Multi-drug Overdose Risperidone, Ziprasidone, Valproate, Trihexyphenidyl, and Clonazepam

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Abstract
Risperidone and ziprasidone are commonly used as first line drugs for the treatment of psychotic disorders and overdose with these agents is increasingly being reported. Relatively few of these reports have involved co-ingestion of multiple psychotropic agents. We report a case of overdose with risperidone, ziprasidone, valproate, trihexyphenidyl and clonazepam in a 25 years female, who recovered uneventfully with supportive management. Notwithstanding the benign outcome in this instance, age, co-ingested drugs, active metabolites and medical co-morbidity are critical issues in overdose with atypical antipsychotics. As prescription of these drugs continues to increase in developing countries, systematic studies evaluating their clinical toxicity and management are necessary. The issues associated with overdose of multiple psychotropic agents and appropriate management policies are highlighted.

INTRODUCTION
Atypical antipsychotics such as risperidone and ziprasidone are considered to have a favourable adverse effect profile relative to traditional antipsychotics. They have emerged as first line drugs for the treatment of schizophrenia and related disorders. They also increasingly account for the majority of poisonings from antipsychotic agents that present to health care facilities. Prevention and management of such overdose are of increasing clinical relevance as prescription of these drugs continues to increase. However, little is known about the toxicology of these agents. Several cases of risperidone overdose have been reported but only few have been associated with co-ingestion of multiple psychotropic agents and none of them are from India.

CASE REPORT
A 25 years single female with an ICD- 10 diagnosis of paranoid schizophrenia—continuous course, had been receiving multiple antipsychotic medications from a private psychiatric hospital elsewhere since 1995. She did not have any known medical illness or history of substance abuse. She was overweight with a Body Mass Index (BMI) of 29. There was no family history of psychiatric morbidity, including suicide. She was admitted to the emergency department of our hospital, around 13 hours after she was reported by her parents (and confirmed from her prescriptions and used drug wrappers) to have consumed an overdose of 22 days supply of her prescription drugs, which included 88 mg of risperidone, 880 mg of ziprasidone, 22 g of divalproex sodium, 44 mg of trihexyphenidyl and 66 mg of clonazepam.

She was unconscious at the time of admission. Her Glasgow Coma Scale score was four, including Eye opening, Verbal response, and Motor response. Her blood pressure was 90/60 mm Hg. Her pulse ranged from 80 to 140 beats per minute and was irregularly irregular. She was afebrile. Her oxygen saturation was 60% with room air. She had bilateral miosis with pupils not reacting to light. She also had generalised hypotonia and her plantar reflexes were bilaterally equivocal. She was struggling with shallow respiration and occasional crepitations were audible during auscultation. However, she did not exhibit myoclonus, seizures, diaphoresis or extra-pyramidal signs.

Her haemoglobin was 11.3 g%, total leukocyte count 12,600/ mm³, differential leukocyte count: neutrophils 83% and lymphocytes 12%, and platelet count 233000/ mm³. Her blood gas analysis revealed: pH 7.407, pCO₂ 29.0 mm Hg and pO₂ of 108.8 mm Hg. Her serum electrolytes were: sodium 142 mmol/ l, potassium 3.8 mmol /l, bicarbonate 25 mmol/ l; her serum calcium was 8.2 mg% and phosphorus 4.2 mg%. Her liver and renal function tests results were within normal limits. Serum valproic acid assay measured more than 200 µg / ml. An electro cardiogram (ECG) showed atrial fibrillation, QT prolongation (QT/QTc 320/502 msec)

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and non-specific changes in the morphology of the ST segment.

She was shifted to the medical intensive care unit where she was intubated and ventilated. An intravenous infusion with normal saline solution was begun and continuous monitoring of ECG, respiration, oxygen saturation and vital signs were instituted. She began to improve with supportive care. Her pupils started reacting to light and her muscle tone was restored. Her Glasgow Coma Scale score was six (E,V,M) after three hours and reached 15 after 24 hours. Her ECG readings then returned to normal. She was taken off the ventilator on the second day.

She was shifted out of the intensive care unit and transferred to the medical ward for further observation. She did not develop any delayed extra-pyramidal signs, seizures, respiratory depression or cardiac abnormalities. As she developed insomnia on the third night of her hospital stay, she was restarted on two mg of oral risperidone and one mg of lorazepam at bedtime. She remained stable subsequently, was discharged from the medical ward on the fourth day and referred to the psychiatry department for further management of her psychotic symptoms and prevention of future suicidal attempts.

**DISCUSSION**

Available literature suggests that both risperidone and ziprasidone are relatively safe with few recorded deaths due to their isolated overdose. This report affirms these findings. However, toxicity may be worsened by extremes of age, substance abuse, obesity, medical co-morbidity, co-ingestion of other agents and may be delayed due to the presence of active metabolites, such as 9-hydroxyrisperidone, especially in slow metabolizers. CYP2D6 isoenzyme metabolizes risperidone and CYP3A4 metabolizes ziprasidone. Here, co-ingestion of risperidone and ziprasidone in massive doses along with hepatic enzyme inhibitor valproate and the potential respiratory depressant, clonazepam did not prove fatal. However, the co-ingestion of trihexyphenidyl and valproate may have protected against the emergence of extra-pyramidal adverse effects and seizures, respectively. As multiple overdoses may become increasingly common, this report provides timely information regarding the toxicology of these agents.

Although the atypical antipsychotic drugs are increasing in popularity, the pattern of clinical effects when taken in overdose is not well defined. Their toxic doses are also highly variable. Common manifestations of isolated overdoses of these agents are listed in Table 1. Risperidone toxicity manifests primarily with mild central nervous system effects and reversible neuromuscular and cardiovascular effects. Endo tracheal intubation, assisted ventilation, and supportive care form the essential components of the management of risperidone toxicity with which symptoms usually resolve within 24 hours; patients often become asymptomatic at 72 hours post ingestion. Observation for dystonia, dysrhythmia and respiratory depression is also important. Patients who take an overdose of ziprasidone should be carefully monitored for QTc prolongation and other ECG changes as well as

### Table 1: System-wise toxicological manifestations of drug overdose

<table>
<thead>
<tr>
<th>Drug</th>
<th>Central nervous</th>
<th>Cardiovascular</th>
<th>Respiratory</th>
<th>GastroIntestinal</th>
<th>Others</th>
</tr>
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*EPS = Extra Pyramidal Symptoms.*
delirium, hemodynamic instability, and anticholinergic side effects. Anti-arrhythmic agents, diphenhydramine, anticonvulsants and vasopressor agents may be required in some cases.

The multiple drug overdose reported herein provides preliminary evidence of safety of these drugs with prompt supportive management, but further studies evaluating their clinical toxicity, pharmacokinetics, drug interactions and management in multiple overdose are necessary. Therapeutic blood level monitoring and sequential serum level monitoring in overdose are yet to be standardized. The relative safety of these agents in comparison with typical anti psychotics, during overdose should be considered as a factor while choosing an antipsychotic in clinical settings. Periodic assessment of suicidal risk and endeavours to curtail irrational polypharmacy are additionally required, as are early detection of overdose and the rapid, coordinated actions of different specialties in ensuring optimal management and a benign outcome.

REFERENCES