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Synthetic Cannabinoid Use Associated with Coagulopathy

Rodent Poison Added to Abused Drugs Leads to Serious Bleeding Problems

By Minh-Ha Tran, DO, Ingrid Perez-Alvarez, MD, and Bridgit O. Crews, PhD

Synthetic cannabinoids have been implicated in outbreaks of serious hemorrhagic problems among users, evidently caused by manufacturers adding rodenticides to the drugs.

Part of a group of drugs classified as new psychoactive substances, synthetic cannabinoids emerged in the early 2000s as a new class of abused drugs. They are synthesized by illicit manufacturers and packaged with misleading labeling designed to avoid prosecution, such as, "not for human consumption" (1,2).

In April 2017, six new synthetic cannabinoids were listed as Schedule I substances (3); however, manufacturers regularly modify synthetic cannabinoid structures in an effort to escape judicial consequences and analytic detection (4). Synthetic cannabinoids are marketed under many names, such as Spice, K2, Black Mamba, and Scooby Snax. Manufacturers produce these products by spraying synthetic cannabinoids—either individually or as mixtures—onto pulverized plant material to resemble incense or potpourri (2).

THC Mimics

Scientists originally designed synthetic cannabinoids as potential therapeutic agents to mimic the effects of delta-9-tetrahydrocannabinol (THC), the primary psychoactive ingredient in marijuana. THC is a partial agonist of the CB1 cannabinoid receptor. CB1 receptors are found throughout the body but are concentrated in the central nervous system. Synthetic cannabinoids bind with higher affinity and induce greater activation of CB1 receptors than THC, leading to physiologic consequences such as anxiety, seizures, psychosis, renal failure, tachycardia, and myocardial infarction (4).

The National Forensic Laboratory Information System, a program of the U.S. Drug Enforcement Agency, collects drug identification results submitted by federal, state, and local laboratories (5). Between 2009 and 2015, the number of synthetic cannabinoids reported to the system rose from 2 to 84 different forms (5). Little is known about the physiological effects or toxicity of the vast majority of these chemicals.

Hemorrhaging Patients

In 2018, a worrisome multistate (Illinois, Indiana, Maryland, Missouri, and Wisconsin) outbreak of hemorrhagic sequelae associated with synthetic cannabinoid use emerged, leading to an April 2018 Outbreak Alert from the Centers for Disease Control and Prevention (6).

An exhaustive evaluation by the Illinois Department of Public Health revealed a connection between synthetic cannabinoid use and presentation with hemorrhagic sequelae among previously healthy users. Tests of samples in at least 18 cases uncovered contamination by brodifacoum, a second-generation long-acting anticoagulant rodenticide (LAAR) in the warfarin family. Related LAARs include difenacoum and bromadialone.

In at least one case, laboratory tests detected brodifacoum in the blood and a metabolite of the synthetic cannabinoid AB-FUBINACA in the blood and urine of a patient presenting with coagulopathy (7). By April 25, 2018, 155 cases (76 confirmed, 79 probable) had been identified, including four hemorrhagic deaths. All of the 81 analyzed clinical blood specimens contained brodifacoum (8).

A recent case series reported confirmatory testing in 15 patients identified as having synthetic can-

Continued on page 2

Inside...

Synthetic Cannabinoids

Continued from page 1

nabinoid-associated coagulopathy at a single center. Testing detected brodifacoum in all 15, difenacoum in five, bromadialone in two, and warfarin in one, indicating that multiple LAARs may be present as hemorrhagic contaminants (9).

Superwarfarins

LAARs such as brodifacoum, also referred to as superwarfarins, are readily available in ready-to-use rodent baits. Figure 1 shows the chemical structure of warfarin and several LAARs. Rapid absorption of LAARs by mammalian species, including humans, occurs primarily through the gastrointestinal tract, skin, and respiratory system. Poisoning can occur after ingestion or occupationally through prolonged skin contact or accidental inhalation during manufacturing.

