MAO-INHIBITOR TOXICITY
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I. PHARMACOLOGY/TOXICOLOGY

Mechanism of action (Therapeutic):
• Irreversibly inactivate monoamine oxidase.
• Leads to increased pool of catecholamines in presynaptic sympathetic nerve terminal.
• Resultant increase in dopamine and norepinephrine thought to be responsible for anti-depressant effect.

Mechanism of toxicity:
• Poorly understood, proposed to be combination of sympathomimetic and sympatholytic properties.

II. PHARMACOKINETICS

• Rapidly absorbed orally.
• Peak levels in 2-3 days.
• Peak MAO inhibition in 5-10 days.
• Metabolized in liver to inactive metabolites which are eliminated in the urine ($T_1/2$ Parnate around 3 hours).
• Clinical benefit may take up to 2 to 3 weeks.
• Clinical effects may persist for up to 2 weeks after discontinuation. (3-5 days for tranylcypromine even though its elimination is complete in 24 hours.)

III. RANGE OF TOXICITY

• Low therapeutic margin.
• 2-3mg/kg considered life threatening.
• 4-6mg/kg consistent with fatalities
• 170mg Tranylcypromine and 375mg phenelzine in acute ingestions have been reported to be fatal.

Available Forms
• Phenylzine (Nardil)
• Isocarboxazide (Marplan)
• Selegiline (Eldepryl; MAOI-B)
• Tranylcypromine (Parnate)
• Pargyline (Eutonyl)

IV. CLINICAL EFFECTS

Onset:
• May be delayed up to 12 hours, onset of disorientation reported to occur as late as 32 hours.
• May be rapid following ingestion of interacting drugs or foods.
• Progresses from CNS excitation to depression.

Signs/Symptoms:

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<th>Cardiovascular:</th>
<th>Hypertension</th>
<th>Palpitations</th>
<th>Asystolic arrest</th>
<th>Flushing</th>
<th>Bradycardia</th>
<th>Hypotension</th>
<th>Tachycardia</th>
<th>Collapse</th>
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<tbody>
<tr>
<td>Respiratory:</td>
<td>Tachypnea</td>
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<td>Pulmonary edema</td>
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<td>Renal:</td>
<td>Renal failure</td>
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<td>Rhabdomyolysis</td>
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<td>Hematologic:</td>
<td>Leukopenia</td>
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<td>Hemolysis</td>
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<td>CNS</td>
<td>Anxiety</td>
<td>Sweating</td>
<td>Irritability</td>
<td>Headache</td>
<td>Delirium</td>
<td>Drowsiness</td>
<td>Obtundation</td>
<td>Hyperreflexia</td>
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V. DIAGNOSIS
• Based on history of ingestion or interaction and S/S
• Blood levels difficult no real "toxic" range.
• Differential includes TCA's, PCP, sympathomimetics, anticholinergics, malignant hyperthermia, neuroleptic malignant syndrome, serotonin syndrome, thyroid storm drug withdrawal, tetanus.

VI. DECONTAMINATION
• If early in presentation or coingestants.
• Emesis ?? (risk of seizures).
• Gastric lavage.
• Activated charcoal.

VII. TREATMENT
A. Emergency and supportive measures. ABC'S, Assess airway, establish IV access.
B. Labs (which may be useful).
• CBC, lytes, glucose (Parnate is a potent insulin secretagogue) BUN/Cr, CPK.
• EKG and cardiac monitor.
• CT scan if suspect intracranial hemorrhage.
• UDS/SDS, APAP, ASA levels if warranted.
C. CNS excitation
  - diazepam or amobarbital boluses.
  - paralytic.
  - caution with sedative/hypnotics
  - caution phenothiazines.
  (reports of coma, HOTN, cardiac arrest).
  - caution narcotics.
D. Hyperthermia
  - pharmacologic agent generally too slow in onset.
  - FANS.
  - sponge baths, cool compresses.
  - ice baths.
  - Paralytics for refractory hyperthermia.
  - dantrolene, bromocriptine if above unsuccessful.
E. Seizures
  - diazepam.
  - phenytoin.
F. Hypertension
  - short acting titratable agents (Nitroprusside).
  - phentolamine.
  - nifedipine.
  - labetolol.
G. Hypotension
  - FLUIDS and Trendelenburg position.
  - mast trousers.
  - cautious use of NE or dopamine.
H. Cardiac arrhythmias
  - difficult to treat.
  - ventricular arrhythmias (Lidocaine, Procainamide).
  - avoid bretylium (initial NE release and then HOTN).
  - bradyarrhythmias (atropine, pacer, epinephrine).
I. Rhabdomyolysis
  - CPK levels.
  - high urine ouptut with IV fluids.
  - alkaline diuresis with sodium bicarbonate may be necessary.

VIII. MONITORING
• Because signs and symptoms of toxicity may be delayed a 24 hour observation period is prudent.
IX. SPECIAL CONSIDERATIONS

A. Drug interactions.
   Indirect acting sympathomimetic amines, other antidepressants, central acting stimulants levodopa, tryptophan, meperidine, dextromethorphan, SSRI's, levorphanol.

B. Drug-food interactions.
   Foods high in tryramine content may precipitate a hypertensive crisis.

REFERENCES