

Severe Adverse Reactions Following Ketoconazole, Fluconazole, and Environmental Exposures: A Case Report

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Abstract In this case report, we describe a 66-year-old man who developed multiple adverse reactions beginning at age 56 after exposure to several azole antifungal drugs including ketoconazole and fluconazole. He also had a history of more than 40 years exposure to chemicals including pesticides, wood preservatives, fertilizers, and welding chemicals. His reactions involved dehydration (requiring several liters of intravenous fluids in less than an hour to alleviate this condition), angioedema, nausea, tinnitus, hypotension, and difficulty breathing. His acute adverse reactions were triggered by a wide range of chemicals including gasoline, diesel fuel, pesticides, chlorine, topical isopropyl alcohol, and paper mill emissions. His acute reactions were also triggered by a wide range of foods such as bananas, apples, milk, white potatoes, and processed sweets. A number of mechanisms could be responsible for his increased sensitivity to chemicals following exposure to fluconazole/ketoconazole, including inhibition of P450 and other detoxification enzymes, acetaldehyde buildup, and neurogenic sensitization.

Key Points

A 56-year-old man with a long history of pesticide and other petrochemical exposures received ketoconazole/fluconazole treatment, which triggered 10 years of many adverse reactions involving dehydration, hypotension, angioedema, tinnitus, and difficulty breathing and other health-related problems.

A spreading reaction developed: After his initial reactions to ketoconazole/fluconazole, the patient developed frequent acute reactions after exposures to common chemicals (like gasoline, diesel fuel, pesticides, topical isopropyl alcohol, and pulp mill emissions) and some common foods (bananas and apples) as well.

The ketoconazole/fluconazole exposure could have triggered the long-term adverse reactions by a number of mechanisms, including inhibition of P450 or other detoxification enzymes, acetaldehyde buildup, neural sensitization, or immune factors.

Introduction

A number of case reports have mentioned hypersensitivity reactions in patients receiving ketoconazole in either oral or dermal form [1–4]. Liu et al. described a 72-year-old woman who developed anaphylaxis and severe hypotension unresponsive to 2 L of 0.9% NaCl intravenous (IV) fluid resuscitation after taking ketoconazole [2].

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We report a case of a 66-year-old man who developed adverse reactions which were self-described as disulfiram-like reactions after exposure to azole antifungal drugs. Over a 10-year period, these acute adverse reactions occurred in response to many common chemicals, many foods, and low-dose naltrexone. It was almost certainly not a true disulfiram reaction since no disulfiram was involved and alcohol was only one of the many chemicals/foods to which the patient reacted.

Disulfiram is a drug given to people with alcohol intake problems which causes unpleasant reactions upon consuming alcohol [5]. Disulfiram inhibits aldehyde dehydrogenase to prevent the normal metabolism of alcohol and causes buildup of acetaldehyde [5]. Consuming alcohol when taking disulfiram can cause a number of adverse reactions including nausea, vertigo, blurred vision, anxiety, hypotension, tachycardia, and flushing [6, 7]. A number of studies have reported that other drugs can produce disulfiram-like reactions, including cephalosporin antibiotics [8], chloramphenicol, furazolidone, metronidazole, and quinacrine [6]. Diflucan, ketoconazole and other azole antifungal drugs have also been associated with disulfiram-like reactions to alcohol [9, 10]. Ketoconazole is a liver toxin, and variations in certain genes which code for proteins such as glutathione transferase, multidrug-resistant proteins, and flavin-containing oxygenases are associated with significant differences in how toxic ketoconazole is to the liver [11].

Case Report

The patient is a 66-year-old man (5'8") of Scottish, German, and American Indian descent. His birth and childhood were relatively uneventful. Starting in his teen years, he was exposed to a wide range of chemicals. From age 18–22, he worked in a fertilizer plant. He was exposed to pesticides after working at an agricultural experimental station between 22 and 26 years, and worked as a pesticide crop dust loader between ages 31 and 34. He was exposed to pesticides while working on a farm part-time most of his adult life. He was also exposed to pentachlorophenol-treated wood for many years in his 20s and 30s. Between 22 and 55, he had prostate problems and was treated with many antibiotics, and also had problems between 22 and 55 with stomach bleeding. In his 30s, he also worked as a welder and lived in a home with kerosene heat.

