Accidental Ingestion of Venlafaxine in a 9 Month Old Infant

B Woodhouse, J Erramouspe

Citation

Abstract
Venlafaxine is a serotonin/norepinephrine reuptake inhibitor approved for adults with depressive, panic, and anxiety disorders. The safety and efficacy of venlafaxine has not yet been adequately established in pediatric patients to allow approval although studies have been reported in children and adolescents with primarily attention-deficit hyperactivity disorder and depression. The intentional or unintentional use of venlafaxine in patients less than 3 years of age has not been extensively reported.

OBJECTIVE: To report the adverse effects following the probable accidental ingestion of venlafaxine in a 9-month-old infant.

CASE SUMMARY: The infant presented to the emergency department about 7 hours after a presumed ingestion of a single 150 mg venlafaxine extended-release capsule. His mother and grandmother described him as having a "drugged look", trembling, shaking, pill-rolling with his tongue, dilated pupils, and other odd behaviors. Upon presentation to the emergency room, he was sedate, had dilated pupils, and had depressed mental status. His urine was positive for phencyclidine (PCP), but a confirmatory test could not be done due to mishandling of the specimen. He was admitted and observed throughout the night. He was acting and eating normally the following morning and was subsequently discharged in stable condition.

CONCLUSIONS: There is minimal information regarding venlafaxine toxicity in infants and children but accidental ingestion may cause a variety of serotonergic, anticholinergic, and neuromuscular adverse effects, mental status changes, and autonomic instability. Supportive care is a reasonable treatment when symptoms are not severe.

INTRODUCTION
Venlafaxine is a serotonin/norepinephrine reuptake inhibitor approved for adults with major depression, panic disorder, generalized anxiety, and social anxiety but not yet approved for pediatric use. Venlafaxine has been studied in children and adolescents with mainly attention-deficit hyperactivity disorder and depression, and a few studies in pediatric patients with autism spectrum and conduct disorders. Adverse effects of venlafaxine in children and adolescents have included nausea, vomiting, abdominal pain, headache, drowsiness, insomnia, restlessness, irritability, dizziness, anorexia, and increased appetite. Venlafaxine has one active metabolite, O-desmethylvenlafaxine (ODV, desvenlafaxine). The half-lives of regular-release tablet formulations of venlafaxine and desvenlafaxine are 5 and 11 hours, respectively. The projected duration of toxicity from venlafaxine extended-release capsule ingestions may be longer than regular-release tablets because of a prolonged absorption phase.

A spectrum of serotonergic-mediated toxic effects can occur with venlafaxine poisonings beginning typically with tremor, hyperreflexia, shivering, diaphoresis, mydriasis, somnolence, anxiety, and/or agitation with mild to moderate exposure. Toxic effects seen with more severe exposure may include mental status changes (agitation, hyperactivity, confusion, delirium, hallucinations), neuromuscular abnormalities (muscular rigidity, hypertonicity, restlessness, clonus, tremors, seizures, rhabdomyolysis), and autonomic instability (increased bowel sounds/diarrhea, tearing, respiratory rate, fever, flushing, hypotension or hypertension, tachycardia, and arrhythmias). The following case describes the effects of a probable acute pediatric ingestion of a single venlafaxine extended-release pill.

CASE REPORT
A previously healthy 9-month-old 8.6 kg Caucasian male presented to the emergency department (ED) about 7 hours after a suspected ingestion of a single 150 mg venlafaxine extended-release capsule (Teva Pharmaceuticals). The boy’s only current medication had been 0.25 mg daily of fluoride, and his immunizations were up-to-date. At 8:00 am, the infant’s grandmother dropped a venlafaxine extended-release 150 mg capsule and could not find it. The boy began acting strange about 2.5 hours later manifested as a refusal to eat and irritability. Seven hours later, the mother and grandmother described the boy as having a “drugged look”,
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trembling and agitated, flushed skin, dilated eyes, rolling his
eyes, pill-rolling with his tongue, seemed to be itchy all
over, and seemed to be reaching out for something that was
not there. The boy was taken to the ED for evaluation.

Upon presentation to the ED, neurologically the boy
appeared sedated with a persistent depressed mental status,
not even awakening during urinary catheterization. His tone
and strength were normal. His eye exam revealed mydriasis
but with eyes equally round and reactive to light. His vital
signs were: Pulse 136 beats/min, blood pressure 84/59
mmHg, respiratory rate 32 breaths/min, temperature 99.7 °F,
and oxygen saturation 100% on room air. His cheeks were
erythematous with a macular rash. The rest of his physical
exam was normal. Laboratory tests ordered upon
presentation included a rapid streptococcal A antigen and
follow-up throat culture (both negative), urinalysis and urine
drug screen. His urinalysis had the following abnormal
results: 20 mg/dL protein, 20 mg/dL ketones, 3-5 red blood
cells, and 4+ mucus. He was considered to be in stable
condition, but was admitted to the general pediatric floor for
further observation. He was empirically given one dose of
100 mg ibuprofen at admission for his temperature of 99.7°F
and 120 mg acetaminophen by mouth later that evening for a
temperature of 100.1°F. His urine drug screen came back
positive for phencyclidine (PCP) using the Phencyclidine
Plus assay (Roche Diagnostics), but this was felt to be a false
positive result from venlafaxine.\(^8\)