Brodifacoum has a high oral toxicity. Although the minimum toxic dose is not well-established, in one case, a patient who consumed a handful of 0.005% brodifacoum bait required 20 weekly doses of subcutaneous vitamin K to resolve the ensuing coagulopathy (10).

The distinguishing characteristics of LAARs include high lipophilicity, long terminal half-life, and a propensity to accumulate in the liver. Brodifacoum produces coagulopathy through inhibition of vitamin K epoxide reductase enzyme (VKOR), which plays a major role in recycling vitamin K 2,3-epoxide into vitamin K hydroquinone, an essential co-factor for the post-translational gamma-glutamyl carboxylation of procoagulant factors II, VII, IX, and X. Although brodifacoum inhibits vitamin K reductase reactions almost immediately, the toxic effects can take several days to manifest because of the time required to deplete vitamin K stores and residual factor activity.

In cases of brodifacoum poisoning associated with crack cocaine and marijuana, users reported lacing their drugs with brodifacoum in an attempt to prolong or potentiate the drugs' effects (11,12). In the recent cases, it is not known why LAARs were placed in the synthetic cannabinoids.

LAAR Poisoning Effects and Treatment

A recent review of LAAR poisoning found that the top five manifestations included hematuria (34%), gingival bleeding (30%), epistaxis (24%), gastrointestinal bleeding (23%), and spontaneous ecchymoses (22%) (13). The most frequently reported symptom with synthetic cannabinoid use was hematuria, occurring in 125 of 155 cases (81%) (8). Owing to the impairment of post-translational carboxylation of vitamin-K–dependent coagulation factors, patients have prolonged partial thromboplastin times and elevated prothrombin time/international normalized ratio (INR) values (6,13).

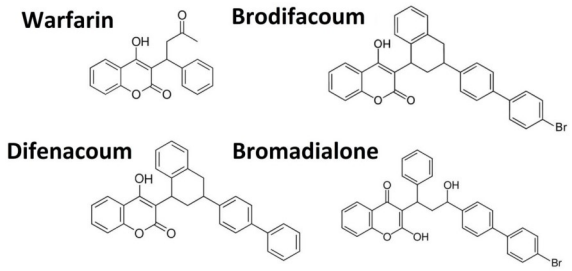

Figure 1. Chemical Structures of Warfarin and Long-Acting Anticoagulant Rodenticides

Acute, life-threatening bleeding requires rapid supplementation of factors through infusion of fresh-frozen plasma or prothrombin complex concentrates (12). In addition, high-dose, long-term therapy with vitamin K is required given the long half-lives (weeks to months) of LAARs in humans (13). A vitamin K shortage during 2018 was attributed to synthetic-cannabinoid–related hemorrhagic cases requiring prolonged vitamin K therapy (14).

Implications for Blood Banks

Three patients in the Illinois outbreak had donated blood or plasma prior to admission, leading to a regulatory update on the website of the AABB (formerly known as American Association of Blood Banks) advising that more restrictive deferral policies may be implemented based on the potential downstream risk posed by blood products from donors who have used synthetic cannabinoids contaminated with LAARs (6,15).

The AABB update suggested that future measures to prevent donation by drug users might include an educational poster regarding synthetic cannabinoids hazards, inclusion of information in donor educational materials, addition of a screening question to the donor history questionnaire, and implementation of deferral policies. Our hospital transfusion service has implemented a number of these measures and, based on half-life estimates for brodifacoum of 16–34 days, imposed a six-month deferral for donors reporting synthetic cannabinoid use (16).

Summary

In conclusion, previously healthy patients who present with unexplained bleeding and elevated INRs should be screened for synthetic cannabinoid use. Use of synthetic cannabinoids may be associated with LAAR poisoning, leading to serious coagulopathy due to vitamin-K antagonism. Local poison control centers should be notified. Treatment may require administration of prothrombin complex concentrates (or fresh-frozen plasma) and vitamin K. The long elimination half-lives of LAARs compared

with infused coagulation factors necessitate careful medical follow up and avoidance of further synthetic cannabinoid use. Patients should be advised to avoid surgical procedures and educated on the risks of non-adherence to vitamin K treatment.