At age 56, his health took a serious downturn after he was treated for several weeks with oral ketoconazole 200 mg twice daily and 0.5% fluconazole cream at the same time for fungal infections on his penis and ears. He soon experienced two episodes of hypotension and trouble breathing which required emergency room care. These

were described by his physician as possibly being a disulfiram-like reaction. He started to experience a wide range of health problems including tinnitus, angioedema, face flushing, raw eyelids, trouble breathing, headache, weakness all over, tremors, burning all over the body, nausea, and a pins and needles feeling. He developed numerous episodes of hypotension and dehydration, which had to be treated with 2–4 L of IV saline given within half an hour.

By age 57, many agents were triggering the patient's acute reactions, which included hypotension, nausea, dizziness, weakness, tinnitus, headaches, and anaphylaxis-like symptoms. Such agents included chemicals such as pesticides, chlorine, gasoline, diesel fuel, artificial fragrances, fertilizers/lime, fresh paint, and formaldehyde-containing products. He has had severe reactions when rubbing alcohol was dabbed on his body for medical procedures. He has never had an alcohol drinking problem or been on disulfiram; however, he has had adverse reactions when drinking even small amounts of ethanol after his exposure to ketoconazole/fluconazole at age 56. He has reacted to various cosmetics such as lotions, mouth washes, and deodorants which may have alcohol and/or other petrochemicals. He also experienced severe reactions several times when exposed to downwind emissions from a large kraft paper mill 8 miles away. He also experienced severe reactions to many foods including bananas, apples, chocolate, white potatoes, milk, and processed sweets such as cookies and cakes. His weight dropped from 180 to 120 pounds over a year, from 56 to 57 years of age (height 5'8"). At age 66, low-dose naltrexone [4.5 mg once daily (QD)], taken off label to reduce risk of autoimmune disease, triggered almost immediate acute reactions. Intradermal skin testing with a solution of petroleum-based ethanol (a sevenfold 1 in 5 dilution of 5% petroleum-derived ethanol) was able to reproduce his symptoms of tinnitus and tachycardia.

Adverse reactions to chemicals, foods, and drugs occur almost daily and sometimes hourly. Severe reactions have continued for several times a month over the past 10 years, and have required giving the patient several liters of saline and occasionally required intubation of the patient.

A 23 and Me (Mountain View California, USA www.23andme.com) saliva genetic test reported high-risk genetic variations for several detoxification enzymes including CYP1A2 C164A, CYP2C9*2 C430T, CYP2D6 S486T, CYP2D6 T100C, NAT2 T341C, and PON1 Q192R. A number of standard liver enzyme function tests conducted at age 56, 57, and 66 were all normal.

The patient's symptoms improved intermittently over a period of minutes to hours when treated with sauna and 200 mg of IV glutathione QD over the past 10 years beginning at age 56. His weight is now back up to 160 pounds as of

late 2017. In December 2017, he was hospitalized with multiple blood clots to his legs.

Discussion

The significance of this case report is the association of an adverse drug reaction with the development of sensitivities to multiple chemicals which are mostly of petrochemical origin. This case gave us the opportunity to learn more about the modes of action that were causing adverse reactions in self-reported drug and chemically sensitive patients.

What makes this case so interesting is the patient's previous significant exposure to multiple toxins and petrochemicals without any overt adverse reactions. It was only after his exposure to azole drugs that he developed severe and sometimes life-threatening reactions to multiple chemicals. It is not clear why he reacted to exposures of common chemicals only after exposure to ketoconazole/fluconazole at age 56 years.

After azole exposure at age 56, he was overtly reactive to alcoholic beverages with signs and symptoms much the same as when exposed to multiple other petrochemicals. But as stated previously, he was never on disulfiram, so what were the mechanisms of his reactivity to petrochemicals and even to some foods? It is understandable how he and his physicians perceived his severe signs and symptoms as being possibly a disulfiram reaction. Several non-peer-reviewed reports have mentioned that disulfiram-like reactions can occur with fluconazole/ketoconazole and alcohol exposure and no disulfiram [9, 10]. However, his adverse reactions are not true disulfiram reactions since no disulfiram was involved and most reactions did not involve alcohol.

Disulfiram inhibits acetylaldehyde dehydrogenase, an enzyme which metabolizes alcohol. It was developed for the treatment of alcoholism, and causes a severe adverse reaction when taken with any alcoholic beverage. Disulfiram is also metabolized to diethylthiomethylcarbamate, which also inhibits the breakdown of acetylcholine by acetylcholinesterase [12].

