

Clinical Review

Phencyclidine Intoxication and Adverse Effects: A Clinical and Pharmacological Review of an Illicit Drug

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INTRODUCTION

Phencyclidine (PCP, “angel dust”) is an infamous hallucinogenic sought for its ability to induce the illusion of euphoria, omnipotence, superhuman strength, and social and sexual prowess. The acronym PCP stems from its organic name 1-(1-phenylcyclohexyl) piperidine, which alludes to its relatively simple production from the arylcyclohexylamine piperidine.^{1,2}

More than 60 designer analogs more toxic than PCP, but able to escape clinical detection, were common before the sale of piperidine and its derivatives became illegal in the United States in 1978. Ketamine is the only one authorized for medical use, and it was often stolen from veterinary offices for its PCP-like effects.³

Like ketamine, PCP was formerly used as a preinduction anesthetic and animal tranquilizer, hence it has street eponyms such as “horse tranquilizer,” hog,” and “elephant”.^{4,5} It was prized for its ability to provide anesthesia and analgesia without triggering cardiorespiratory depression, but was soon recalled when patients experienced psychosis, agitation, and dysphoria post-operatively.⁶

PCP has re-emerged as a drug of abuse in this decade since its decline after the 1980s. In 1979, 12.8% of twelfth graders had used PCP, whereas in 1997 only 3.9% had used this drug.¹ However, phencyclidine continues to be found in PCP-laced marijuana cigarettes (“whacko tobacco”), and has been detected in up to 24% of street marijuana samples. Regrettably, exposure to the smoke and butts of these cigarettes has resulted in many cases of occult pediatric PCP intoxication.³

Pharmacology

PCP is available as a white crystalline powder (“angel dust”), tablet (“PeaCe Pill”), crystals, and liquid (“whack”); with these

varied forms, it can be snorted, smoked, ingested or injected intravenously or subcutaneously.^{1,7,8}

A typical PCP-laced marijuana cigarette contains 1 to 10mg of the drug. The average tablet varies in weight from 1 to 6 mg.^{3,9} Only 0.25 mg of IV solution is required to produce sedation, compared to 10mg required via ingestion or inhalation.¹⁰

Inhalation accounts for 70% of usage, however, because onset of action occurs in 2-5 minutes, without the complications of injection. Effects may take 15 to 60 minutes when ingested orally.^{3,6,11,12} Phencyclidine is a weak base that is lipid, water, and alcohol soluble, giving it an extraordinary volume of distribution of 6.2 L/kg.¹² Thus, the relationship between dose, serum level, and effects varies depending upon body habitus, nutritional state, and alcohol coingestion.^{3,13,14}

Walberg et al. did not find any direct relationship of serum concentration of PCP and the clinical pattern of intoxication in a case series of 216 patients with “pure” PCP intoxication.¹⁵ This lack of correlation of plasma concentration and clinical effects of PCP is poorly understood. Additionally, no relevant data or literature could be found to correlate PCP concentrations in the cerebrospinal fluid (CSF) with the clinical effects of the drug.

In animal experiments PCP-binding antibodies actually increased serum concentrations of PCP, indicating that they simply alter its distribution.¹⁶ PCP levels are highest in adipose tissue, and because of its slow, uneven release from lipid stores, the half-life of PCP is believed to be three days.^{3,13} Due to the brain’s high lipid content and ion trapping, cerebral levels of PCP may be nine times serum levels, allowing its CNS effects to last from seven hours to as long as seven days in chronic users.¹⁷

Regardless of the method of administration, significant amounts of the weakly basic PCP are actively secreted into the acid milieu of the stomach, accumulating to levels up to

50 times higher than serum levels, where it is then reabsorbed in the small intestine. Fortunately, however, 90% of the drug is metabolized on first pass via oxidative hydroxylation in the liver. These metabolites are then glucuronidated for renal excretion with the 9% of active drug that is excreted directly.¹²

