CASE REPORTS AND CLINICAL VIGNETTES

Imported Fenproporex-based Diet Pills from Brazil: A Report of Two Cases

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Banned amphetamine-based anorectics are illicitly imported into the United States (US), but little is known regarding the harm these diet pills pose to US residents. A 26-year-old woman using imported diet pills presented with a two-year history of intermittent chest pains, palpitations, headaches and insomnia. Urine toxicology screen detected amphetamines and benzodiazepines. Fenproporex and chlordiazepoxide were detected in her pills. Her symptoms resolved after she stopped using diet pills. A 38-year-old man using imported diet pills presented after his occupational urine screen was significantly positive for amphetamine. Fenproporex and fluoxetine were detected in his pills. These cases illustrate the potential harm from imported prescription diet pills that combine fenproporex with benzodiazepines, antidepressants, diuretics, laxatives and other substances. Increasing physicians' awareness of imported diet pill use may improve care of patients suffering from the pills' many adverse effects.

KEY WORDS: amphetamines; immigrant health; anorectics; fenproporex; adverse drug reaction.
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INTRODUCTION

The US Food and Drug Administration (FDA) has banned the great majority of amphetamine-based anorectics.[1] However, FDA-banned appetite suppressants are commonly prescribed in many parts of the world, especially in South America.[2] The second most commonly consumed amphetamine-based anorectic worldwide is fenproporex.[2] Due to lack of efficacy and safety data, fenproporex has never been approved by the FDA. Initially developed to provide appetite suppression without stimulant effects, fenproporex has since been found to have addictive potential.[3] Fenproporex is rapidly converted in vivo into amphetamine[4] and the latter can be detected in urine for up to 60 hours after ingestion.[5] The United Nations has warned that overprescribing of amphetamine-based anorectics in South America could contribute to their international distribution.[2] In fact, the international availability of fenproporex, combined with Internet sales and other illicit markets, has led to its distribution within the US.[6–8]

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In Europe and South America untested amphetamines have been combined with multiple prescription medications to create potentially hazardous diet pills.[9,10] Physicians prescribe these diet pills which often combine fenproporex with benzodiazepines, selective serotonin reuptake inhibitors, diuretics, laxatives, thyroid hormones and other substances.[9,10] One study documented that 18% of young immigrant Brazilian women visiting a primary care practice had used these compounded diet pills while they were living in the US.[7] Given their availability in the US, the FDA has issued a warning regarding the use of fenproporex-based compounded diet pills.[6]

Despite the FDA warning, little is known regarding the harm these diet pills cause individuals in the US. Most providers in the US are unaware of the existence of these pills, and only one previously published case report describes the medical consequences of fenproporex-based anorectics in the US.[8] The following case reports provide further evidence of the risks these imported diet pills pose to US residents.

CASE REPORTS

Patient 1

A 26-year-old female presented with a two-year history of multiple physician visits for a variety of unexplained symptoms including chest pain, palpitations, headaches, insomnia, nausea and fatigue. Her medical history was unremarkable, and she had no history of eating disorders or recreational substance abuse. She was a divorced single mother.

Her presenting symptoms began when she started using compounded diet pills from Brazil in an effort to lose weight following pregnancy. She did not suffer from post-partum depression, and she began using the diet pills when she stopped breastfeeding her infant daughter at 6 months of age. After she lost 30 lbs, she stopped the pills for one month during which time she experienced cravings for the diet pill, but her other symptoms resolved. She started to regain the weight and restarted the diet pills; at which point her symptoms recurred. She acquired the pills from an acquaintance and paid $120 for a month's supply of three different types of pills. She was instructed to take one of each type of pill twice daily. The pill vials were labeled in Portuguese and included the names of another person, a physician, and a pharmacist as well as a regional council of pharmacists' license number.

Physical exam revealed a seated blood pressure of 100/70 mm Hg and pulse 106 beats per minute, standing blood

pressure 80/60 mm Hg and pulse 120 beats per minute, body mass index (BMI) 24.7. She appeared tired and weak, the heart rate was tachycardic with a regular rhythm, and the remainder of her exam was normal. Results of laboratory tests included leukocyte count of 11,400/μL (normal 4–10,800/μL) and platelets 422,000/μL (normal 150–400,000/μL). Hemoglobin, complete metabolic panel, thyroid stimulating hormone, iron studies, folate and vitamin B12 were normal. Her urine toxicology screen was positive for amphetamines (1,000 ng/mL d-methamphetamine was used as a cutoff for "positive") and benzodiazepines (a concentration of 200 ng/mL oxazepam was used as a cutoff for "positive"). Her electrocardiogram revealed sinus tachycardia.

