INVEGA® (paliperidone ER)
Overdose of INVEGA

SUMMARY

- Premarketing experience reported that among the few cases of overdose, the highest estimated ingestion of INVEGA was 405 mg. Observed signs and symptoms included extrapyramidal symptoms and gait unsteadiness.[1]
- A retrospective analysis of 801 cases of INVEGA exposure (either supratherapeutic doses or overdoses) from the National Poison Data System found that 35% of patients had no clinical effects, 30.8% had minor clinical effects, 33.7% had moderate clinical effects, and 0.5% had major clinical effects. There were no deaths.[2]
- From case reports, the highest reported ingestion of INVEGA was 756 mg. Observed signs and symptoms included mild tachycardia and mild to moderate dizziness.[3]
- Potential signs and symptoms include exaggeration of the known pharmacological effects of paliperidone, i.e., drowsiness and somnolence, tachycardia and hypotension, and QT prolongation.
- Torsade de pointes and ventricular fibrillation have been reported in a patient in the setting of overdose.
- Paliperidone is the major active metabolite of risperidone. Overdose experience reported with risperidone can be found in the OVERDOSAGE section of the RISPERDAL Full Prescribing Information.[1]
- There is no specific antidote to INVEGA. Therefore, appropriate supportive measures should be instituted, and close medical supervision and monitoring should continue until the patient recovers. Consideration should be given to the extended-release nature of the product when assessing treatment needs and recovery.[1]
- See the Management of Overdosage section of the INVEGA Full Prescribing Information for additional treatment considerations in the management of paliperidone ER overdose.[1]

NATIONAL POISON CENTER OBSERVATIONAL STUDY

Tsay et al (2014)[2] conducted a retrospective, observational case series review of single-agent INVEGA overdoses that were reported to the National Poison Data System (NPDS) between January 2007 and June 2012.

Study Design/Methods

- Cases included in this study had all of the following information available from the database: patient's age and gender, the product involved, the dose and dose certainty (exact, estimate, or maximum possible), the clinical effects observed, the treatments administered, where the treatments were given, and the medical outcomes.
- The primary endpoint was to determine the severity of the exposure, graded as minor (minimal clinical effects with no residual disability), moderate (more pronounced or prolonged clinical effects which usually required treatment but were not life-threatening and did not result in residual effects or disability), or major (life-threatening effects or events leading to significant residual disability or disfigurement).
- The secondary endpoint was to determine if there was a relationship between the dose ingested and medical outcome. For this endpoint, only acute exposures were evaluated, and medical outcomes were evaluated in 3 groups of patients: children <6 years old, children 6-12 years old, and patients ≥13 years old.

Results

- 801 cases were included in the study (45.4% female, 54.3% male, 0.2% unknown). The age of the study population was <6 years (17.5%), 6-12 years (8.4%), ≥13 years (73.9%), and unknown age (0.2%).
- The reasons for INVEGA overexposure were suspected suicide (39.6%), unintentional general (21.1%), therapeutic error (15.7%), adverse reaction (11.9%), intentional misuse (5.7%), unknown intent (3.5%), intentional abuse (2.4%), and withdrawal (0.1%). By age group, children <6 years old were more likely to be overexposed to INVEGA due to unintentional general reasons (93.6%), children 6-12 years old were more likely to be overexposed due to therapeutic errors or adverse reactions (68.7%), and patients ≥13 years were more likely to be overexposed due to suicide attempts (53.2%).
- Of the 801 cases of INVEGA overexposure, 35% resulted in no clinical effect, 30.8% resulted in minor clinical effect, 33.7% resulted in moderate clinical effect, and 0.5% resulted in major clinical effect. There were no deaths.
- The most common clinical effects observed in patients overexposed to INVEGA were drowsiness/lethargy (28.7%), tachycardia (23.3%), dystonia (14.2%), agitation/irritability (5.5%), and tremor (4.5%). The incidence of these effects was fairly consistent across the 3 age groups with the exception of dystonia which occurred in 26.9% of the children 6-12 years old and 10-13.7% of patients in the other age groups (P=0.0027).
- Serious clinical effects such as hypotension (3.5%), conduction disturbances (2.0%), ECG changes (0.8%), seizures (0.6%), respiratory depression (0.5%), and coma (0.5%) occurred infrequently.
- Patients treated at a healthcare facility (n=564) received activated charcoal (25.7%), intravenous fluids (32.4%), antihistamines (21.1%), and/or benzodiazepines (9.4%). Most patients were managed in the emergency department (40.3%), but others were admitted to the ICU (15.2%), a psychiatric facility (12.6%), or a non-critical care unit (14.9%).
- Dosage information was available for 365 patients who were acutely exposed to INVEGA. In children <6 years old, the median dose associated with no clinical effects (6 mg) was significantly lower that the dose associated with minor or moderate clinical effects (12 mg, P=0.047 and P=0.02 for the two comparisons).
    - In children aged 6-12 years, there were no significant differences in outcomes based on dose.
    - In patients ≥ 13 years old, the median dose for no effect and minor effect were significantly higher than the median dose for moderate effect (P=0.037 for both).
- Four cases met the criteria of a major medical outcome. Three of the 4 patients experienced symptoms that included tachycardia and lethargy, and half of the patients experienced dystonic reactions, dyskinesia, and/or tremors.