Learning Objectives

After reading this article, the reader will be able to discuss the mechanisms of toxicity for long-acting anticoagulant rodenticides such as brodifacoum and list the common clinical findings in poisonings they cause.

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Minh-Ha Tran, DO, is a clinical professor of pathology and laboratory medicine and medical director of transfusion medicine at the University of California Irvine (UCI) Medical Center in Orange. Email: minhhat1@uci.edu. Ingrid Perez Alvarez, MD, is an assistant clinical professor of pathology and laboratory medicine and associate medical director of transfusion medicine at UCI Medical Center. Email: iperezal@uci.edu. Bridgit O. Crews, PhD, DABCC,TC is an assistant clinical professor in pathology and laboratory medicine and director of clinical chemistry and toxicology at UCI Medical Center as well as a member of the Clinical & Forensic Toxicology News *board of editors. Email: crewsb@uci.edu.*

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Spam Grows from Questionable Publications and Conferences

"Predatory" Journals and Meetings Barrage Researchers with Unwanted Solicitations

By Matthew D. Krasowski, MD, PhD

The past decade has seen a large increase in new scientific and medical journals, many of which operate solely online. Some of these journals have attracted attention for their questionable quality, unclear editorial oversight, and use of mass emails for marketing (1–7).

The term "predatory journal" has been used to denote journals of poor quality that use aggressive email marketing to researchers and scientists. Their peer review of articles may be minimal or absent, and they sometimes promise rapid review and publication. These journals typically charge fees for publication and are operated by commercial entities as opposed to established scientific societies or organizations. A single publisher may offer a large array of journals, sometimes with a single editor for many publications.

Spoof Article Investigation

To investigate the presence of peer review by these journals, one researcher constructed a bogus "spoof" article containing implausible data from a fake author and fictitious institute and submitted it to more than 300 open access journals (8). The data in this spoof study was intentionally deeply flawed methodologically. The article contained graphs that showed the opposite of what was claimed in the text. The English in the article was technically grammatically correct but had been altered by running it through an online translator to a foreign language and then back to English, with some manual editing to keep the English understandable.

Astoundingly, 157 journals accepted the study and only 98 rejected it, with the remainder either not replying or rendering no decision. Some journals went derelict in the course of the study, with their websites becoming inactive or being taken down. Those journals that accepted the article did so without any revisions or with requests to alter minor features such as font or article formatting.

Meetings and Conferences

Similar to these predatory journals, there has been growth in meetings or conferences of potentially low quality and scientific value (sometimes termed "fraudulent" or "predatory" conferences) (3,9,10,11). These conferences are also commonly organized by commercial entities and advertise via mass emails. There has been less scholarly analysis of these conferences compared to journals, but common themes include organization by companies or individuals as opposed to established scientific organizations, high fees even for presenters, and lack of transparency regarding the meeting's structure and content. Such conferences may be in a variety of countries and solicit researchers for a variety of activities. In the worst cases, the conference is fictitious or of poor quality.

Email Barrage

The practical effect for those in medical and scientific professions is an inbox full of unsought emails that advertise or solicit for these journals and conferences (3,9,12–14). The emails may include invitations to submit articles or join editorial boards. For conferences, the emails may be invitations to present data, serve on speaker panels, or organize sessions. One early-career researcher reported receiving over 500 emails from journals and conferences in the year following his first publication as corresponding author (9). Most of these invitations were for journals and conferences outside his field of interest.

