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CASE REPORT

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Intravenous Abuse of Propylhexedrine

The Benzedrex® nasal inhaler is an over-the-counter device used for the symptomatic treatment of nasal congestion resulting from head colds and hay fever. The active ingredient is propylhexedrine, a local vasoconstrictor. While only two deaths due to propylhexedrine are in the medical literature [*1*], abuse of the drug occurs with greater frequency than realized. Since 1974, the Dallas County Criminal Investigation Laboratory has detected propylhexedrine in syringes in twelve cases submitted by local police agencies. In a recent six-month period, the Office of the Medical Examiner for Dallas County has encountered three deaths resulting from intravenous injection of propylhexedrine as well as two deaths from other causes in which the deceased had been injecting this drug. Two of the individuals dying of propylhexedrine abuse showed vascular changes in the lungs, apparently caused by chronic intravenous injection of this drug.

Case Reports

Case 1

A 19-year-old Negro male was found lying unresponsive in the street. He was transported to Parkland Memorial Hospital where he was pronounced dead. The case was then referred to the Medical Examiner's Office. Additional information obtained prior to the autopsy disclosed that the deceased had been "shooting drugs" all afternoon in a nearby apartment. Witnesses stated that he had removed the cotton wick from Benzedrex® nasal inhalers, heated this material in water, and then injected the solution intravenously. Empty Benzedrex® containers and a syringe were recovered from the apartment.

Postmortem examination revealed needle tracks in the right antecubital fossa with recent hemorrhage in the underlying subcutaneous tissue. The heart weighed 340 g and was normal in configuration. The right and left lungs weighed 800 and 750 g, respectively. On sectioning, the parenchyma was firm and congested. Microscopic examination of the lungs revealed massive desquamation of alveolar lining cells, focal intra-alveolar hemorrhage, and acute passive congestion. Neither foreign body granulomata nor

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refractile material visible under polarized light was present in the lungs. The muscular arteries of the lungs appeared normal. The liver showed an increased number of mononuclear cells in the portal areas, a finding often seen in individuals with a history of intravenous drug abuse. Comprehensive toxicologic screening for alcohols; alkaline, acidic, and neutral drugs; and narcotics revealed only the presence of propylhexedrine. Table 1 gives the concentrations of propylhexedrine found in the autopsy specimens.

TABLE 1—*Deaths from propylhexedrine.*

Tissue	Case 1	Case 2	Case 3
Blood, mg/dl	0.20	0.03	0.13[a] 0.16[b]
Vitreous, mg/dl	0.11	0.05	0.22
Urine, mg/dl	6.95	...	...
Bile, mg/dl	0.94	...	...
Liver, mg/100 g	0.74	0.13	0.58
Kidney, mg/100 g	0.40	0.18	0.53

[a] Antemortem blood sample, 3 h prior to death.
[b] Postmortem blood sample.

Case 2

A 17-year-old Negro female was found dead, facedown on the bathroom floor. According to her sister, she had a history of drug abuse. Two months prior to her death, she had passed out for 5 h after injecting propylhexedrine. On the floor next to the body was a cap from a Benzedrex® inhaler and a syringe. Postmortem examination revealed needle puncture sites in both arms with recent hemorrhage in the left antecubital fossa. The heart weighed 300 g and showed right ventricular hypertrophy, with the right ventricle 7 mm thick. The right and left lungs weighed 700 and 600 g, respectively. On sectioning, the pulmonary parenchyma was congested with a rubbery consistency. Microscopic examination revealed severe medial hypertrophy and intima hyperplasia of the small muscular arteries of the lungs (Fig. 1). Plexiform and angiomatous lesions were absent. The alveolar septa were thickened, secondary to diffuse fibrosis and acute passive congestion. Birefringent crystalline material, embedded in foreign-body granulomata, was present in the pulmonary parenchyma. Toxicological screening for volatile substances; acid, alkaline, and neutral compounds; and narcotics was negative, except for the presence of propylhexedrine (Table 1).

Case 3

A 24-year-old Negro male was brought to Parkland Memorial Hospital in a semiconscious condition, with shallow respiration and no palpable pulse. He had been found unconscious by his wife, who, while in another room, had heard him collapse. The wife stated that he was a heroin user but had not used this drug in over six months. On admission, he suffered a respiratory arrest and aspirated. He was resuscitated and his blood pressure was maintained by vasopressor drugs. Following two additional episodes of cardiorespiratory arrest, the patient died 3 h after admission. Blood was obtained on admission for toxicologic analyses.

