Brief Report

Neurotoxic Reaction to Lindane in an HIV-Seropositive Patient

An Old Medication's New Problem

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Scabies is a common infestation for patients of all ages throughout the world. One of the standard therapies for scabies is 1% lindane lotion. Lindane has been associated with neurotoxic reactions, specifically seizures. We describe a case of a middle-aged adult man with human immunodeficiency virus (HIV) infection who was found to have typical scabies and was treated with a single topical application of lindane. Two hours after the application, the patient experienced a new-onset generalized seizure. We believe that the triad of HIV infection, medications that reduce seizure thresholds, and percutaneous absorption factors, in the aggregate, induced the seizure. We believe that lindane should not be prescribed for patients with HIV infection.

Key words. HIV seropositivity; scabies; benzene hexachloride (lindane); administration, cutaneous; seizures.
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Scabies is a contagious pruritic dermatosis caused by the *Sarcoptes scabiei* mite. It continues to be a common infestation for people of all ages, especially among imprisoned or institutionalized populations.[1] For more than 40 years, one of the standard therapies for scabies has been 1% lindane lotion or cream.[2] Lindane has become the most commonly prescribed scabicide in the United States and throughout most of the world.[3]

Lindane has been associated with systemic adverse reactions including those affecting the nervous system.[2,4,5] One of the most serious sequelae involves neurological stimulation, producing, most notably, seizures. Seizures can lead to hypoxemic acidosis and can result in neurological deficits or death. Most reported and anecdotal cases of such adverse reactions have involved inappropriate use or ingestion. Neurotoxicity associated with appropriate use of the scabicide is rare and appears to involve those patients—infants, children, the malnourished, and the elderly—in whom concomitant factors increase cutaneous absorption.[6-8] We report a case of lindane poisoning in a 38-year-old prisoner with the human immunodeficiency virus (HIV).

Case Report

A 38-year-old Hispanic male prisoner, known to be HIV-seropositive for 2 years, was admitted to the psychiatry service at Kings County Hospital. The dermatology service was consulted approximately 3 weeks after his admission for evaluation of a generalized pruritic rash. The patient was alert and oriented and denied any medical history of cutaneous disorders or drug allergies. His height and weight were 168 cm and 72 kg, respectively.

Physical examination revealed numerous erythematous papules 1 to 2 mm in diameter. There were excoriations and lichenification in his finger webs, axilla, waist, and groin. Burrows were evident. No nodules in the groin area were noted. A scraping was positive for mites, eggs, and fecal pellets. A diagnosis of typical scabies was made. Additionally, the patient had mild seborrheic dermatitis of the scalp, face, neck, and trunk, and tinea cruris. At the

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time of examination, the patient was taking 100 mg of chlorpromazine twice daily, which had been initiated on the day of his admission for violent agitation. Neither the patient nor his family had a history of seizures.

Lindane 1% lotion was prescribed. The patient had been sponge-bathed approximately 45 minutes before 2 oz of the lotion was applied. After the medication was administered by one of the staff nurses, the patient dressed himself. Two hours later, he began experiencing generalized tonic-clonic seizure activity. Intravenous diazepam and phenytoin were administered. The seizure lasted approximately 30 minutes. During the interim, the patient's clothing was removed and his body was washed to remove residual lotion. He was intubated for severe hypoxic acidosis and transferred to the intensive care unit. No further seizures occurred.

Results of a toxicology screen and all blood tests at that time were within normal limits. Urine and blood cultures were negative. Cryptococcol and toxoplasmosis titers were within normal limits. A lumbar puncture revealed no abnormalities. A VDRL test was nonreactive. Acid-fast bacilli tests were negative. The CD4 count was 200 cells/μL. A chest radiograph showed no active disease. A computed tomographic scan of the head was interpreted as being consistent with encephalopathy. No enhancing intra- or extra-axial lesion was noted.