Ketoconazole/fluconazole exposure could increase sensitivity to a wide range of chemicals and drugs since they are potent inhibitors of many P450 cytochromes such as cytochrome P450 (CYP) 3A [13, 14]. Ketoconazole has been described as inhibiting the metabolism of at least 15 types of CYP enzymes including 1A1 and 2; 1B1; 2A6; 2C8, 9, & 19; 2D6; 2E1; 2F1; 3A4&5, 7; 4F2; 11B1; and 51A forms [14]. Ketoconazole binds to and produces conformational changes of CYP3A4 which affect activity [15]. The CYP enzymes are involved in the biotransformation of a large percentage of the drugs currently available [13, 16]. P450 enzymes are also involved in

detoxifying many environmental chemicals including pesticides and also can activate some chemicals into more toxic forms [16–19]. Many pesticides either induce or inhibit P450 activity [18, 20], and at least ten P450 forms are involved with pesticide detoxification/metabolism [19].

Genetic variation in many P450 genes and other chemical detoxifying genes can cause significant differences in enzyme detoxification among various humans and may play an important role in the development of sensitivity to chemicals [21, 22]. Several studies have reported significant genetic variation in P450 enzymes between humans with sensitivity-related illness or chemical sensitivity and healthy controls [23–25]. Our patient had several mutations associated with increased risk of chemical sensitivity, organophosphate toxicity, and asthma including CYP1A2 C164A, CYP2C9*2 C430T, CYP2D6 S486T, CYP2D6 T100C, NAT2 T341C, and PON1 Q192R. The CYP1A2, 2C9 and 2D6 genes are known to be inhibited by ketoconazole [14] and are also inhibited by certain pesticides [19]. Such genes with altered frequencies among the chemically sensitive include CYP2D6 and NAT2 [25], SOD2 [23], and CYP2C9*2&3 and CYP2D6*4&41 [24]. The patient also had a mutation in the NAT2 T431C gene, which has also been associated with increased asthma risk [26]. PON1 mutations have been associated with significantly greater risk of organophosphate pesticide toxicity [27, 28]. It is reasonable that the patient's genetics made him more susceptible to ketoconazole/fluconazole and other chemical exposures, along with other mechanisms described above, such as inhibition of aldehyde dehydrogenase and the P450 enzymes.

Why did the ketoconazole/fluconazole exposure trigger long-term adverse reactions starting at age 56? The patient had been exposed rather heavily to pesticides and other petrochemicals during his adult life. The most likely explanation seems to be that the combined exposure of antifungals, pesticides and other chemicals caused a long-term decline in P450 enzyme activity or damaged other enzyme systems. Maybe the oral ketoconazole caused some long-term liver damage which interferes with detoxification, although standard liver enzymes were normal in this case. The patient could be developing a "spreading phenomena" in which significant chemical exposure leads to sensitivity to more and more chemicals [29, 30]. Exposure to pesticides has been described as a major trigger in developing long-term generalized sensitivity to many different chemicals [31–34]. Perhaps the cholinesterase-inhibiting properties of carbamate and organophosphate pesticides play a major role in developing chemical sensitivities. Pesticide exposure has also been associated with a range of adverse health effects including asthma, many types of cancer, and many types of neurological diseases including Parkinson's disease and Alzheimer's disease [35, 36].

Many factors can trigger sensitivity to chemicals. Besides genetic factors, drug/chemical exposure-related increased

sensitivity to common chemicals may possibly occur by a variety of mechanisms including brain alterations and neurogenic inflammation/kindling [37–42], immune alterations [37–39, 41], stimulation of the nitrogen oxide/peroxynitrate pathway [43], and damage/irritation to the respiratory tract [41, 44]. Additional testing of the patient for toxicology/biochemical data (such as measurement of activity of various P450 enzymes, measurement of metabolites, inflammation and oxidative damage) might elucidate the biochemical pathways involved with his adverse reactions to drugs and chemicals.

Conclusion

This case describes a patient who developed sensitivity to many chemicals and foods following exposure to azole drugs. There are multiple ways in which drugs can trigger adverse reactions to other chemicals such as the disulfiram-like reaction or acetylaldehyde syndrome, inhibition of P450 enzymes, neurogenic inflammation/kindling, and immune mechanisms. Thus, drug-induced chemical sensitivity can be caused by any of these mechanisms or even by all. More research is needed to determine the precise biochemical mechanisms of these adverse reactions triggered by ketoconazole/fluconazole exposure.

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Compliance with Ethical Standards

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Informed consent Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent may be requested for review from the corresponding author.

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