manifested by motor abnormalities (twitching, rigidity, seizure), dysrhythmias (wide QRS, ventricular dysrhythmia, heart block), anticholinergic signs (mydriasis, dry mucosa, hypoperistalsis), or cardiovascular collapse at presentation. Flumazenil should not be used until the effects of neuromuscular blocking agents have worn off.
Flumazenil should not be used in patients who are benzodiazepine dependent or who have been given for control of a life-threatening condition.

Supportive treatment

Hypotensive episode: Infuse 10 to 20 milliliters/kilogram of isotonic fluid and keep the patient supine. If hypotension persists, administer dopamine or norepinephrine.

Dopamine

Preparation: Add 400 milligrams to 250 milliliters of normal saline or dextrose 5% in water to produce 1600 micrograms per milliliter or add 400 milligrams to 500 milliliters of normal saline or dextrose 5% in water to produce 800 micrograms per milliliter.

Dose: Begin at 5 micrograms per kilogram per minute progressing in 5 micrograms per kilogram per minute increments as needed. Norepinephrine should be added if more than 20 micrograms/kilogram/minute of dopamine is needed.

Caution: If ventricular dysrhythmias occur, decrease rate of administration. Extravasation may cause local tissue necrosis; administration through a central venous catheter is preferred.

Norepinephrine

Preparation: Add four milligram norepinephrine to 250 milliliters of dextrose 5% in water to produce a concentration of 16 micrograms/milliliter.

Dose: Adult: begin infusion at 0.5 to 1 microgram/minute and titrate to maintain adequate blood pressure (American Heart Association, 2005).

Child: begin infusion at 0.1 microgram/kilogram/minute and titrate to maintain adequate blood pressure.

Caution: Extravasation may cause local tissue ischemia, administration by central venous catheter is advised.

Respiratory depression and/or failure: Intubation and mechanical ventilation may be required in patients who develop life-threatening respiratory depression.

Elimination enhancement method:

Hemodialysis: Forced diuresis or Hemodialysis are ineffective

Criteria for emergency department discharge:

Patients who remain asymptomatic following an adequate duration of emergency department monitoring (eg, 4-6 hours) may be considered for discharge. Patients who present with
symptoms of overdose should only be considered for discharge upon complete resolution of symptoms.

**Complications:** Respiratory depression, hypotension

**Contraindications:** Not mentioned

**References:**