A physical examination in the intensive care unit revealed a postictal and confused patient. By day 5 after the seizure, a neurological examination found the patient to be significantly demented; he was able to follow simple commands and verbally communicate a few words with minimal comprehension. No cranial nerve abnormalities were noted and no weakness or sensory loss was evident. There was a mild right upper extremity tremor and a generalized hyperreflexia with positive Babinski's signs bilaterally. Frontal release signs were present. On day 7 postseizure, an electroencephalogram was performed and interpreted as consistent with encephalopathy. The patient's rash gradually worsened over the next 8 days. Permethrin 5% cream was prescribed on day 9 postseizure. His rash gradually resolved over the next several days.

Gas chromatography studies performed 18 hours after the seizure identified a lindane serum concentration level of 46 parts per billion (PPB). At the laboratory where the studies were done, levels greater than 20 PPB are considered toxic. Results of sequential serum concentrations are shown in Figure 1. Cerebral spinal fluid levels were not reported because of a technical error. The patient's neurological status has remained stable. No new seizure has occurred in the 3 months since his initial seizure.

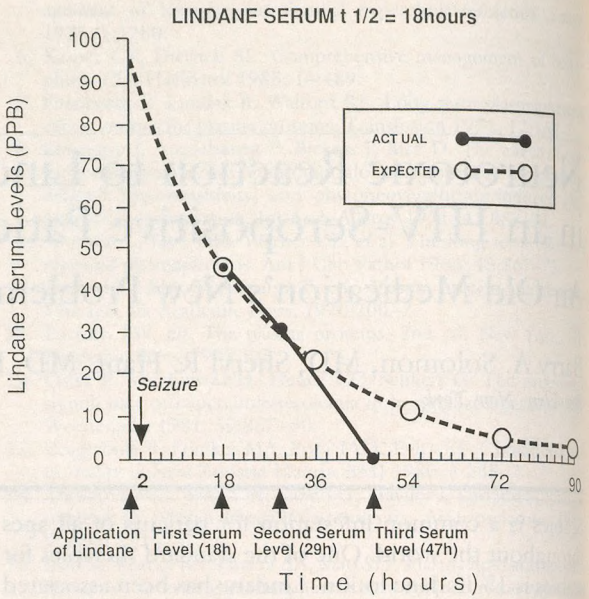

Figure 1. Plotted actual and expected serum lindane levels recorded in hours after topical application utilizing a lindane serum t ½=18 hours. PPB denotes parts per billion.

Background

Our case appears to be unique in the literature. It is the report of a male adult with mild to moderate epidermal barrier dysfunction. His medication and medical condition may have reduced his seizure threshold sufficiently so that a single topical application of lindane induced a generalized seizure. Since several factors may have independently combined at one instant to induce the patient's seizure, we will review each one separately.

Percutaneous Absorption

Percutaneous absorption is a complex process that has been studied extensively but is still poorly understood and highly individualized.[9,10] Wester and Maibach,[9] in their classic review on percutaneous absorption, emphasized the multilevel complexities involved in percutaneous absorption, several of which apply to this case.

HYDRATION. Studies and reported cases have demonstrated that hydration of the skin increases penetration of certain drugs, including lindane.[2,8,9,11] This results in an elevated systemic absorption probably secondary to increased percutaneous absorption with heat-associated dermal vasodilatation.

EPIDERMAL BARRIER DYSFUNCTION. Epidermal barrier dysfunction affords greater systemic absorption of medications and contributes to the toxic reaction.[12] Wester and Maibach[9] demonstrated that stripping of the stratum

corneum increased penetration by a factor of 4, and when the site was occluded, increased penetration by a factor of 20. Except for malnourishment cases,[13] all prior case reports of seizures induced by topically applied lindane have involved inappropriate or multiple applications of lindane, or lindane treatment of infants or the elderly. Ginsburg et al[11] demonstrated that children with large areas of weeping excoriated skin had higher lindane blood levels than did siblings with normal skin. Friedman[7] reported a case of a boy aged 3 years 9 months who had congenital ichthyosiform erythroderma but no history of seizures. The child bathed 30 minutes before routine application of lindane and experienced a tonic-clonic seizure 3 hours after the application.