Some researchers have published on attempts to limit these and other unsolicited emails by blocking specific email domains or unsubscribing, but these measures are time-consuming and have a limited and temporary effect (15). Like email spammers, these journal publishers or conference organizers may change email addresses and domain names frequently and try to disguise the country of origin for the email (15–18). Attempts to unsubscribe may be ignored or even lead to increases in spam.

Characteristics of Suspect Journals

As noted above, the adjective predatory has been applied to academic journals and conferences of potentially poor quality and low scientific value, although this term does not yet have a standard definition (1–7). Most of the literature to date has focused on predatory journals, with some studies aimed at identifying key characteristics (16–19).

The recurring patterns of mass marketing emails from potentially predatory journals include misspellings in the email body, claims of rapid peer review and publication, vague claims of being indexed in resources such as MEDLINE or PubMed (for example, "some journals have been indexed in PubMed or PubMed Central"), a claim of impact factor despite the recent launch of the journal, aggressive submission deadlines, and an overly broad scope of topics covered by the publication (such as anything within biological or physical sciences) (16–20).

Mass emailing also means that recipients often receive information on journals outside of their area of expertise (9,15). In the email text and on the journal home page, details on peer review, database inclusion, and impact factor may be nebulous or inaccurate. Table 1 summarizes some of the common features of potentially predatory journals. Common

Table 1. Characteristics of Potentially Predatory Journals

Email Advertisements and/or Website	Journal Itself
Misspellings and grammatical errors	Not included in recognized journal databases/resources
Claims of rapid review and/or publication	Close similarity in name to a more recognized journal
Vague claims of inclusion in journal databases/resources	Wide scope of scientific areas covered
Claims of impact factor despite recent launch of journal	Single editor for multiple journals for publisher
Aggressive deadlines for article submission	Few articles accessible on journal website
Scope of journal well outside of scientific field of email recipient	Details on editorial oversight vague or absent

spam filters may identify some of these emails as junk mail, but many emails slip through. One challenge for spam filters is that there may be nothing inherently offensive or suspicious in the text.

Assessing an Unknown Journal

One common approach to assessing the quality and legitimacy of a journal is to determine whether the publication is included in established databases or resources that have defined criteria and review practices. These resources serve as a sort of "whitelist" of journals that have met defined metrics for quality (21). Table 2 summarizes a number of these resources, which include EMBASE, Journal Citation Reports, MEDLINE, PubMed Central, and SCOPUS. Some of them are free to the public on the Internet while others are proprietary. One limitation is that it takes time even for high-quality journals to meet the criteria for inclusion, especially those that slowly accumulate publications in their early history. This can make evaluation of newer journals difficult in the short-term (22).

Another approach is the development of "blacklists" of potentially predatory or low-quality journals (21,23,24). The most visible example of this approach was Beall's List, a widely used but now defunct listing published by a University of Colorado librarian (25–27). Although Beall did define a number of characteristics associated with potentially predatory journals, some criticized his approach for a lack of transparency and the potential for misjudging journals that were actually of reasonable quality. One challenge is that some characteristics of predatory journals, such as publication fees, publication by a commercial entity, rapid review, and coverage of wide areas of science, are not unique to these publications (21,23,24).

Legal threats from journal publishers may have played a role in the dissolution of the list. Since the discontinuation of Beall's List in 2017, a group of anonymous contributors put together a website list called Stop Predatory Journals based in part on Beall's List (28). There is also a commercially available blacklist known as Cabell's blacklist (29).

There are limitations to the blacklist approach. First, the reasons a journal appears on a blacklist may not be transparent, a criticism that some levied against Beall's List (27). There may also not be a clear way to adjudicate disputes when a journal's publisher questions its inclusion on the list. Second, the rapid growth of journals makes it challenging to keep up. The quality of a journal can decline if it is acquired by a different publisher (as happened with a Canadian cardiology journal) or it makes changes in its editorial control (30).