Phencyclidine is believed to have several sites of action in the central nervous system, all of which act synergistically to result in anesthesia and analgesia. It has greatest affinity for the NMDA (N-methyl-D-aspartate) receptor complexes in the hippocampus, neocortex, basal ganglia, and limbic system.¹⁸ There are three major neuronal interactions of PCP, which occur at serum concentrations compatible with life up to 1 µM/mL. PCP has a decreasing affinity to NMDA receptors, to the neuronal norepinephrine (NE), dopamine (DA), and serotonin (5-HT) reuptake system and to the σ opioid receptors.^{6, 18} At moderate doses of 1 to 5mg orally, PCP inhibits dopamine, norepinephrine, and serotonin reuptake, and increases dopamine and norepinephrine production by stimulating tyrosine hydroxylase, resulting in dopaminergic and sympathomimetic effects.^{19, 20}

The NMDA-Phencyclidine complex includes a calcium channel stimulated by excitatory neurotransmitters such as

glutamate, glycine, and aspartate, but inhibited by phencyclidine at a PCP-specific binding site.¹⁹ Paradoxically, PCP also causes CNS excitation via glutamate release at the presynaptic metabotropic receptors. Metabotropic receptors are G-protein rather than ion-gated channels.²¹ (Table 1)

CLINICAL MANIFESTATIONS

Over 50% of adult patients present with the classic toxidrome of PCP intoxication: violent behavior, nystagmus, tachycardia, hypertension, anesthesia, and analgesia.^{1, 7, 22, 23}

The clinical picture may wax and wane between extreme agitation and sedation, because PCP can produce CNS stimulation and depression through its different clinical effects in the CNS. With increasing concentrations, the drug binds to NMDA receptors, acts as a monoamine reuptake inhibitor, stimulates σ -opioid receptors, as well as nicotinic, muscarinic and GABA receptors.^{6, 18} Sedation and loss of inhibition tend to occur with ingestions of 1 to 5 mg, with the CNS findings of slurred speech, violent behavior and blank staring, horizontal, vertical, or rotatory nystagmus, ataxia, hyperthermia, and seizures at these doses (Table 2).^{3, 6, 9, 14, 23}

PCP's most unusual feature is that doses of 5 to 10 mg orally may induce acute schizophrenia, including agitation, psychosis, audiovisual hallucinations, paranoid delusions, and catatonia. Doses greater than 10 mg usually result in coma.^{3, 11, 12} In animal experimental studies PCP is used to investigate the neurochemical basis of schizophrenia. Low doses of phencyclidine have produced patterns of metabolic and neurochemical changes in rodent brains that resemble those in brains of schizophrenic patients.²⁴ A typical PCP-induced coma is manifested as an unresponsive patient whose eyes remain open.^{1, 10}

The very characteristics that made PCP ideal for anesthesia at moderate doses – absence of cardiorespiratory depression or muscle hypotonia – make it dangerous at higher recreational doses. It produces sympathomimetic signs such as hypertension, tachycardia, and diaphoresis similar to cocaine, and cholinergic signs like bronchospasm, salivation, urinary retention, flushing, and miosis, similar to opiates. The most common of these are tachycardia and hypertension.^{1, 25}

PCP has also been shown to be a direct cardiac irritant, and may induce arrhythmias and vasospasm. In addition, muscle tone becomes exaggerated, and patients may exhibit hyperreflexia, and myoclonic, dystonic or choreoathetoid movements such as opisthotonos and torticollis.⁹ Complications of this hypertonic muscle activity include hyperthermia and rhabdomyolysis.^{9, 14, 17, 26}

Respiratory depression requiring intubation is uncommon in PCP intoxication; however, patients may exhibit irregular breathing, with episodes of both apnea and tachypnea.^{9, 22} Furthermore, pharyngeal and laryngeal reflexes become hyperactive, and sympathomimetic effects create bronchorrhea,

Table 1. Pharmacology of Phencyclidine (PCP) in the central nervous system

- PCP has contrary actions on the glutamate transmission, explaining its different effects
 - Inhibits the ion flux at the NMDA glutamate receptor
 - Increases glutamate transmission at non-NMDA receptors (G-protein mediated response)
- Inhibits the GABAergic output
- Decreases DA and NE uptake
- Increases the DA and NE levels by stimulating the enzyme tyrosine hydroxylase