AGE. Previously reported cases of seizures induced by topically applied lindane have involved children or the elderly.[7,8,13] In infants and children, the ratio of cutaneous surface area to body weight can be up to three times that of an adult.[9] Therefore, when the application area of skin is equal in the infant and the adult, systemic absorption and availability in the infant is greater. In the elderly, the skin undergoes changes, mostly degenerative, which affect epidermal barrier function.[8] It is at these extremes of age that the risk of systemic absorption of lindane increases.

ANATOMIC SITE. Extent of absorption depends on the anatomic site to which the compound is applied.[14] Compared with the cutaneous absorption rate of the forearm, the genitalia (eg, scrotum) usually have a 42-fold and the axilla a 3.6-fold increased cutaneous absorption rate.[9,10,15]

PERCUTANEOUS ABSORPTION OF LINDANE. Feldmann and Maibach[10] determined that after applying 0.25% lindane solution to normal human forearm skin for 24 hours, approximately 10% of the lindane was absorbed. Ginsburg et al[11] demonstrated in children that peak blood concentrations of lindane are observed at 6 hours after routine topical application of 1% lindane lotion. In Friedman's case report,[7] the child had a seizure approximately 3 hours after a single topical application of lindane cream.

Seizure Threshold

HIV INFECTION AND SEIZURES. Seizures occur frequently in HIV-infected patients.[16] In a hospital-based study in New York City, a 12% incidence of new-onset seizures in patients with HIV infection was reported.[17] Detectable causes include mass lesions, infections, and HIV encephalopathy. Holtzman et al[18] demonstrated that HIV encephalopathy was the identified cause of seizures in 24% of HIV-infected patients with new-onset seizures. The presumed mechanisms include the diffuse muting of the subcortical driving force for normal brain activity, possible diffuse cortical irritability, and other effects of the pathologic changes induced by HIV.

MEDICATIONS AND SEIZURES. Certain medications, especially those that affect the central nervous system (CNS), are potentially epileptogenic. Chlorpromazine is an antipsychotic drug that produces a proconvulsant effect by lowering the seizure threshold, even at recommended dosages.[19] Lindane is a fat-soluble compound that has the ability to be stored in human tissue and in the CNS for protracted periods,[2] even after topical application.[4,20] Litterst and Miller[21] demonstrated in dogs that levels of lindane in the CNS were 5 to 12 times higher than the levels of lindane in the blood. In guinea pigs, Solomon et al[22] found that the levels of lindane in the brain were 10 times greater than in the blood following topical application of 1% lindane. Davies et al[4] were the first to report that after topical application, levels of lindane in human brains demonstrated a higher (threefold) concentration as compared with serum levels. One of lindane's adverse side effects includes seizures.

Discussion

The patient's age and mild to moderate epidermal barrier dysfunction differentiate this case from previously reported cases of seizure induced by topically applied lindane. Regarding the cutaneous factors, the patient was sponge-bathed prior to application of the medication. Based on case reports of seizures after topical lindane application, it is clear that there is increased percutaneous absorption after hydration. Further, the patient was HIV-seropositive. Patients with HIV have been noted to have higher mite burdens[23] and extensive, exaggerated invasion, often necessitating repeated or sequential treatment.[24] Our patient also had a mild degree of seborrheic dermatitis and a moderate degree of inflamed tinea cruris. These are all important observations because in this scenario, several of Wester and Maibach's[9] factors of percutaneous absorption came into play. First, lindane was applied generally, in particular to the scrotum and axilla. The concomitant inflammation from the tinea and seborrheic dermatitis and exaggerated infestation enhanced the normal percutaneous absorption of the medication. Second, the replacement of the patient's street clothes after application of the medication could be perceived as tantamount to semiocclusion. Under such circumstances, a 4- to 20-fold increase in cutaneous penetration ratio could occur.[9]

Neurologically, subcortical structures, primarily the thalamus, have excitatory and inhibitory input on the synchronization of cortical neurons.[25] Further, there is a 3- to 12-fold preferential storage of lindane in the CNS as