Third, it is difficult to evaluate new journals (22). Some will become established, but this can be hard to assess in its early phases. The quality and reputation of a journal can certainly improve over time. Fourth, journals vary in intent and purpose. Some journals cater more to researchers in developing nations who may encounter barriers to publishing. Some focus on speculative or controversial content that can be difficult to publish in traditional journals (11,31). Last, labeling a journal as potentially predatory carries a risk of legal action by the publisher.

Other Types of Academic Spam

Although unwanted emails from journals and conferences have attracted the most attention, researchers and scientists receive a range of other unsolicited emails. These include daily briefs, advertisements, and solicitations for surveys that can offer honoraria for participation. The entities that send these emails may use corresponding author email addresses associated with journal articles or other publications. In some cases, the emails mention a publication by the recipient as an introduction. Researchers have not yet published studies of these other categories of unsolicited emails, but they are likely to share

Table 2. Selected Journal Databases/Resources

Database	Number of Journals Included	Number of Records	Publisher	URL
CINAHL	5,500	6,000,000	EBSCO	https://health.ebsco.com/products/the-cinahl-database
EMBASE	8,500	32,000,000	Elsevier	https://www.embase.com/login
Journal Citation Reports	11,500	2,200,000	Clarivate Analytics	https://clarivate.com/products/journal-citation-reports/
MEDLINE	5,200	25,000,000	U.S. National Library of Medicine	https://www.nlm.nih.gov/bsd/medline.html
PubMed	30,000	29,000,000	U.S. National Library of Medicine	https://www.ncbi.nlm.nih.gov/books/NBK3827/
PubMed Central	7,460	5,200,000	U.S. National Library of Medicine	https://www.ncbi.nlm.nih.gov/pmc/
Scopus	5,000	71,000,000	Elsevier	https://www.elsevier.com/solutions/scopus

the characteristics of the questionable journals and conferences.

Implications for Forensic and Toxicology Fields

The issue of potentially predatory journals and conferences impacts all areas of science. I recently analyzed the emails sent to my institutional email address for seven consecutive days and found 111 unsolicited emails, including 69 for journals and 42 for conferences. Of these, five journals had forensic and/or toxicology in the name and this was the focus of eight conferences. The burden of emails probably varies in part based on exposure of the recipient's email address in publicly accessible locations such as PubMed, journal websites, and scientist databases.

The rapid increase in new journals and conferences, combined with the ease of mass advertising by email, means that researchers and scientists will inevitably receive solicitations from these entities. It is important to perform due diligence when considering submission to an unfamiliar journal or attendance at a conference. Education of trainees in scientific and medical fields should include information helpful in assessing the quality of journals and conferences along with strategies for choosing journals for publishing.

Learning Objectives

After reading this article, the reader will be aware of the existence and characteristics of "predatory" journals and conferences and be able to recognize some of their marketing tactics.

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Matthew D. Krasowski, MD, PhD, is a clinical professor and vice chair of clinical pathology and laboratory services in the department of pathology at the University of Iowa Hospitals and Clinics in Iowa City. He chairs the Clinical & Forensic Toxicology News *board of editors. Email: mkrasows@healthcare.uiowa.edu.*

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Vitamin D Can Lead to Toxicity

Confusion about Supplement Potency Can Lead to Ingestion of Extreme Doses

By John P. Lee, DO, and Matthew D. Krasowski, MD, PhD

Interest in vitamin D has increased significantly over the past two decades, spurred by the vitamin's possible connections to cancer prevention, cardiovascular health, and the immune system—as well as concerns about the possibility of widespread deficiency (1).

This attention has prompted significant increases in both vitamin D supplementation and laboratory testing for 25-hydroxyvitamin D [25(OH)D], the main circulating form of vitamin D (2,3).

There is scientific controversy surrounding what level of vitamin D is optimal. In 2011, an Institute of Medicine report defined deficiency as below 20 ng/mL, and considered any level higher than that to be adequate for bone health (4). Later that year, the Endocrine Society published clinical practice guidelines that defined the optimal level as 30 ng/mL or higher, and noted many people fall below this (5).