CASE REPORTS

Case Reports Regarding Overdose in Patients Receiving Paliperidone ER

Case Description	Findings & Treatment of Overdose
Cheung et al (2020)[4] reported a case of multi-drug overdose in a 21-year-old female with bipolar disorder with psychotic features. The patient attempted suicide by ingesting 7- paliperidone ER 6 mg tablets, 20- cariprazine 3 mg tablets, 7 -mirtazapine 15 mg	The patient experienced tachycardia, palpitations and atypical chest pain in her right shoulder with radiation to her sternum, jaw and right arm. The EKG indicated a PR interval ≥ 206 following both suicide attempts and a heart rate ranging from 90 to 140 beats per minute. The patient had atypical chest pain and first-degree atrioventricular block (AVB) with paradoxical sinus tachycardia, which resolved with the discontinuation of paliperidone and mirtazapine and aggressive intravenous fluids.

tablets, 2- sumatriptan 100 mg tablets, 7- topiramate 50 mg tablets, and 2- naproxen 220 mg tablets. Two months later the patient attempted suicide again by overdosing on an unknown amount of paliperidone ER and mirtazapine.	Proarrhythmic effects occurred during both admissions. The patient was discharged on aripiprazole, topiramate and mirtazapine after her first admission. Following her second admission she was discharged on buspirone, oxcarbazepine, hydroxyzine and trazodone.
Yaylaci et al (2019)[5] reported an overdose case in a 16-year-old male adolescent diagnosed with conduct disorder. The patient ingested 28 paliperidone ER 9-mg tablets 2 days prior, with suicidal intentions.	The patient was brought to a psychiatric outpatient unit due to escalating agitation and aggressive behavior towards the staff. At the time of his admission, the patient's medication included sodium valproate 1000 mg/day and olanzapine 7.5 mg/day. Four hours after being admitted, his motor activity decreased, and he became apathetic and increasingly drowsy. Shortly after mentioning the overdose of paliperidone ER, he lost consciousness, and became unresponsive to both verbal and painful stimuli. His laboratory test results including routine hematology and biochemical tests were normal, other than an elevated creatine kinase (624 U/L) which subsequently showed a pattern of decline. The patient was monitored in the intensive care unit, and after 36 hours of supportive treatment, the patient became fully conscious and oriented.
Wong et al (2016)[6] reported a case of prolonged posture-evoked tachycardia in a patient experiencing a paliperidone overdose. A 23-year-old female deliberately ingested 504mg of paliperidone extended release (ER) tablets in addition to 400mg of quetiapine IR and 15mg of zopiclone. On presentation to the ER, the patient had a heart rate of 96 bpm and blood pressure of 130/70 mmHg. She was admitted for observation after a 12-lead ECG reflected a heart rate of 110 bpm, indicating sinus tachycardia.	The patient began to experience pre-syncopal symptoms approximately 10 hours after ingestion, and her heart rate increased to 140-180 bpm while ambulating. She also experienced tachycardia upon minimal exertion as well as with any changes in posture. Narrow-complex tachycardia was seen on serial ECGs with maximum heart rates of 190 bpm 40 hours after ingestion (when serum paliperidone concentration was approximately 883 ng/mL) with no associated elevations in the QT interval. The tachycardia continued for approximately 72 hours. The patient was discharged with a heart rate of 100 bpm and confirmed normal conduction intervals. The authors recommend extended cardiac monitoring post-ingestion of doses of paliperidone 5 times normal or >0.4mg/kg.
Avcil et al (2016)[7] reported a case of attempted suicide in a 45-year-old female. A family member reported that the patient ingested amisulpride 28 g, diazepam 250 mg, valsartan 2,240 mg, aripiprazole 45 mg, and paliperidone ER 21 mg. The patient arrived in the emergency department approximately 2 hours after ingestion of medications.	Patient showed signs of severe hypotension, severe depression of the CNS and respiratory system, a prolonged QT interval and atrial fibrillation. Pertinent lab values included a sodium level of 133 mmol/L, potassium level of 2.8 mmol/L, pH of 7.22, PCO_2 of 30.7 mmHg, PO_2 of 70.3 mmHg, HCO_3 of 12.9 mmol/L, lactate level of 7.0 mmol/L, and a prolonged QTc interval of 547 ms. Therapy for the patient included fluid and electrolyte replenishment, dopamine, norepinephrine, flumazenil, sodium bicarbonate, mechanical ventilation, gastric irrigation, and activated charcoal. Furthermore, intravenous lipid emulsion (ILE) was started at a rate of 100 ml/h and continued for 4 hours. ILE was started because of its ability to bind lipid soluble agents in the tissues and blood. All of the medications ingested by the patient had lipophilic characteristics. Plasma exchange (PE) was performed and repeated at 18 and 36 hours to eliminate valsartan due to its high lipoprotein binding and low volume of distribution. Following these procedures, the ECG turned to sinus rhythm, the QT interval shortened to 541 ms,