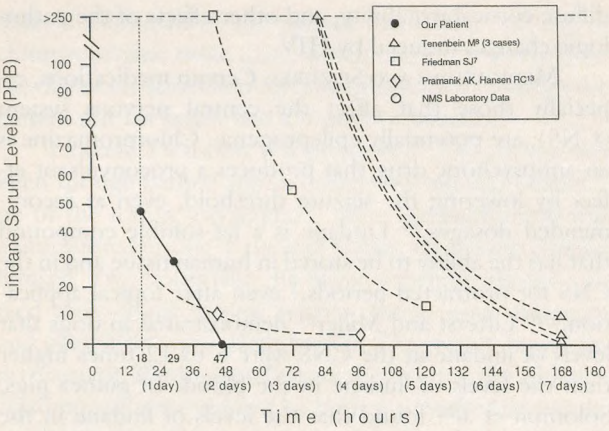

Figure 2. A comparison of serum levels in all reported cases of seizure induced by a single topical application of lindane. PPB denotes parts per billion. (NMS Laboratory Data obtained through personal communication with the director, 1994.)

compared with serum. In this patient, confounding factors (HIV infection and medications) affecting both the subcortex and cortex allowed for the propagation of epileptogenic activity.

After review of prior case reports, two questions remain: (1) was the patient able to cutaneously absorb a sufficient amount of lindane in 2 hours to cause his seizure? and (2) was the seizure caused by a single factor, such as HIV infection, or by multiple factors?

The first issue is whether the patient would have had a seizure within 2 hours after the application if lindane had been the only inciting agent. There is no reason to believe that peak serum levels at 6 hours[11] are necessary or sufficient to initiate a seizure, especially in certain persons. Friedman[7] reported a case of seizures induced by topically applied lindane after only 3 hours.

The next issue is whether the toxic serum level of lindane (46 PPB) could have, by itself, induced a seizure in this adult patient. Figure 2 demonstrates a comparison of serum lindane levels in all reported cases of seizures induced by a single topical application. Tenenbein[8] reported lindane-induced seizures in three elderly patients, and Friedman[7] in one young child. Serum lindane levels for all these patients have been extrapolated to a time of 18 hours postseizure to time-adjust their levels with our patient's. NMS Laboratory, which performs a majority of our region's lindane levels, has data for eight single-application seizure cases, all of which had serum levels greater than 80 PPB at 18 hours (personal communication, director, NMS Laboratory, 1994). Figure 2 demonstrates that at 18 hours, serum lindane levels of all reported cases, except for the case of a marasmic infant reported by Pramanik and Hansen,[13] were greater than 80 PPB. When compared with previously reported cases of seizure induced by a single topical application of lindane, our patient's serum level of lindane was not quite one half, and in some cases, less than one sixth the level of the others. Thus, it is possible that our patient's seizure was solely a result of the toxic levels of lindane. Furthermore, several similar episodes of seizures in HIV-seropositive patients following application of lindane that occurred in several San Francisco clinics recently have been communicated to two of the authors (B.A.S., E.M.C.).

Could the seizures have been related solely to the patient's HIV infection and encephalopathy? We cannot prove the negative. It is possible that a patient could have his first and only seizure 2 hours after lindane was applied to his body without lindane being a factor.

Conclusions

We believe that in this case the triad of medications (chlorpromazine and lindane), HIV infection, and percutaneous absorption factors (epidermal barrier dysfunction, skin hydration, and occlusion) were sufficient in combination to reduce the patient's seizure threshold so that a single application of lindane induced a seizure.

The National Pediculosis Association (NPA) established a public reporting registry in May 1994 for issues related to scabies and lice (personal communication, Deborah Altschuler, Executive Officer, NPA, October 24, 1994). Of the initial 280 adverse drug reactions reported as of September 1994, 69.3% involved the use of lindane. The reported reactions were primarily seizures, behavioral changes, neuromuscular complaints, and complications with pregnancy and delivery. The NPA data suggest that there is a greater incidence of severe adverse reactions associated with the use of lindane than previously believed and that the *improper* application of lindane is the rule rather than the exception.

It is difficult to manage scabies in patients with HIV, particularly those who are severely immunosuppressed. Repeated treatment with a scabicide and use of sequential agents may be necessary. We recommend against prescribing lindane for patients with HIV infection or a reduced seizure threshold from any cause. If lindane is used as a scabicide, we recommend the establishment of protocols, the salient features of which are listed in the Appendix.