The two major dietary forms are vitamin D_2 (ergocalciferol, derived from fungus) and vitamin D_3 (cholecalciferol, derived from animal sources) (6). Humans can obtain vitamin D_2 or D_3 from dietary sources (including supplements and fortified foods) or produce vitamin D_3 endogenously from skin exposure to ultraviolet B rays. Recommended vitamin D daily requirements range from 600 to 2000 IU/day for adults, 1,000 to 2,000 IU/day for infants, and up to 4000 IU/day for children over 12 months (5).

Vitamin D Toxicity

While vitamin D deficiency has attracted the most attention, an increasing number of published reports have investigated its toxicity (6–10). Vitamin D toxicity is not common, but its incidence may be increasing due to the wider use of supplements (3,11,12).Vitamin D toxicity (hypervitaminosis D) is associated with very high plasma/serum concentrations of 25(OH)D coupled with clinical signs and symptoms such as hypercalcemia, vomiting, constipation, and nephrocalcinosis (calcium deposits in the kidney) (6,11). One challenge in making this diagnosis is that high 25(OH)D levels do not always correlate with toxic signs and symptoms such as hypercalcemia.

It is difficult to define a "toxic" threshold concentration for 25(OH)D. Clinical laboratories, including commercial reference laboratories, may thus vary in the thresholds they use to report potentially toxic 25(OH)D concentrations (6,13). The lowest plasma/serum 25(OH)D level associated with clinical toxicity reported in the literature is 80 ng/mL, described in a single patient (14). Other studies have proposed 125 ng/mL or 200 ng/mL as reasonable minimum concentrations for toxicity risk (12,15).

A detailed retrospective study conducted over 16 years at our hospital system (an academic medical center in the Midwest) identified only four cases with a clear clinical diagnosis of hypervitaminosis D (16). Of these 4 patients, the lowest plasma/serum 25(OH)D was 194 ng/mL. These findings are similar to other reports of clinically symptomatic hypervitaminosis D occurring only with plasma/serum 25(OH)D of about 200 ng/mL or higher (12). In multiple studies, potentially toxic concentrations of 25(OH)D did not strongly correlate with plasma calcium concentrations and hypercalcemia (12,15,16).

Factors Associated with High Concentrations

A variety of evidence suggests that toxic 25(OH)D concentrations most commonly occur with sustained ingestion of vitamin D_2 or D_3 supplements that average about 50,000 IU or higher per day (12,15,16). Data in pediatric populations is limited, but a 2014 review by a Pediatric Endocrine Society committee identified errors in manufacturing, formulation, or prescription dose as factors in documented cases of vitamin D toxicity in children. Some of these errors resulted in total intake exceeding 1,000,000 IU (15).

Evidence for minimum toxic thresholds comes from both ingestion studies and the observation that sun exposure does not generally produce hypervitaminosis D (18). Endogenous 25(OH)D_3 production from sunlight exposure reaches a maximum at about 20,000 IU per day; past a certain point, excess sunlight degrades the metabolic precursors to 25(OH)D, limiting further production. Consequently, populations living in equatorial regions or individuals with high sunlight exposure (such as lifeguards or surfers not wearing sunscreen) do not experience vitamin D toxicity.

Conventional wisdom also holds that vitamin D toxicity should not result from the use of tanning beds, although some case reports suggest that very intense, chronic use of tanning beds by light-skinned individuals can produce vitamin D toxicity (19,20).

Single massive overdoses of vitamin D can occur, but even single doses as high as 2,000,000 IU, as described in a dosing error for two nursing home patients in the Netherlands, can be tolerated without serious acute toxicity (21).

Prescription Formulations

Vitamin D formulations high enough to be associated with toxicity are typically available by prescription only in the U.S. but can be obtained over-the-counter in other countries (6,12,16). The vitamin D content of over-the-counter pills and tablets is typically only in the range of 200–2,000 IU, with the

lower range common in multivitamins and the higher amount in vitamin D-only supplements (6). Chronic ingestion of 50,000 IU per day via these smaller doses is usually not practical for those who attempt it.