Postmortem examination revealed the heart to weigh 360 g. There was right ventricular hypertrophy with the right ventricle 7 mm thick. The right and left lungs weighed 850 and 700 g, respectively. The lungs were airless with a rubbery consistency. Microscopic examination of the lungs revealed foreign body granulomata containing birefringent crystalline material. Approximately the same number of granulomata were present in this case as in Case 2. The alveolar septa were thickened, secondary to interstitial

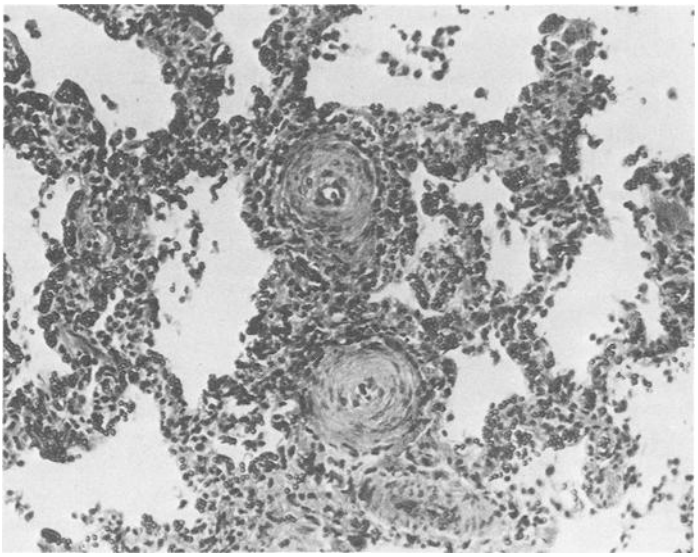

FIG. 1—*Hypertrophy and hyperplasia of small muscular arteries of the lung and thickened alveolar septa in Case 2.*

fibrosis and acute passive congestion. The small muscular arteries of the lungs showed a moderate degree of intimal hyperplasia and medial hypertrophy. Comprehensive toxicological screening was negative, except for the presence of propylhexedrine (Table 1).

Case 4

A 23-year-old Negro male was placed in the Dallas County Jail in an excited, apparently intoxicated state. He was seen by a fourth-year medical student, who found him hyperactive, excited and almost "climbing the walls." He was then placed in a cell. Eighty minutes later, he was found dead in a sitting position with his head suspended by a noose constructed from his shirt.

Postmortem examination revealed neck injuries, secondary to the hanging, as well as other minor contusions and abrasions, which occurred during the arrest. There were needle tracks in both antecubital fossae with recent hemorrhage in the subcutaneous tissue of the left fossa. The heart weighed 380 g and was grossly unremarkable. The right and left lungs weighed 450 and 420 g, respectively. Microscopic examination of the lungs revealed foreign-body granulomata and refractile crystalline material in the same quantity as in Cases 2 and 3. The alveolar septa were unremarkable. There was no hypertrophy or hyperplasia of the small muscular arteries of the lungs. Complete toxicological screening revealed a blood alcohol concentration of 186 mg/dl and the presence of propylhexedrine (Table 2).

TABLE 2—*Propylhexedrine concentrations in deaths from other causes.*

Tissue	Case 4[a]	Case 5
Blood, mg/dl	0.25	0.08
Vitreous, mg/dl	0.05	...
Urine, mg/dl	...	...
Bile, mg/dl	0.57	...
Liver, mg/100 g	0.44	...
Kidney, mg/100 g	0.21	...

[a] Blood ethanol: 186 mg/dl.

Case 5

A 27-year-old Negro male and two friends attempted to hijack some marijuana. Attempting to flee, he was shot twice in the back. He was transported to Parkland Memorial Hospital where he died approximately 2 h after the shooting.

At autopsy, there were two gunshot wounds of the back with associated injuries of the internal organs. The heart weighed 285 g and appeared unremarkable. The right and left lungs weighed 700 and 500 g, respectively. Microscopic examination of the lungs revealed foreign-body granulomata and refractile material in approximately the same quantity as in Cases 2, 3, and 4. A few small foci of early bronchopneumonia were present. The alveolar septa were unremarkable. There was no hypertrophy or hyperplasia of the small muscular arteries of the lungs. A routine drug screen on the blood for alcohols, and acidic, alkaline, and neutral drugs, including free morphine, revealed only the presence of propylhexedrine (Table 2).

