Massive Lindane Overdose with Toxicokinetics Analysis

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Abstract

Background Lindane is a possible carcinogen with known teratogenicity and immunologic and neurotoxic properties. Despite reports of seizures, coma, and death associated with its use as well as banning of its environmental use by the Environmental Protection Agency (EPA), the US Food and Drug Administration (FDA) still allows treatment with lindane as a second-line scabicide and pediculicide. We present a case of a massive suicidal ingestion of lindane in which the patient survived the ingestion, though he did expire shortly thereafter from an unrelated cause pre-discharge.

Methods Pharmacokinetic analysis of serum lindane concentrations was performed with Phoenix® WinNONLIN®. The estimated distribution half-life for lindane was 10.3 h, and the terminal half-life was 162.9 h, much longer than the previously reported terminal half-life of 25–36 h. Because of this long half-life, repeated lindane exposures may lead to accumulation of lindane in the tissues.

Result After overdose, toxicity may be delayed and full recovery may be prolonged.

Keywords Lindane · Pharmacokinetics · Scabicide · Pediculicide · Overdose

Introduction

Benzene hexachloride (1,2,3,4,5,6-hexachlorocyclohexane) was first synthesized by Michael Faraday in 1825. All eight stereoisomers of 1,2,3,4,5,6-hexachlorocyclohexane have been investigated for their insecticidal properties [1, 2]. The gamma isomer, commercially referred to as lindane, has the greatest potency as an insecticide [1]. Lindane is a possible carcinogen with known teratogenicity and immunologic and neurotoxic properties [3]. Medical grade lindane products are purified and contain 99 % gamma isomer [4]. Despite reports of seizures, coma, and death associated with its use as well as banning of its environmental use by the Environmental Protection Agency (EPA) [5], the Food and Drug Administration (FDA) still allows treatment with lindane as a second-line scabicide and pediculicide [6]. We present a case report of a patient who survived a non-accidental overdose of a concentrated lindane solution (though this patient subsequently died from an unrelated event). Analysis of serial lindane serum and tissue levels from postmortem analyses 12 days after ingestion demonstrated the highest serum levels ever reported and that lindane likely accumulates in tissues, and its terminal half-life is longer than previously reported.

Case Report

A 56-year-old male intentionally ingested approximately 12 oz of an insecticide containing 20 % lindane in a witnessed

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suicide attempt. Twenty minutes post ingestion, he was alert with a BP of 90/50 mmHg, pulse 80/min, respirations 18/min, and temperature 36 °C. Thirty minutes post ingestion, he vomited approximately 6 oz of white liquid that “smelled of petroleum distillate.” In the emergency department, the patient underwent gastric lavage until the effluent was clear and was administered 30 g of activated charcoal. His level of consciousness progressively declined, and at 75 min post ingestion, he was intubated for airway protection.

Between 3 and 14 h post ingestion, the patient had multiple seizures. The first was a focal seizure followed by three brief generalized tonic-clonic seizures, then an additional focal seizure. The seizures were treated with intravenous diazepam, phenobarbital, and phenytoin. Arterial blood pH was 6.76 and 7.05 after the initial focal seizure and the first generalized seizure, respectively. Treatment with three ampoules of sodium bicarbonate corrected the pH to 7.34. No further seizures occurred throughout the hospital course.

Eighteen hours after the ingestion, although still intubated and receiving supplemental oxygen, the patient was awake, responsive, and following commands appropriately. Arterial blood gases taken while on mechanical ventilation were pH 7.47, PCO₂ 33 mmHg, and PO₂ 158 mmHg. His urine was described as yellow and “greasy” appearing. An EEG obtained at this time showed no seizure activity. No further medications for treatment of seizure were administered following the initial episode. At 43 h post ingestion, he was extubated.

On hospital day 3, the patient developed runs of premature ventricular contractions and premature atrial contractions, which stopped after treatment with intravenous lidocaine. On hospital day 5, the patient developed atrial fibrillation/flutter which converted to normal sinus rhythm after 1 mg of digoxin and 5 mg of verapamil intravenously.

The patient’s neurological examination on hospital day 6 demonstrated an ataxic, wide-based gait. He was awake and alert but had slurred speech. He was described as paranoid and depressed with defects in higher mental functioning demonstrated by not being able to recognize figures traced on his palm and the inability to correctly multiply 3 times 17.

Repeat neurological examination on hospital day 12 revealed persistent abnormalities. He demonstrated poor memory, loss of task focus, and inadequate mentation. Although no longer ataxic, he demonstrated defects in fine motor coordination. Tragically, on this day, he successfully committed suicide by cutting his femoral artery.

Methods and Results

Permission was obtained from the patient’s family to analyze and report serum and tissue lindane levels. At autopsy, there were no gross or microscopic abnormalities of the brain, heart, liver, muscles, or kidney. The pesticide manufacturer analyzed serum and tissue for alpha, beta, gamma, and delta isomers of benzene hexachloride (BHC). The limits of detection of manufacturer’s serum assay for all the isomers were reported to be 0.01 mcg/mL except for beta-BHC, which had a limit of detection equal to 0.02 mcg/mL. The limit of detection for the tissue samples was 10 mcg/g. The results of the analyses are presented in the Table 1 and illustrated in Fig. 1.

