Forensic Science International 284 (2018) 141–145

Contents lists available at ScienceDirect

Forensic Science International

journal homepage: www.elsevier.com/locate/forsciint

Review Article

Is LSD toxic?

David E. Nichols[a,*], Charles S. Grob[b]

[a] Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC 27599, USA
[b] Department of Psychiatry, Harbor-UCLA Medical Center and Los Angeles Biomedical Research Institute, Torrance, CA 90509, USA

ARTICLE INFO

Article history:
Received 27 November 2017
Received in revised form 3 January 2018
Accepted 6 January 2018
Available online xxx

Keywords:
LSD
Toxicity
Death
Positional asphyxiation
Maximal restraint
Hog-tying

ABSTRACT

LSD (lysergic acid diethylamide) was discovered almost 75 years ago, and has been the object of episodic controversy since then. While initially explored as an adjunctive psychiatric treatment, its recreational use by the general public has persisted and on occasion has been associated with adverse outcomes, particularly when the drug is taken under suboptimal conditions. LSD's potential to cause psychological disturbance (*bad trips*) has been long understood, and has rarely been associated with accidental deaths and suicide. From a physiological perspective, however, LSD is known to be non-toxic and medically safe when taken at standard dosages (50–200 μg). The scientific literature, along with recent media reports, have unfortunately implicated "LSD toxicity" in five cases of sudden death. On close examination, however, two of these fatalities were associated with ingestion of massive overdoses, two were evidently in individuals with psychological agitation after taking standard doses of LSD who were then placed in maximal physical restraint positions (*hogtied*) by police, following which they suffered fatal cardiovascular collapse, and one case of extreme hyperthermia leading to death that was likely caused by a drug substituted for LSD with strong effects on central nervous system temperature regulation (e.g. 25i-NBOMe). Given the renewed interest in the therapeutic potential of LSD and other psychedelic drugs, it is important that an accurate understanding be established of the true causes of such fatalities that had been erroneously attributed to LSD toxicity, including massive overdoses, excessive physical restraints, and psychoactive drugs other than LSD.

Contents

1. Introduction

Lysergic acid diethylamide (LSD) is a semi-synthetic natural product derived in nature from the rye fungus, *Claviceps purpurea*. It was first synthesized in 1938 by Swiss chemist Albert Hofmann, who was at that time exploring the putative medicinal effects of a series of ergot derivatives. Hofmann, five years later in 1943, accidentally discovered the unique psychological effects of the compound he identified as LSD-25, which he found was profoundly psychoactive at remarkably low microgram level doses. From the early 1950s, through the 1960s considerable clinical research activity with LSD raised hopes and enthusiasm that a valuable new treatment tool would be available to psychiatrists and other mental health professionals, particularly for use in cases that were refractory, or treatment resistant, to the standard mainstream approaches of that time. In all, about 1000 clinical case reports were published from the early 1950s through the 1960s, discussing

* Corresponding author.
E-mail addresses: drdave@purdue.edu, denichol@email.unc.edu (D.E. Nichols), cgrob@labiomed.org (C.S. Grob).

https://doi.org/10.1016/j.forsciint.2018.01.006
0379-0738/

treatment of approximately 40,000 subjects, mostly with LSD [1]. Comprehensive reviews of clinical outcomes of experimental LSD studies conducted in the United States and the United Kingdom during the 1950s and 1960s identified very low rates of adverse effects [2–4]. FDA-approved clinical studies of LSD ended with the passage of the controlled substances act (CSA) of 1970. Recently, however, controlled clinical studies have been resumed in Europe, although not as yet in the United States [5–12].

Although LSD is now classified as a Schedule 1 drug with no safe or recognized therapeutic use, its informal use by the public has continued over the past 50+ years [13,14]. Of particular note, however, is that reports of psychological adverse events outside of formal and approved research settings have notably declined over the past several decades. That is likely attributed to use of lower doses, access to better and more accurate information, improved psychological preparation, and greater attention given to supportive environmental conditions.

Experts now generally recognize that LSD is an extremely physiologically safe substance, when moderate dosages are used (50–200 μg) in controlled settings, with only modest elevations of blood pressure, heart rate, and body temperature noted [8,15,16]. It is estimated that 10.2% of the current U.S. population has ever taken LSD [17], giving an estimate that approximately 31 million people have ever used LSD, with not a single documented death due to LSD at recreational doses [17–19].

Although fatalities after LSD use can occur when the intoxication leads the user to carry out dangerous activities such as walking across a busy highway, attempting to swim, rock climbing, etc., there are only two documented cases where LSD presumably directly led to fatality. In both cases, post-mortem analysis indicated that the decedents had ingested massive doses of LSD.