GABA: γ - aminobutyric acid

NMDA: N-methyl D-aspartate

DA: dopamine

NA: norepinephrine

Modified after Williams and Keyes (Williams, 2001 #16) and Brust (Brust, 1999 #6)

Table 2. Neuropsychiatric and clinical effects of PCP at different doses

<u>Estimated ingested amount</u>	<u>Clinical effects</u>
2-5 mg (Stage I)	Unpredictable, drunk, euphoric, disoriented, combativeness, rage obscenity. Alternating periods of lethargy and fearful agitation: waxing and waning. Decreased but intact pain perception, midpoint pupils, nystagmus, ataxia differentiates PCP from stimulants.
5-25 mg (Stage II)	Stupor, mild coma, intact response to deep pain, muscle contractions, bizarre postures.
More than 25 mg (Stage III)	Comatose with no response to deep pain, hyperthermia, convulsions, death.

Modified after Milhorn HT (Milhorn, 1991 #7) and Williams and Keyes (Williams, 2001 #16)

which exacerbate the risk of airway obstruction in an already obtunded patient.^{9, 22, 27}

Non-traumatic causes of death include cardiopulmonary arrest, intracranial hemorrhage in hypertension, and hyperkalemia secondary to rhabdomyolysis.^{9, 22} Most deaths in PCP-intoxicated patients, however, result from patients' violent behavior, rather than direct effects of the drug.^{1, 14, 23, 28} The bizarre and violent behavior generated by PCP, combined with its analgesic effects, may result in significant self-inflicted trauma. Patients have walked into traffic, jumped from buildings, and even enucleated their own eye.²⁹

Patients recovering from PCP exposure may undergo an emergence reaction as the drug is eliminated, consisting of psychosis, bizarre behavior, or depression that may last from

days to weeks.²⁸ Prolonged psychosis is more commonly seen in chronic abusers, and is a poor prognostic sign, as the patient may go on to develop true schizophrenia. Depression, anxiety, irritability, restlessness, anergia, and disturbances of thought and sleep have been described in as little as a day of abstinence in chronic abusers. Oculomotor hyperactivity, tremor, diarrhea, and piloerection were reported within 8 hours of abstinence in monkeys chronically administered PCP.³⁰

Effects of PCP in Children

Ikonomidou et al. point out that during the period of rapid growth of the mammalian brain, neuronal apoptosis can be triggered by the transient blockade of the glutamate.³¹ Olney's animal experimental findings support the induction of neuronal cell death by NMDA antagonists like PCP. Different brain regions display different age-dependent vulnerabilities to NMDA receptor-blocking drugs, leading to different patterns of neuronal loss depending on the time of exposure.³² In humans, the brain growth spurt period starts in the sixth month of gestation and extends to the third year of life.³¹

Thus, young children are very sensitive to PCP, and develop serious neurologic signs with minimal exposure. They can become intoxicated from passive inhalation of secondhand smoke, or by ingesting the butts of PCP-impregnated cigarettes.¹³ These signs may present as listlessness, irritability, and poor feeding in newborns, and should immediately raise suspicion for intoxication.¹³ Different forms of choreoathetosis were seen in half of the cases. Hypertension and seizures are the next most common signs in infants, seen 30 and 20% of the time, respectively.¹³ Blood pressure elevations are common during the first six hours of intoxication, but usually resolve spontaneously.