She successfully stopped using the diet pills two months later; at which time she experienced depressive symptoms lasting three weeks but did not seek medical care. Her symptoms subsequently resolved. On follow-up at two years after cessation of imported diet pill use, she was not using any anorectics and had gained 30 lbs (BMI 30.7). The results of her pill analysis by gas chromatography/mass spectrometry are presented in the Table 1.

Table 1. Results of Analyses of Patients' Imported Pills

Pill description	Medications listed on vials and listed quantity in milligrams*	Results of GC/MS analyses†
Patient 1		
Vial #1 small white	Fenproporex 45	Fenproporex
Vial #2 medium white and red	Chlordiazepoxide 15 Bromazepam 3	Chlordiazepoxide
Vial #3 large green	Fluoxetine 30 Furosemide 40 Cascara 250 Senna 170 Bile salts 50 Glucomannan 130	None detected
Patient 2		
Vial #1 small white	Methylethanolamine 30	Fenproporex
Vial #2 large brown	Fluoxetine 10 Furosemide 10 Ascorbic acid 10 Boldo 12 Potassium chloride 16 Cascara 178 Senna 120 Aluminum hydroxide 80 Chlordiazepoxide 5	Fluoxetine

Results of gas chromatography/mass spectrometry (GC/MS) analyses of patients' imported pills. *Medication names were translated from Portuguese. †Many pill components listed would not be detected using our clinical laboratory's GC/MS technology

Patient 2

A 38-year-old man presented after he was suspended from his job as a municipal truck driver following a positive amphetamine urine screen. He began using diet pills from Brazil two weeks before he tested positive on an occupational amphetamine screen. He acquired the pills from an acquaintance. The pills cost $110 for a month's supply, and he was instructed to take one pill from each of two vials twice daily. The vials, labeled in Portuguese, included the names of another patient, a physician, and a pharmacist as well as a regional council of pharmacists' license number. While he was taking the diet pills, he experienced insomnia and palpitations. He reported losing 12 pounds in two weeks.

He had no significant past medical history. He lived with his wife and two children. He had tried intranasal cocaine as an adolescent, but had not used any illicit drugs since that time. He had no formal or informal social connections to Patient 1.

A physical exam, performed two weeks after he had discontinued the diet pills, revealed a BMI of 29.5 and was otherwise unremarkable. His complete blood count, glucose and thyroid stimulating hormone were normal. His occupational urine drug analysis by gas chromatography/mass spectrometry (performed two weeks prior to the evaluation) was positive for amphetamines at 5,393 ng/mL and negative for cannabinoids, cocaine, opiates and phencyclidine hydrochloride. He stopped using the diet pills immediately after the positive urine toxicology screen. His insomnia and palpitations resolved. The results of his pill analysis by gas chromatography/mass spectrometry are presented in the Table 1.

DISCUSSION

These cases demonstrate that US residents can suffer serious health and social consequences from the use of imported prescription diet pills. Patient 1 had multiple medical visits over a two-year period for unexplained chest pain, palpitations and other symptoms likely due to the unreported use of imported compounded diet pills. Patient 2, a municipal truck driver, was suspended from his work for suspected amphetamine abuse as a consequence of imported compounded diet pill use. Because of ease of availability via the Internet[11] and other illicit networks,[7] the health and economic consequences of imported diet pill use may be widespread within certain communities in the US.