Pharmacokinetic analysis was performed with Phoenix® WinNONLIN®. For ease of analysis, the dose was assumed to be 6 oz or 35 g based on the history. Both one-compartment and two-compartment models were evaluated. The best model fit of the data was determined by the Schwartz criterion (SC) and Aikake information criterion (AIC) provided in the WinNONLIN diagnostic packet. A two-compartment model (Fig. 1) best fit the data (one compartment SC=−10.26, AIC=−6.95; two compartment SC=−23.25, AIC=−17.73). A two-compartment model makes the assumption that, post absorption into the central compartment of highly perfused tissues, the drug distributes between the central and peripheral compartments at a variable rate. In this patient, the estimated distribution half-life for lindane was 10.3 h and the terminal half-life was 162.9 h.

Discussion

Previous studies have reported shorter half-lives for lindane than that observed in the current study. Feldman and Maibach [2] administered labeled lindane to healthy volunteers and found a urinary excretion half-life of 26 h after intravenous dosing. Rao et al. [7] reported a case of an ingestion of 8 oz of 20 % lindane; at 12 h, this patient had a serum lindane concentration of 1.3 mcg/mL. Analysis of the serum concentrations indicated a serum half-life of 24 h. Aks et al. [8] reported three cases of lindane ingestion; using only two points for half-life analyses, these authors reported a

Table 1 The concentration of various isomers of BHC from serum samples in mcg/mL and tissue in mcg/g obtained at autopsy

Isomer	Serum	Brain	SQ Fat	Muscle	Liver	Kidney
γ-BHC	0.248	1.77 ^a	132.83	2.02 ^a	7.38 ^a	6.11 ^a
^b Ratio	1	7.1	535.0	8.1	29.9	24.6
α-BHC	0.002 ^a	0.35 ^a	1.005 ^a	0.016 ^a	0.025 ^a	0.044 ^a
β-BHC	ND	ND	0.04 ^a	ND	0.007 ^b	ND
δ-BHC	ND	ND	0.035 ^a	ND	ND	ND

ND not detected

^a Below laboratory limit of detection

^b Tissue/serum ratio of γ-BHC (lindane)

Fig. 1 Plot of lindane concentrations over time

distributional lindane half-life of 2.5–4 h and a terminal half-life of 24–35 h.

The reported half-lives in the above cases were based on blood samples collected over a shorter period than the current case. The half-life reported by Feldman and Maibach [2] was based on only three urine collections during the first 24 h. Aks et al. [8] based their half-life estimates on samples obtained over 40 h while Rao et al. [7] had samples up to 120 h. If the terminal half-life is longer than the sampling period, the actual half-life cannot be accurately estimated. In the current case, serum levels were obtained over 282 h. Because of this extended sampling period, the actual elimination kinetics of lindane are more likely to be accurately described.

Modeling of the current patient's lindane serum concentrations revealed a two-phase process, an initial 24-h distribution phase and a terminal elimination phase of 163 h. Please note we are not considering a separate absorption phase apart from distribution in our analysis, though under certain circumstances, absorption of lindane may be quite prolonged [9]. Based on this analysis, it appears that the serum half-lives

described in prior reports actually described the first phase of a biphasic elimination process. This first phase is predominately the distribution of the lindane from the serum into fat and other tissues. The terminal half-life, which represents the metabolism and excretion of lindane from the body, appears to be much longer. This is consistent with the findings of Thybaud and Caquet [10] in freshwater snails which showed a 0.7-h half-life for lindane in the central compartment and a 130.2-h half-life in the peripheral compartment.

A study reported in the Swedish literature by Kolmodin-Hedman [11] measured plasma levels of lindane in exposed workers. The mean concentration 24 h after exposure was 4.0 ng/mL, and at 1 week post exposure, it was 2.2 ng/mL. This approximately 50 % decrease over 1 week is also consistent with the 163-h half-life estimate in this case.

For small ingestions, consideration of the terminal elimination phase and its half-life may not be clinically relevant because distribution into tissues is associated with improvement in CNS toxicity. However, for large ingestions, the terminal elimination phase for lindane must be considered.

Fig. 2 Plot of various liver function tests over time where GGT gamma glutamyltransferase, ALKP alkaline phosphatase, ALT alanine aminotransferase, AST aspartate

Using the modeled half-life of 163 h, it would take approximately 30 days to eliminate 95 % of the ingested BHC. This patient had unexpected cardiac arrhythmias on days 3–6 which required therapy. Further, this patient was still demonstrating residual neurological deficits at the time of his death 12 days later. Therefore, it is clear that for large ingestions, prolonged observation is warranted.

Unlike the patient reported by Rao et al [7], who died soon after ingesting a large amount of lindane, our patient survived the initial lindane ingestion. Further, it is likely that had he not been successful in his second suicide attempt, his lindane ingestion would not have been fatal. At autopsy, the gross and microscopic tissue examinations were essentially normal and even his liver enzymes which had been abnormal had leveled off or returned to normal by the time of his death (Fig. 2).

A difficulty in the interpretation of these findings is the lack of a true known dose. It is impossible to know the exact amount of lindane absorbed in this case—if all 12 oz of the 20 % solution that was reported to have been ingested had been absorbed then the amount would have been approximately 70 g. However, vomiting occurred and some was removed by gastric lavage.

In summary, we report a case of suicidal oral lindane ingestion. Analysis of serum samples from this patient indicated that the human elimination half-life for lindane is much longer than the 24–36 h previously reported. Although it was not possible to determine the exact half-life, it is thought to be closer to 160 h. Because of this long half-life, repeated exposures can lead to accumulation of lindane in the tissues. After overdose, toxicity may be delayed and full recovery may be prolonged.

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Conflict of Interest The authors whose names are listed on the title page certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), in the subject matter or materials discussed in this manuscript.

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