Seizures, apnea, and respiratory depression are documented more frequently in children than adults; however, they rarely require intubation. Violent behavior is less common in children, which may explain the lack of mortality reported in children.^{13, 33} Mild intoxication in children may present as lethargy alternating with agitation, a dull trance-like stare, horizontal or vertical nystagmus, miosis, truncal ataxia, choreoathetosis, hypersalivation, and mild hypertension, and may last from 12 hours to over three days.^{9, 10, 33} Severe intoxication, including unresponsiveness with an open-eyed stare and short intermittent generalized seizures, may last up to six days.³³

Diagnosis

Phencyclidine intoxication is a diagnosis that must be suspected clinically so that the appropriate tests are ordered for confirmation. The differential diagnosis of the clinical picture created by PCP includes other intoxications, schizophrenia, intracranial pathology, hypoxia, hypoglycemia, hyponatremia, sepsis, meningitis and encephalitis, thyroid storm, and neuroleptic

malignant syndrome. PCP intoxication shares many features with overdoses of cocaine, amphetamines, anticholinergic agents, hallucinogens, and withdrawal from benzodiazepines. Therefore, a qualitative urine toxicologic screen has become mandatory standard of care for any patient, infant or adult, with altered mental status of unknown etiology.¹³ Although earlier literature describes three dose-related stages of PCP intoxication, quantitative PCP levels do not correlate well with clinical findings and thus should not guide clinical management.^{1, 6, 13, 20, 22}

The simplest way to confirm suspected PCP intoxication is via qualitative chromatographic or immunologic urine drug screen, since 9% of the active drug is excreted directly by the kidneys.¹¹ The urine is usually positive for 2-4 days after PCP use, but after chronic exposure the test results can be positive for over a week.³⁴

Several drugs like diphenhydramine, dextromethorphan, and venlafaxine and its derivatives may cause a urine specimen to test positive for PCP if tests other than gas chromatography/mass spectrophotometry (GS/MS) are used, such as the fluorescence polarization immunoassay or high pressure liquid chromatography.^{35, 36}

Bond et al. report a case of a 13-year-old girl who presented with a massive venlafaxine overdose and a false positive fluorescent-polarized immunoassay for phencyclidine in the urine. The GS/MS, however, identified venlafaxine as the only substance present in the serum.³⁷ Conversely, urine drug screens may be negative in the face of alkaline urine, since phencyclidine is a weak base. In this situation, saliva or gastric contents can be analyzed for PCP.³³

Because PCP-induced seizures, myoclonic activity, and trauma may result in rhabdomyolysis, serum potassium, blood urea nitrogen, creatinine, and creatine phosphokinase (CPK) should be ordered any time it is suspected. Serum CPK is the preferred screening method for rhabdomyolysis, because the presence of urinary myoglobin may be transient.^{22, 26} Capillary and serum blood glucose levels are also recommended since PCP has been associated with hypoglycemia in 20% of patients.⁹

Management

The management of PCP intoxication begins just as any other intoxication would. First, the patient's airway, breathing, circulation, thermoregulation, and neurologic status must be stabilized. The patient should then be restrained and sedated if necessary to prevent self-inflicted injury, which is the most common cause of morbidity and mortality in these patients.^{6, 14, 23, 29, 38}

Chemical restraints are preferred over physical restraints, which may exacerbate the risk of rhabdomyolysis.^{9, 22, 26} Benzodiazepines are recommended in patients without psychosis, as antipsychotics can amplify PCP-induced hyperthermia, dystonic as well as anticholinergic reactions, and lower the seizure threshold.^{3, 38} However, haloperidol has been described as a useful treatment

for PCP-induced psychosis provided the patient is not hyperthermic. The risks of lengthening of the QT interval, torsade de pointes and adverse neurologic effects limit the use of haloperidol in PCP-intoxicated patients. Due to their more favorable side effect profile, atypical antipsychotics like olanzapine or ziprasidone would be a better choice than haloperidol when treating PCP-induced agitation and psychosis. Diphenhydramine 50mg IV or 1mg/kg can be used to treat PCP-induced (or haloperidol-induced) dystonic symptoms, but should be administered after a urine sample is obtained for toxicologic screening, since it may cause the specimen to test falsely positive for PCP.¹³ Diphenhydramine may also cause tachycardia and problems with thermoregulation via its anticholinergic effects, so the benefits of its use should be weighed against its potential side effects. Patients should then be closely observed in a dark and quiet environment, with minimal auditory and tactile stimuli so as not to provoke violent outbursts.³

As with all intoxications, a blood glucose measurement should be obtained, and 100 mg thiamine and dextrose 50% should be administered if the blood sugar is abnormally low. Naloxone, to treat potentially coingested opiates, is not necessary in patients with adequate respiration.