	and the patient's blood pressure improved. The patient was extubated after 40 hours and discharged after 4 days with a QTc of 425 ms.
Liang et al (2012)[8] reported a case of overdose in a 34 year-old Chinese man with a diagnosis of schizophrenia. The patient was prescribed paliperidone 12 mg/day and ingested 48 mg over a 2-day period in addition to atenolol 50 mg and simvastatin 40 mg. The patient presented to the emergency department with a clear consciousness, no suicidal ideation, and denies use of illicit drugs, herbals, or alcohol	No significant EPS symptoms were observed, while vital signs and physical examination were unremarkable. Laboratory tests revealed a serum creatinine 7.19 mg/dL and a blood urea nitrogen of 56 mg/dL. The patient was admitted for acute renal failure with metabolic acidosis and received a thorough work up which ruled out other causes of acute renal failure. Renal function improved with IV hydration and sodium bicarbonate treatment. Serum creatinine dropped to 2.80 mg/dL after 5 days and 1.50 mg/dL after 9 days. The patient was re-started on paliperidone 12 mg/day on day 10. At 3 months following discharge, his serum creatinine was 1.14 mg/dL.
Levine et al (2011)[9] reported a case of overdose in a 14 year-old female with a history of depressive disorder and psychosis not otherwise specified. Patient was prescribed paliperidone 6 mg/day and venlafaxine 75 mg/day. She ingested 180 mg paliperidone ER in a suicide attempt but denies ingesting venlafaxine as part of her overdose. Patient was admitted to the emergency department (ED) 1 hour following ingestion.	The patient was afebrile with mild tachycardia (pulse rate: 119 beats/min; blood pressure: 130/72 mmHg). She did not have any other symptoms and was awake and alert without evidence of sedation. Laboratory Results were normal for CBC count, electrolyte levels, and hepatic function. Tachycardia resolved 5 hours after ingestion. The patient was transferred to an inpatient psychiatric hospital 20 hours after ED admission. Upon arrival, she was tachycardic (130 beats/min; blood pressure: 114/61 mmHg) and was sent back to the ED. About 6 hours after returning to the ED, she developed a narrow complex tachycardia (190 beats/min). Patient received 6 mg and 12 mg of adenosine, with no change in symptoms. She also received 1 liter of normal saline. Her heart rate decreased to 120 beats/min over the next 30 minutes. After transfer to the pediatric ICU, she was lightheaded with positional changes, with no abnormal ECG. Serum paliperidone concentration was 170 ng/mL (therapeutic: 4.8 to 16.5 ng/mL; additional studies[10-12] indicate the therapeutic range may vary between 4.4 to 52 ng/mL) 40.5 hours after ingestion. About 39 hours post-ingestion, she experienced a narrow complex tachycardia again (190 beats/min; blood pressure: 97/44 mmHg) and experienced light headedness. Mild tachycardia remained for about 90 hours post-ingestion and she was lightheaded for about 2 days. Following supportive care and IV fluids, she was medically cleared and transferred back to the inpatient psychiatric facility.
Gill et al (2010)[3] reported a case of overdose in a 37 year-old female patient with a history of schizophrenia. Patient was prescribed paliperidone ER 12 mg/day but ingested 756 mg due to auditory command hallucinations. She was admitted to the emergency department 4 hours after ingestion of tablets	The patient was fully alert with stable vital signs (blood pressure of 113/73 mmHg, heart rate: 91 bpm) and a normal sinus rhythm with no QT prolongation. Blood gases, blood counts, renal function, liver function, and creatinine kinase were all within normal limits. She received treatment with gastric lavage and activated charcoal. She experienced mild tachycardia (100-110 bpm) once admitted to the medical ward which returned to normal 3 days later. Patient also experienced mild to moderate dizziness for 2 days. Blood pressure and vital signs all remained normal. Patient was transferred to the psychiatric ward and discharged 1 week later in good condition.
Bez et al (2010)[13] reported a case of overdose in a 24 year-old female patient with a diagnosis of	Patient presented to emergency room 6 hours after ingesting the tablets. She had restlessness, agitation, akathisia, mild confusion, disorganized behavior, loss of orientation (time and

