Atypical Antipsychotics

As Poison in Overdose

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Atypical antipsychotics have rapidly gained acceptance for psychotic disorders because of their improved safety and efficiency profiles in therapeutic doses.

Several million persons who have an increased risk of suicide receive atypicals. The number of reported overdose cases is certain to increase.

Previously published overdose cases describe characteristic symptoms related to unique neuro receptor affinities patterns of atypicals, which include:

- serotonergic $5HT_{2A}$, $5HT_{2c}$, *etc.*;
- dopaminergic D_1, D_4, *etc.*;
- adrenergic α_1, α_2;
- histamine $H_1$and
- muscarinic M_1, *etc.*

The severity of symptoms correlates with the size of the drug overdose and additional drugs ingested. Aggressive supportive therapy is required to reduce morbidity and prevent death.

John's Overdose

- John, 26, has an established diagnosis of schizoaffective disorder.
- He has ingested ≥ 800 mgs of olanzapine.
- Upon arrival, he was semi-conscious with a Glasgow Coma Scale score of 5-6, obtunded, agitated, combative in 4-point restraint and incoherent.
- He showed marked dystonic movements in all four limbs and truncal dystonia.
- Heart rate: 120/min in regular sinus tachycardia with raised respirations, diaphoretic, but afebile.
- His pupils were sluggishly reactive to light.

For more on John, go to page 72.

Recovery time course

With aggressive supportive treatment (ruling out additional causes of toxic delirium) clinical recovery parallels the fall in measured serum levels. Peak levels of < 1,000 mg/L can be seen in two to three hours after ingestion with an acutely worsening neuro psychiatric state.

A rapid fall in atypical levels in the first 24 hours with

More on John

- Evidence of rhabdomyolysis.
- Creatinine kinase elevated to 810 IU/L.
- Diffuse non-specific ST and T wave changes, but QRS CI T and Tc intervals were normal.
- Level 2 sedation was achieved with midazolam and propofol after intubation to protect his airway.
- Leukocyte count elevated to 15,000 cells/m^3.
- Olanzapine levels were not available.
- His dystonia and akathisia settled and he subsequently complained of myalgia and dry mouth.
- Meiosis (opiate-like) was also slow to recover.

olanzapine is a result of drug distribution to tissues, metabolism by the CYP 1A2 and CYP 2D6 systems and the supportive measures of gut decontamination.

Non-linear pharmacokinetic behaviour results from first pass liver metabolism, 40% by the capacity limiting P450(CYP)2D6 isozyme cytochrome.

Recovery is often slow with an average estimated 30 to 40 hours. Intubation may be required for as long as five days. This depends on the drug half-life and metabolites.

Combination overdoses with alcohol and other psychotropic medications produce very severe symptoms and profound central nervous system depression (Glasgow Coma Scale < 7).

Pharmacology and toxicology

The clinical picture of an atypical overdose is largely influenced by the agent involved and concurrent ingestants. Factors, such as onset of action, half-life and metabolites, must be considered.

General pharmacodynamics and pharmacokinetics

a) Olanzapine pharmacokinetics
- Time to peak concentration: 6 hours
- 60% oral bioavailability
- 93% protein binding
- Volume distribution: 1,000 L/kg
- Extensively hepatic metabolism
- 2 inactive metabolites
- Half-life: 30 hours

b) Risperidone pharmacokinetics
- Time to peak concentration: 1 hour
- 70% oral bioavailability
- 90% protein binding
- Volume distribution: 1 L/kg to 2 L/kg
- Extensively hepatic metabolism
- 1 active metabolite (equivalent to parent)
- Half-life (parent): 20 to 30 hours
- Haf-life (metabolite): 21 to 30 hours

c) Quetiapine pharmacokinetics

- Time to peak concentration: 1.5 hours
- 9% oral bioavailability
- 83% protein binding
- Volume distribution: 10 L/kg
- Extensively hepatic metabolism
- 20 metabolites (2 active)
- Half-life: 6 hours

d) Clozapine pharmacokinetics

- Time to peak concentration: 2.3 to 3 hours
- 55% to 60% oral bioavailability
- 97% protein binding
- Volume distribution: 6 L/kg
- Extraheptic and hepatic metabolism
- 3 metabolites (1 active)
- Half-life (parent): 8 hours
- Half-life (metabolite): 13.2 hours

Atypical drug interactions

- Interactions may be pharmacodynamic or pharmacokinetic
- Exaggerated anticholinergic, central nervous system, respiratory antidepressant and hypotensive effects
- Metabolism via hepatic CYP 450 1A2 and 2D6
- Selective serotonin reuptake inhibitors and atypicals

Drug use controls

- Safety
- Prevention of stockpiling
- Community-based issues
- Monitoring
- General principles of prescription safety

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