Experimental Observations

A recently purchased Benzedrex® inhaler was utilized by an experimental subject for the purpose of obtaining blood concentrations after *inhalation* of propylhexedrine. The subject placed the inhaler in each nostril and inhaled 15 times while occluding the opposite nostril. After completion of the inhalation, blood samples were taken at 10 and 30 min. Urine specimens were collected at the 10-min interval and at 135 min. The results of analysis of these specimens are shown in Table 3.

TABLE 3—*Propylhexedrine concentrations after inhalation.*

Specimen	Propylhexedrine Concentration, mg/dl
Blood (10 min)	0.001
Urine (10 min)	0.004
Blood (30 min)	0.001
Urine (135 min)	0.060

Toxicological Method

Propylhexedrine in body fluids and organs was detected and quantitated by gas chromatography, after extraction by *n*-butylchloride, using a modification of the procedure of Foerster and Mason [*2,3*]. A 5-ml aliquot of body fluid or 5 ml of a tissue homogenate (1:4 in water) was treated as described. In some cases, qualitative confirmation was made by gas chromatography-mass spectrometry. Pure propylhexedrine for quantitation was obtained by extraction of the cotton wick from a new Benzedrex® inhaler.

Discussion

Propylhexedrine, the active ingredient in the Benzedrex® nasal inhaler, was developed as a substitute for amphetamine, which had been used in Benzedrine® inhalers. Benzedrine® inhalers were removed from the market because they were a readily available source of amphetamine and were subject to extensive abuse.

Propylhexedrine is a potent local vasoconstrictor that has only one twelfth of the central nervous system stimulating effect of amphetamine sulfate.[3] The Benzedrex®

[3] Personal communication, H. J. Anlage, Smith Kline & French Laboratories, Philadlephia, July 1973.

inhaler contains 250 mg of propylhexedrine, 4.5 mg of menthol, and various aromatic compounds. Disassembling the Benzedrex® inhaler reveals a cotton plug saturated with these chemicals. Abusers of the Benzedrex® inhalers either swallow the cotton plug or heat it in water, dissolving propylhexedrine into a solution for intravenous injection (Fig. 2).

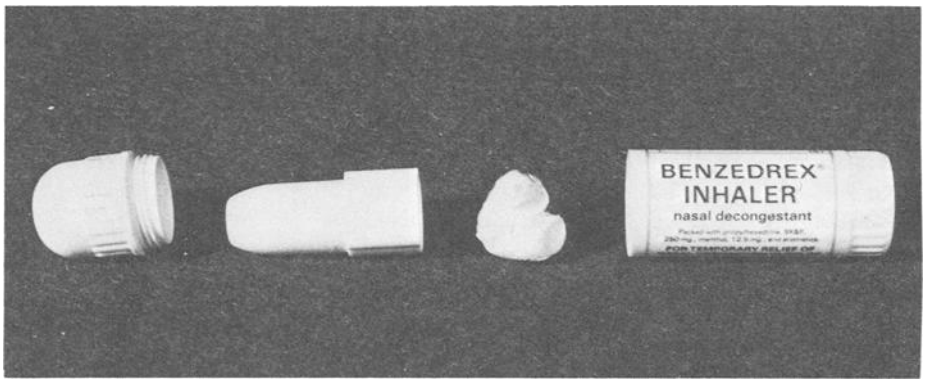

FIG. 2—*Disassembled Benzedrex® inhaler with cotton plug.*

Oral ingestion of as little as 250 mg of propylhexedrine has caused palpitation, headache, chest pain, shock, and myocardial infarction in a 22-year-old man [*4*]. While such intoxication had been described, the study by Sturner et al was the first report of deaths from this compound [*1*].

Our experimental observations in the subject inhaling propylhexedrine establish blood concentrations to be expected after "therapeutic" use (Table 3). The maximum quantity detected at 10 min after inhalation (0.001 mg/dl) was only $\frac{1}{30}$ of that quantity detected in the blood of the individual showing the lowest blood concentration of the seven cases of propylhexedrine abuse (Table 1, Case 2). The maximum recorded blood concentration of propylhexedrine (0.27 mg/dl) (Table 4, Case 1S) in an individual injecting the substance intravenously represents 270 times that found after inhalation.

TABLE 4—*Propylhexedrine concentrations in previously reported deaths* [1].

Tissue	Case 1S[a]	Case 2S
Blood, mg/dl	0.27	0.18
Vitreous, mg/dl	...	0.17
Urine, mg/dl	...	1.26
Bile, mg/dl	...	...
Liver, mg/100 g	1.18	0.28
Kidney, mg/100 g	0.95	0.15

[a] Blood ethanol: 122 mg/dl.