2. Deaths associated with LSD

Gable [20] estimated that the lethal oral dose of LSD in man is 14 mg, based on the reported LD50 in rabbits and one elephant. He later [21] revised his estimate of the lethal blood concentration based on mouse and rat studies as 4.8 μg/mL, and revised the lethal oral dose of LSD in humans to be 100 mg, citing Griggs and Ward [22] that a fatal LSD dose ingested was equivalent to 800–1600 times the usual street dose then of 200–400 μg. In the case report described by Griggs and Ward [22] the liver concentration of LSD was reported as 31.2 μg/mL (31,200 ng/mL). They extrapolate, based on a study in cats, that the decedent in this case may have received an LSD dose equivalent to about 320 mg intravenously, or "23 times the previously calculated lethal human dose."

In a case reported by Fysh et al. [23], the cause of death was stated to be poisoning by LSD, but sufficient details are lacking to determine the actual dose ingested. In that report, a 25-year-old male died 16 h after being admitted to the hospital, but it is not reported how much earlier his LSD ingestion occurred. Analysis of ante-mortem serum gave 14.4 ng/mL, but if analysis of his plasma had been carried out more proximal to his ingestion of the drug, this concentration would have been much higher.

These latter two cases document death by LSD overdose, but only from massive doses of drug that might be available directly from a manufacturer, and not from a typical distributor of recreational dosage forms such as blotters or liquid solutions.

Even so, heroic doses of LSD can be ingested without fatality when supportive hospital care is readily available. Klock et al. [24] report on massive LSD overdose in eight patients who nasally insufflated pure LSD tartrate powder, believing it to be cocaine. They were admitted to the emergency room within 15 min after insufflation. Five patients were comatose, and most were extremely hyperactive with severe visual and auditory hallucinations. All had sinus tachycardia, widely dilated pupils, emesis, flushing, and sweating. Fever developed in four and diarrhea in two. Transient hypertension was present in three patients but no patient had convulsions. Specimens of blood were obtained on admission. Blood concentrations of LSD were measured for four patients as high as 26 ng/mL. Gastric concentrations of LSD were as high as 7.0 mg/100 mL (or 70,000 ng/mL). After supportive therapy all eight patients fully recovered within 2–3 days.

Fatality also has occurred when LSD users were having a "bad trip" and were subsequently restrained with hog-tying type restraint. In a report by O'Halloran and Lewman [25] a 14-year old boy reportedly on a bad LSD trip jumped through a window and cut his leg. He was screaming obscenities, talking incoherently, and spitting. Police were called and it took four adults to restrain him and transport him to the hospital emergency room. His constant struggling prevented attempts to suture his lacerations. He was placed prone on a hospital gurney with his hands cuffed behind his back, and was transported three blocks to a juvenile detention center. Still struggling and spitting, he was placed in soft restraints *and hogtied*. Manual pressure was applied to his back and shortly thereafter he went limp. After being carried to a padded room and placed prone on the floor, within a minute he was discovered to be unconscious and not breathing. He was rushed back to the hospital where he died after seven days in a coma. Tests of admitting blood samples from the hospital were positive only for LSD. The authors of this report considered it to be death due to restraint asphyxiation in "excited delirium." We shall return to the notion of excited delirium later in this discussion.

In a case described by Reay et al. [26] a victim was a 28-year-old healthy male who was house sitting and drinking beer with his brother most of one afternoon. Later, the brothers went out to their van for a trip to the store, noticed that someone had tampered with their van, and began shouting at each other. Neighbors assumed they were fighting and called police. Two police officers arrived and tried to calm the brothers and get them to go into their house. At some point, a records search found outstanding traffic warrants on the victim. The victim would not quiet down and became increasingly agitated. When faced with the option of going into the house or being arrested, he ran. A pursuit and struggle ensued. He was struck several times with nightsticks, once to the head. After the victim was partially subdued prone on the ground, a witness to the event ran out and held the victim's legs. Several officers arrived to help restrain and hogtie the victim. Once the victim was finally restrained, and while still resisting and complaining, he was placed in a prone position in the back of a patrol car on a narrow, molded plastic, one-piece seat. While en route to the jail, the victim slipped down and became wedged between the front and back seats with his left shoulder partway up the back of the front seat and his right shoulder against the bottom panel and foot well of the back seat. About three min later, his breathing was "gurgly" and the transporting officer called a Code 3 upgrade to paramedics. Medics arrived at the jail about the same time as the officer and victim. Approximately 4 min had elapsed during the trip from the scene to the jail. The victim was unresponsive when removed from the patrol car. Despite all efforts, he never regained any vital signs and was pronounced dead. Toxicologic tests found a blood alcohol level of 0.12 g/100 mL, a LSD blood level of 3.2 ng/mL, a THC blood level of 4.1 ng/mL, and THC blood metabolite level of 108 ng/mL. No other drugs or chemical findings of note were present. Death was attributed to positional asphyxia.

Most recently, two deaths have been attributed to LSD toxicity. The first case is that of a 30-year-old male with a history of asthma but no other significant past medical history. According to his wife, he ingested a small quantity of LSD, after which he became frightened and claustrophobic. He ran approximately a quarter mile through a commercial area and a bystander contacted police to report his erratic behavior. Upon arrival, police ordered a K-9