The amphetamine derivative fenproporex was detected in both of the patients' pills. Despite concern regarding its safety,[6] fenproporex is frequently prescribed in Brazil.[2,12] Solange Nappo and her colleagues have documented that over 10,000 prescriptions for fenproporex were written in one year in two Brazilian cities with a combined population of 450,000.[12] However, very little data support its use. Since the 1970s, only one controlled trial of fenproporex for weight loss has been published in which 60 participants were randomized to treatment with fenproporex or placebo for six months and were followed for an additional month.[13] Participants randomized to placebo lost 5.3% of their weight and to fenproporex lost 8.8% of their weight, but these results are limited by the fact that more than a quarter of participants were lost to follow-up.[13] In addition, participants who received fenproporex were more likely to report constipation, joint pains, insomnia, diaphoresis, bruising, blurred vision and tremor.[13]

Little data exist to support the benefits of fenproporex for weight loss, and its use presents many potential health risks. Because it is an amphetamine derivative, it may pose similar risks as those of the other amphetamine-derived anorectics.[1] Among the most significant of these was an outbreak of pulmonary hypertension that was traced to aminorex in Europe in the 1960s[14] and mitral valve disease associated with fenfluramine/phentermine use in the US in the 1990s.[15] Although data on fenproporex is limited, case reports have described a link with suicide attempts,[3]

addiction,[3,16] subarachnoid hemorrhage [17] and morphea.[18] Given the lack of monitoring of fenproporex use, it is certainly possible that other life-threatening events are currently occurring but unrecognized.

In addition to its adverse health effects, the use of fenproporex may lead to negative economic and legal consequences. Urine toxicology screening is used in many occupational settings to detect amphetamine abuse.[19] Amphetamine screening tests are commonly considered positive if the concentration of urine amphetamines exceeds 1,000 nanograms per milliliter.[19] After an initial positive screen, a concentration of greater than 500 nanograms per milliliter is a common threshold when performing repeat testing.[19] Although consumption leads to urinary excretion of fenproporex, fenproporex is not detected by commonly used clinical urine tests.[4] However, since fenproporex is rapidly converted in vivo into amphetamine, the amphetamine metabolite is readily detected by commercial urine toxicology tests.[4] Consumption of a low daily dose of 10 mg of fenproporex led to the detection of amphetamine within 3 hours in urine with peak urinary levels greater than 4,000 nanograms per milliliter.[4] Patient 2's urine amphetamine level, over 5,000 nanograms per milliliter, is consistent with the published literature.

These two patients were consuming fenproporex within a compounded diet pill. In Brazil, prescriptions for these compounded diet pills are usually obtained from physicians in private practice who often market themselves as obesity experts.[20] Prescriptions are brought to special pharmacies, *farmácias de manipulação*, where the diet pills are prepared.[21] These pills usually contain three to six prescription medications and often combine amphetamines, benzodiazepines, antidepressants, diuretics, thyroid hormones, laxatives and other substances.[20,22] None of the medications included in these diet pills are indicated for the treatment of obesity according to commonly accepted practice guidelines.[23,24]

In one study, two-thirds of diet pill users experienced side effects, most commonly insomnia, anxiety, palpitations, fatigue and nausea/vomiting.[7] In addition to a case report of severe abdominal pain in the US,[8] case reports from Spain have described the association of these compounded diet pills with hyperthyroidism,[25] hypokalemia,[26] and syncope.[26]

An additional concern is that compounded diet pills might not include the medications that they are reported to contain. For example, analysis of Patient 1's pills in vial #3 did not reveal fluoxetine, although it was listed on the label. Furthermore, Patient 2's vial #1 listed "methylethanolamine" but instead included fenproporex. It is possible that instead of the listed medications other substance may be included in compounded pills, and these contaminants can have life-threatening consequences. Although it has yet to be documented with these pills, errors in compounding diet pills have lead to renal failure and cancer.[27]

A limitation of these case reports is that many of the substances listed on the patients' bottles such as furosemide, bromazepam and various laxatives would not have been detected by gas chromatography/mass spectrometry by the clinical laboratory. Although it was not possible to determine the precise components of these patients' pills, these cases demonstrate that clinical laboratories can detect the amphetamine, benzodiazepine and selective serotonin reuptake inhibitor components commonly included in these imported diet pills.

While these prescription diet pills remain available, US residents will continue to suffer health and economic consequences from their use. Clinicians should be aware of the composition and dangers of the fenproporex-based diet pills imported from South America. When caring for patients concerned about their weight, physicians should review the use of alternative weight loss techniques, including imported diet pills. Given the wide variety of potential adverse effects from the medications included in these diet pills, patients attempting to lose weight who experience unexplained symptoms should be specifically questioned regarding the use of imported diet pills.

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