schizophrenia. The patient was prescribed paliperidone ER 3 mg/day but ingested 81 tablets of paliperidone ER 3 mg (total of 243 mg) after an anger outburst.	place), and delusions. She was also hypertensive (150/95 mmHg), tachycardic (127 bpm), and had mildly elevated creatine kinase (475 U/L). Initial ECG readings showed sinus rhythm and ventricular extrasystoles with no QTc prolongation. The patient received one dose of activated charcoal and gastric lavage and intravenous saline for hydration in the ICU. Twelve hours after admission, blood pressure and heart rate decreased (135/85 mmHg and 93 bpm, respectively), and ECG showed a normal sinus rhythm. After 48 hours, initial symptoms were absent, except for delusions, disorganized behavior, and mildly increased spontaneous speech. Patient was gradually started on intramuscular zuclopenthixol decanoate 200 mg/15 days, olanzapine 20 mg/day, and biperiden 4 mg/day and was discharged 7 weeks after initiating treatment.
Chang et al (2010)[14] reported a case of overdose in a 28 year-old male patient with schizophrenia, alcohol dependence with full remission, and alcohol-related liver cirrhosis. The patient was prescribed paliperidone ER 9 mg/day. For the three days prior to admission, he self-medicated with 27 mg/day paliperidone ER (81 mg over 3 days).	The patient presented to the ER with anxiety, agitation and restlessness. He was hypertensive (150/98 mmHg) and tachycardic (100 beats-per-minute) with a normal sinus rhythm and QTc (corrected QT) interval (350 ms). His consciousness was clear with a full score on the Glasgow Coma Scale. -Laboratory Results were normal except for hyperammonemia (103 µg/dL) and moderate chronic hepatitis. Patient was gradually tapered off paliperidone over two days while titrated to quetiapine 300 mg/day. Restlessness and anxiety subsided within 2 weeks. Blood pressure and pulse returned to baseline, without QTc prolongation or any cardiovascular events during hospitalization. Consciousness remained clear without drowsiness or sedation.
Cunningham et al (2010)[15] reported a case of multi-drug overdose in a 22 year-old male patient with a history of bipolar disorder, attention-deficit hyperactivity disorder, dependent personality traits, and polysubstance dependence. The patient ingested 42 mg paliperidone, 7500 mg bupropion, 750 mg sertraline, and 3 mg lorazepam. Urine drug screen was positive for amphetamines and benzodiazepines.	Patient was initially admitted to the intensive care unit and transferred to the psychiatric unit once stable. Two days following ingestion of medications, patient experienced sustained muscular spasms of the neck (stiff, arched neck) and jaw (stiff). His tongue was enlarged and protruding. Vital signs, ECG, serum creatine kinase, and lactate dehydrogenase were within normal limits during this event. He was also afebrile and alert and oriented. Patient received intramuscular diphenhydramine, and after a few minutes, the dystonic reactions resolved. No additional acute dystonic events occurred during hospitalization. No psychotropic medications have been restarted.
Gerst et al (2009)[16] reported a case of overdose in a 14 year-old African American male diagnosed with bipolar affective disorder. The patient ingested paliperidone ER 3 mg x 18 tablets (54 mg total)	In the intensive care unit, the patient displayed symptoms of sialorrhea, abnormal tongue movements, dystonic neck, and questionable psychosis. Supportive care-neuroleptic malignant syndrome was ruled out based upon symptomatology and laboratory findings. Mild systemic events resolved over a five-day period.
Elko et al (2009)[17] reported a case of an accidental overdose in a 5 year-old male. Paliperidone ER 27 mg was ingested however the time of ingestion was unknown	The patient presented with sinus tachycardia, EPS; drooling, stiffness throughout the body, and could communicate only by nodding his head Gastric detoxification was not attempted. EPS symptoms were controlled with multiple treatments of diphenhydramine and benzotropine. Lorazepam was required for agitation and hallucinations. Symptoms gradually subsided and the patient was discharged after 30 hours.

LITERATURE SEARCH

A literature search of MEDLINE® (and/or other resources, including internal/external databases) pertaining to this topic was conducted on January 16, 2024.

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