When interviewed, both
the mother and grandmother appeared appropriately
concerned and willing to cooperate with all requests of the
pediatrician, nurses, and pharmacist. The boy’s initial
sedation/depressed mental status, mydriasis, and
erythematous macular rash on the cheek had resolved by the
next morning. He was acting and eating normally and was
discharged. Due to specimen mishandling, a confirmatory
test for urine PCP (by gas chromatography mass
spectrometry) could not be performed since no additional
urine could be obtained prior to patient discharge. The
grandmother was contacted the day after discharge and said
he was still acting normally and that she had never found the
dropped capsule despite additional searching.

DISCUSSION

Postmarketing surveillance data shows that the most
common adverse effects seen with venlafaxine overdose in
adults include tachycardia, altered consciousness, and
mydriasis. Seizures and vomiting are also often reported.\(^5\)

There are minimal data regarding pediatric
ingestion/overdose of venlafaxine in the literature. Miller,
McGoodwin, and Hagemann reported anticholinergic-type
side effects in a 10-year old male after a medication error
lead to accidental ingestion of venlafaxine 150 mg twice
daily for two days.\(^9\) He presented with mild tachycardia,
dilated pupils, drowsiness, tremor, hallucinations, and
urinary retention. A urine drug screen was not done. The
patient was admitted and developed abdominal pain and
constipation the following day. His symptoms resolved 4
days after discontinuation of venlafaxine, and he was
discharged.

Venlafaxine is known to cause various anticholinergic-type
effects (e.g. dry mouth, constipation, urinary
hesitancy/retention) but the only one manifested by the
infant in our case was his dilated pupils (mydriasis).\(^9\)

Complete recovery with treatment of an 11-month-old who
ingested 600 mg of desvenlafaxine (active metabolite of
venlafaxine) has been reported but no other details are
available.\(^5\)

Asymptomatic children who inadvertently ingest less than
5.5 mg/kg of venlafaxine may be managed at home.
Symptomatic children, those who have taken deliberate
ingsestions, and those inadvertently ingesting 5.5 mg/kg or
greater of venlafaxine should be admitted and observed in a
healthcare facility for at least 24 hours if a extended-release
formulation has been ingested (at least 6 hours for regular-
release). They may be released after this provided their
symptoms have resolved and vital signs are normal. In this
case the child was admitted due to his symptoms and the
possibility that he may have ingested as much as 17 mg/kg
of extended-release venlafaxine, and observed until
asymptomatic (approximately 24 hours).\(^5\)

Activated charcoal may be considered in asymptomatic or
minimally symptomatic patients if they present within a one
hour of ingestion. The mainstay management for venlafaxine
ingsestions is supportive care (e.g. isotonic fluids,
vasoressors, antiarrhythmics, antiemetics, and sedatives).
Benzodiazepines are the treatment of choice in children with
agitation, mild serotonergic effects, hyperadrenergic vital
signs, and seizures. Cyproheptadine, a serotonin receptor
antagonist may be considered to minimize serotonergic
effect of venlafaxine overdose, but only in extreme severe
cases of serotonin syndrome.\(^7\)

Venlafaxine has been documented to cause false positive
results for PCP on urine immunoassay tests. A 48-year-old
female treated with 225 mg venlafaxine, 100 mg
lamotrigine, and 2 mg lormetazepam daily had positive PCP
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urine tests. Further testing (by GC/MS) was done, and her urine was only positive for the medications she was prescribed; no PCP was found. Another article described 3 cases of positive PCP urine tests in patients taking venlafaxine and no other medications known to cause PCP false-positive results. Confirmatory urine tests in each of these cases were negative for PCP. A venlafaxine overdose in a 13-year-old girl also showed false-positive results for PCP. She had ingested 7200 mg of venlafaxine, and confirmatory tests were only positive for venlafaxine and O-desmethylvenlafaxine, not PCP.

It is plausible that this infant could have been administered PCP, although all medical personnel involved in interviewing his caregivers felt this was unlikely. The most common reactions to PCP ingestion in young children and infants are lethargy, strange behavior such as a blank stare, agitation, miosis, ataxia, and nystagmus. Probable causality was found between the signs and symptoms manifested by this infant and acute venlafaxine ingestion using the Naranjo probability scale. A key sign in this case is the infant’s dilated pupils since it is a common manifestation of venlafaxine overdose and is rarely seen with PCP ingestion in infants. The main eye sign seen with PCP intoxication is nystagmus.

CONCLUSION

A variety of toxic symptoms may present when children and infants ingest venlafaxine (serotonergic- and anticholinergic-mediated effects, mental status changes, neuromuscular abnormalities, and autonomic instability). These adverse effects generally subside with time and treatment with supportive care.

References

Author Information

Brittany Woodhouse, PharmD
Resident, Idaho State University College of Pharmacy, Idaho Drug Information Service

John Erramouspe, PharmD
Professor, Idaho State University College of Pharmacy