However, frequent ingestion of prescription formulations with dosage as high as 50,000 IU can produce hypervitaminosis D. These high-dose formulations are typically intended to treat severe vitamin D deficiency and not meant for daily use except temporarily in the early stage of managing these patients. When used weekly or monthly (as commonly intended), 50,000 IU formulations are not likely to cause toxicity. Toxicity has also been reported from pharmaceutical errors resulting in vitamin D content much higher than intended (7).

Toxicity in Young Children

Infants and young children are at special risk for vitamin D toxicity because they receive their supplements through liquid formulations. Multiple studies have demonstrated symptomatic hypervitaminosis D caused by dosing mistakes with liquid formulations (3,9,16,22,23). A common error is confusion between a "drop" and "dropperful" in dosing by parents trying to supplement their children's diets.

In our own retrospective study, 2 of the 4 cases of symptomatic hypervitaminosis D were young children (4-month-old boy and 3-year-old girl) whose parents misunderstood this difference and administered very large amounts of vitamin D over weeks (16). The 4-month-old boy had received 100,000 to 150,000 IU per day, and the 3-year-old girl 40,000 to 80,000 IU per day. Both children required hospital admission after presenting with hypercalcemia, nephrocalcinosis, failure to thrive, weight loss, and gastrointestinal symptoms.

In the same vein, a third case of symptomatic hypervitaminosis D in this study occurred in a 62-year-old patient who took a high-potency liquid formulation (recommended dose of 1 drop or 2,000 IU) due to difficulty with swallowing pills. Confusion in dosing was also suspected as the underlying problem, leading to daily doses exceeding 50,000 IU.

Many other case reports or series in the literature document similar problems with dosing of vitamin D liquid formulations (9,10,24). For infant formulations, the intended dose is often 400 IU, but the amount for liquid taken can vary. Some liquid formulations use a dropperful, such as the Enfamil D-Vi-Sol (Mead Johnson, Chicago, IL), in which 1 dropperful (1 mL) delivers 400 IU. For others, the dose is a single drop, such as the Baby Ddrops (Ddrops Company, Woodbridge, ON, Canada), for which 1 drop contains 400 IU. High-potency vitamin D drops may contain 2,000 IU per drop, such as the Liquid Vitamin D_3 Drops (Bluebonnet Nutrition Corp, Sugar Land, TX).

A simple search of the websites for retailers offering pharmacy products will often reveal multiple liquid formulations with similar dosing to the three examples above. Some published case reports noted that problems occurred when parents switched from one formulation to another without noticing the change in dosing from dropperful to drop.

Summary

Vitamin D toxicity is not common but can produce serious symptoms. Literature reports over the past 10 years have demonstrated two main scenarios for symptomatic vitamin D toxicity: chronic, daily use of high-dose vitamin D formulations (50,000 IU or higher) and dosing confusion with liquid preparations. Multiple case series have shown dosing errors with pediatric liquid formulations resulting in vitamin D toxicity. Standardization of liquid vitamin D formulations and administration methods could enhance safety.

Learning Objectives

After reading this article, the reader will be able to describe the potential health consequences of vitamin D excess and identify common scenarios for symptomatic vitamin D toxicity (hypervitaminosis D).

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John P. Lee, DO, is a pathology resident at the University of Iowa Hospitals and Clinics in Iowa City. E-mail: john-p-lee@uiowa.edu. Matthew D. Krasowski, MD, PhD, is a clinical professor and vice chair of clinical pathology and laboratory services in the department of pathology at the University of Iowa Hospitals and Clinics as well as the chair of the Clinical & Forensic Toxicology News *board of editors. E-mail: mkrasows@healthcare.uiowa. edu.*

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