The three deaths due to propylhexedrine reported in this paper represent a spectrum of reactions to this drug. Case 1 is an example of acute intoxication. The blood concentration of 0.20 mg/dl is 200 times that found after inhalation. Microscopic examination of the lungs in Case 1 revealed normal-appearing arteries and alveolar septa with no foreign granulomata present. Case 2 represents the other end of the spectrum. It shows the sequelae of chronic abuse of this medication. The blood

concentration of 0.03 mg/dl is relatively low compared to the first case. The small pulmonary muscular arteries showed medial hypertrophy and intima hyperplasia. The right ventricle was hypertrophied. It is our suggestion that the vasculature changes are due to the direct action of propylhexedrine, a potent vasoconstrictor on the pulmonary vasculature. We feel that repeated injections of this drug lead to hypertrophy and hyperplasia of the vessel walls, pulmonary hypertension, and subsequent cor pulmonale. The pulmonary foreign-body granulomata, secondary to intravenous drug injection, are not felt to be the cause of these vascular changes. The number of granulomata present is not unusual for individuals who inject illicit drugs intravenously. With other illicit drugs, the vascular changes seen in this case are not present. Further evidence arguing against the granulomata as the cause of the vascular lesions is the observation that in Cases 4 and 5, in which no pulmonary vascular changes were present, there were approximately the same number of granulomata as in Case 2.

Even though there was only a small amount of propylhexedrine in the blood in Case 2, we believe it to have had sufficient pressor effect that, when added to a cardiorespiratory system already compromised by severe pulmonary disease, death ensued. Another possibility that has to be considered is that the low quantity of drug present at death could be due to metabolism during several hours of comatose survival after injection of the drug. The low liver and kidney concentrations, however, provide evidence against such a supposition.

Case 3 lies between the two extremes. The blood concentrations of propylhexedrine were intermediate in quantity. The lungs showed a moderate degree of hypertrophy of the muscular arteries. The heart exhibited right ventricular hypertrophy.

That there must be a wide range of susceptibility to the toxic action of this drug can be seen by comparing the blood concentrations in the three cases in which death was due to propylhexedrine to those in the two deaths (Cases 4 and 5) that were not due to propylhexedrine (Tables 1 and 2). The blood concentration in Case 4 is the highest of all the five cases, yet death was due to hanging.

Review of the cases reported by Sturner et al [*1*] indicated that their first case is an example of acute intoxication with a blood concentration of 0.27 mg/dl (Table 4). Microscopic slides of the lungs of this individual were obtained and examined. The lungs did not show vascular changes of the muscular arteries, alveolar wall thickening, or foreign-body granulomata. Their second case, while showing a high blood concentration, also showed pulmonary fibrosis with thickening of the alveolar septa. Sturner et al did not attribute these changes to the drugs because the patient also had emphysema and SC hemoglobinopathy. In the light of the pulmonary changes seen in our two cases, there is a possibility that these changes in their case also represents the sequelae of chronic abuse of propylhexedrine.

Summary

Propylhexedrine, a local vasoconstrictor, is the active ingredient in the Benzedrex® nasal inhaler. In a six-month period, the Office of the Medical Examiner of Dallas County has encountered three deaths resulting from intravenous injection of propylhexedrine. Two of these individuals showed vascular changes in the lungs, apparently from chronic intravenous injections of this drug.

Body distribution of the drug was determined in all of the cases by gas chromatographic analysis. An experiment was conducted to determine "therapeutic blood concentrations" in which a normal subject inhaled propylhexedrine from the Benzedrex® inhaler. The maximum blood concentration was only 1/30 of the minimum concentration encountered in the reported cases.

References

[1] Sturner, W. Q., Spruill, F. G., and Garriott, J. C., "Two Propylhexedrine-Associated Fatalities: Benzedrine® Revisited," *Journal of Forensic Sciences,* Vol. 19, No. 3, 1974, pp. 572–574.
[2] Foerster, E. and Mason, M. F., "Preliminary Studies on the Use of *n*-Butyl Chloride as an Extractant in a Drug Screening Procedure," *Journal of Forensic Sciences,* Vol. 19, No. 1, 1974, pp. 155–162.
[3] Garriott, J. C. and Latman, N., "Drug Detection in Cases of 'Driving Under the Influence'," *Journal of Forensic Sciences,* Vol. 21, No. 2, 1976, pp. 398–403.
[4] Marsden, P. and Sheldon, J., "Acute Poisoning by Propylhexedrine," *British Medical Journal,* Vol. 1, No. 5802, 1972, p. 730.

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