References

1. Estes SA, Estes J. Therapy of scabies: nursing homes, hospitals, and the homeless. Semin Dermatol 1993; 12:26–33.
2. Solomon LM, Fahrner L, West DP. Gamma benzene hexachloride toxicity: a review. Arch Dermatol 1977; 113:353–7.
3. Schacter B. Treatment of scabies and pediculosis with lindane preparations. J Am Acad Dermatol 1981; 5:517–27.

4. Davies JE, Dedhia HV, Morgade C, et al. Lindane poisonings. Arch Dermatol 1983; 119:142–4.
5. Milby TH, Samuels AJ, Ottdooni F. Human exposure to lindane; blood lindane levels as a function of exposure. J Occup Med 1968; 10:584–7.
6. Telch J, Jarvis DA. Acute intoxication with lindane (gamma benzene hexachloride). Can Med Assoc J 1982; 126:662–3.
7. Friedman SJ. Lindane neurotoxic reaction in nonbullous congenital ichthyosiform erythroderma. Arch Dermatol 1987; 123:1056–8.
8. Tenenbein M. Seizures after lindane therapy. J Am Geriatr Soc 1991; 39:394–5.
9. Wester RC, Maibach HI. Cutaneous pharmacokinetics: 10 steps to percutaneous absorption. Drug Metab Rev 1983; 14:169–205.
10. Feldmann RJ, Maibach HI. Percutaneous penetration of some pesticides and herbicides in man. Toxicol Appl Pharmacol 1974; 28: 126–32.
11. Ginsburg CM, Lowry W, Reisch JS. Absorption of lindane (gamma benezene hexachloride) in infants and children. J Pediatr 1977; 91:998–1000.
12. Lange M, Nitzsche K, Zesch A. Percutaneous absorption of lindane in healthy volunteers and scabies patients. Arch Dermatol Res 1981; 271:387–99.
13. Pramanik AK, Hansen RC. Transcutaneous gamma benezene hexachloride absorption and toxicity in infants and children. Arch Dermatol 1979; 115:1224–5.
14. Feldmann RJ, Maibach HI. Regional variation in percutaneous penetration of 14C cortisol in man. J Invest Dermatol 1967; 48: 181–3.
15. Maibach HI, Feldmann RJ. Regional variation in percutaneous penetration in man. Arch Environ Health 1971; 23:208–11.
16. McArthur JC. Neurologic manifestations of AIDS. Medicine 1987; 66:407–35.
17. Wong MC, Suite ND, Labar DR. Seizures in human immunodeficiency virus infection. Arch Neurol 1990; 47:640–2.
18. Holtzman DM, Kaku DA, So YT. New-onset seizures associated with human immunodeficiency virus infection: causation and clinical features in 100 cases. Am J Med 1989; 87:173–7.
19. Oliver AP, Luchins DJ, Wyatt RJ. Neuroleptic induced seizures. Arch Gen Psychiatry 1982; 39:206–9.
20. Kramer MS, Hutchinson TA, Rudnick SA, et al. Operational criteria for adverse drug reactions in evaluating suspected toxicity of a popular scabicide. Clin Pharmacol Ther 1980; 27:149–55.
21. Litterst CL, Miller E. Distribution of lindane in brains of control and phenobarbital pretreated dogs at the onsent of lindane-induced convulsions. Bull Environ Contam Toxicol 1975; 13:619–24.
22. Solomon LM, West DP, Fitzloff IF, et al. Gamma benzene hexachloride in guinea-pig brain after topical application. J Invest Dermatol 1977; 68:310–2.
23. Funkhouser ME, Omohundro C, Ross A, et al. Management of scabies in patients with human immunodeficiency virus disease [letter]. Arch Dermatol 1993; 129:911–3.
24. Orkin M, Maibach HI. Scabies therapy—1993. Semin Dermatol 1993; 12:22–5.
25. Dempsey EW, Morrison RS. The production of rhythmically recurrent cortical potentials after localized thalamic stimulation. Am J Physiol 1941/2; 135:293–300.

Continued on page 296