Gastric lavage is controversial, and should only be used after consultation with a toxicologist. Activated charcoal at standard dose of 1 g/kg is strongly recommended in suspected PCP ingestion to prevent further absorption of the drug during its entero-hepatic recirculation, and serial doses may be necessary to prevent later redistribution from lipid stores.^{34, 39} An intoxicated patient should always be assessed first for deterioration of mental status, aspiration potential and possible airway complications before administering charcoal.

Patients must be on continuous cardiac monitoring because of the frequency and severity of cardiac symptoms.^{9, 33} Diastolic hypertension >115 mmHg may be transient, or fall after sedation, eliminating the need for further treatment.

There are case reports of intracerebral hemorrhage secondary to hypertension.⁴⁰ Additionally, Welch et al. describes several cases of intracerebral hemorrhage in infants that were not visualized on CT and have been diagnosed by lumbar puncture, suggesting that physicians should have a low threshold for performing this procedure in the face of hypertension and neurologic abnormalities, especially in children.¹⁰

In the past, PCP elimination was thought to be enhanced by urinary acidification via ammonium chloride or ascorbic acid; however, this is no longer recommended because acidic urine increases the risk of acute tubular necrosis secondary to myoglobinuria in rhabdomyolysis.^{22, 26} Furthermore, only 9% of PCP is excreted in the urine.^{11, 12} Urinary acidification will not affect the 91% that is metabolized by the liver, and thus will not increase overall removal of the drug. Hemodialysis is also ineffective because it simply removes the drug from the serum, clearing the path for redistribution from lipid stores. Hemodialysis is, however, a treatment option for renal failure caused by rhabdomyolysis. Renal failure is considered to

be far more dangerous than PCP intoxication; therefore patients with rhabdomyolysis should be aggressively treated with fluids, sodium bicarbonate, mannitol and furosemide.

Status epilepticus should be treated with airway protection and IV benzodiazepines or phenobarbital. The patient should not be paralyzed after rapid sequence intubation (RSI) because it is then virtually impossible to monitor whether seizures are still ongoing, short of continuous EEG monitoring.³⁸ Hyperthermia greater than 40°C may be the combined result of PCP-induced myotonic activity, seizures, and rhabdomyolysis, and should be aggressively treated with mechanical cooling measures. Benzodiazepines are a useful adjunct to prevent shivering and provide sedation.

Disposition

Patients with rhabdomyolysis, hyperthermia, altered mental status, seizures, significant injuries, or pediatric age require hospitalization. Children require continuous monitoring to note fluctuations in consciousness, cardiorespiratory stability, and for suction of excess oral secretions.

Mildly intoxicated patients should return to normal functioning four to eight hours after ingestion, whereas larger ingestions may require weeks. Infants have been reported to need from 48 hours to four days to recover.¹³ Delayed recovery should be closely monitored in the ICU, because these patients may experience depression, anxiety, and severe psychiatric disturbances in the post-high period.

Finally, it is important to investigate the source of intoxication, whether it be in an adult who is unknowingly inhaling PCP-laced marijuana cigarettes, or more tragically, a child who is unwillingly exposed to secondhand smoke.¹⁰

SUMMARY

In conclusion, phencyclidine is a unique, paradoxical drug that produces central nervous system depression and peripheral and central nervous system stimulation. Because of its relative safety and euphoric effects, we are beginning to see a recurrence of PCP's street popularity. Hallmark clinical findings of PCP intoxication are nystagmus, hypertension and a mental status, which is often described as dissociative anesthesia. In higher doses patients become unconscious and can succumb to pulmonary aspiration and cardiovascular collapse. The most disturbing behavioral effects of PCP are violent, aggressive and bizarre behavior with self-mutilation tendencies.

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