Clinical Biochemistry 68 (2019) 55–57

Contents lists available at ScienceDirect

Clinical Biochemistry

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

Case Report

Severe hot flashes and hospitalization after supposed niacin flushing in a woman undergoing pre-employment urine drug testing

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ARTICLE INFO

Keywords:
Hot flashes
Niacin
Drugs testing

1. Introduction

With the increasing number of drug users and drug overdose related deaths, drug abuse has become a healthcare and social problem. Drug testing is an important tool for identifying drug abusers and monitoring patient compliance.

One of the major challenges of urine drug testing is interference. Drug abusers often try to pass drug testing by substituting their urine with synthetic urine obtained from various sources, ingesting different products to "flush out" drugs or adulterating urine samples with various chemicals (e.g., bleach) that would interfere with the analytical process of drug detection.

Flushing and detoxification agents are often presented as "effective" means for deceiving drug testing. Products rich in caffeine and diuretics are consumed to increase the output of urine and produce diluted urine, leading to concentrations of drugs of abuse (DOA) below the limits of detection. Another commonly used method is based on "rapid detoxification" and elimination of DOA and their metabolites by intense sweating (e.g., exercise, heat exposure) or consumption of various supplements. Metabolites of many of the illicit drugs, such as cannabinoids and cocaine, can be stored within the adipose tissue and released slowly, leading to their detection upon testing. Vitamin B_3, which includes three forms: nicotinamide (niacinamide), niacin (nicotinic acid) – the most commune form, and nicotinamide riboside is an anti-hyperlipidemic agent, is able to favorably affect lipids metabolism. Niacin consumption at high doses, although associated with a variety of side effects, is often used by drugs users as a method of fast detoxification, despite the fact that its utilization for this purpose is not substantiated by scientific evidence.

We present a case with direct laboratory evidence of niacin overdose, which was possibly used in a potential attempt to pass the drug test in the context of the patient's drug testing. Nevertheless, no objective evidence was obtained in order to confirm the use of niacin as an attempt to circumvent the scheduled urine drug test.

2. Case presentation

A 53-year-old woman presented at a urine collection site for a sample collection as a part of the pre-employment requirements (drugs, alcohol and cotinine testing). While forms and collection were completed, she started to develop skin redness and strong hot flashes around the face, neck, chest and arms, followed by a strong itching and skin burning sensation, red patches on the abdomen and shoulders, nausea, slight lightheadedness, mild tremor, and panic with hyperventilation. The woman was seated with persisting symptoms while the paramedics were contacted. Then the patient was transported to the Emergency Department (ED) where further investigations were pursued.

Upon initial ED examination, her body temperature was 101.3 °F (38.5 °C) with dry, strong flushing over most of the upper body, slightly increased pulse rate (115 beats/min, normal range: 60–100 beats/min) and ventilation rate (19 breaths/min, normal range: 12–15 breaths/min) without difficulty breathing, blood pressure of 122/60 mmHg, and mild anxiety. The patient complained of strong itching and skin burning

Abbreviations: ABGs, Arterial Blood Gases panel; AG, Anion Gap; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; BUN, Blood Urea Nitrogen; CBC, Complete Blood Count; CMP, Complete Metabolic Panel; ECG, Electrocardiogram; ED, Emergency Department; DOA, Drugs Of Abuse; OTC, Over The Counter; TSH, Thyroid Stimulating Hormone; IR, Immediate-release; SR, Sustained-release; ER, Extended- release

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https://doi.org/10.1016/j.clinbiochem.2019.04.005
Received 20 December 2018; Received in revised form 29 March 2019; Accepted 7 April 2019
Available online 08 April 2019

sensation. The hand tremor was discreet, barely detectable. Laboratory initial evaluation revealed a normal glucose concentration, normal levels of liver enzymes including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), slightly elevated blood urea nitrogen (BUN) (21 mg/dl or 7.5 mmol/l, normal range: 6–20 mg/dl or 2.1–7.1 mmol/l), normal concentrations of thyroid stimulating hormone (TSH) and free thyroxin (fT4), and unremarkable electrolytes as well as complete blood count (CBC). Arterial blood gases (ABG's) analysis showed normal pH, but slightly low pCO_2 (34 mmHg, normal range: 35–45 mmHg), slightly elevated lactic acid (2.1 mmol/l, normal range: 0.5–2.0 mmol/l) and anion gap (AG) (17 mmol/l, normal range: 8–16 mmol/l). No serum ketone bodies, alcohol, acetaminophen and aspirin were detected. Urinalysis was unremarkable. The patient did not complain of any abdominal or chest pain, no palpitations were detected and electrocardiogram (ECG) was normal. The patient stated that she was overall healthy, with no known medical history. She mentioned that she had not eaten since last evening (approximatively 16 h ago), but she specified that she had ingested a few tablets of multivitamins with a glass of water in the morning before rushing to the urine collection site. Since the patient mentioned that she had ingested vitamins and considering her flushing symptoms, blood niacin was tested and the result was 69.40 μg/ml or 563.71 nmol/ml (reference range: 0.50–8.45 μg/ml or 4.06–68.63 nmol/ml). Most of the symptoms continued for a little while and a decision was made to hospitalize her for observation.

During the observation, the patient was hydrated with 500 ml IV fluids. Symptoms disappeared in a few hours after hospitalization. Within 24 h, the patient was discharged. At the time of discharge, all routine laboratory results (Comprehensive Metabolic Panel, CBC, ABGs, serum pH and lactate) and functions were normal and none of the previous symptoms were present.

Urine drug screening test was negative; with normal specific gravity (SG), creatinine and pH.

Urine sample was not sent for confirmation, as the medical team considered it is unnecessary.

3. Discussion

Skin flushing is a sudden reddening of the face, neck, or upper chest due to a suddenly increased blood flow. There are multiple conditions associated with facial skin flushing in adults (Table 1).

While certain conditions or circumstances triggering skin redness can be fast and easily ruled in/out, some require further investigations. Careful assessment of medical history, clinical presentations, and laboratory evaluations can support differential diagnosis and establish the final diagnosis for appropriate management.

Table 1
Conditions associated with facial skin flushing.

Conditions associated with facial/upper body skin flushing
High fever
Hormonal changes (e.g. menopause and pregnancy)
Hyperthyroidism
Rosacea
Carcinoid syndrome
Intoxication with alcohol
Niacin overdose
Allergic reactions
Certain infectious disease in children (e.g. Scarlet Fever and Fifth Disease aka "slapped cheek disease")
Medication (e.g. vasodilators such as Nitroglycerin, doxorubicin, opiates)
Heat exposure
Panic attack
Psychological distress/emotional triggers (e.g. embarrassment, anger, anxiety, tension, agitation, stress)
Strenuous exercise
Consumption of hot or spicy foods

Probably the most common cause of skin flushing in women who have passed reproductive age is hormonal changes during perimenopause and menopause. The decrease in estrogen production, combined with sharp, local vasodilation seems to be the culprit [1]. Since this patient's symptoms lasted for a few hours, hot flashes caused by hormonal changes were unlikely.

Increased blood flow in the skin along with peripheral vasodilatation may be responsible for facial flushing, accompanied by warm feeling and sweating in patients with hyperthyroidism, e.g., Graves' disease. [2]. As both TSH and fT4 were normal for this patient, thyroid conditions as the cause of the hot facial flashes and skin burning sensation were ruled out.

Carcinoid syndrome is the result of overproduction of serotonin and kallikrein due to the presence of abdominal carcinoid tumors. One of the most important clinical finding is flushing, mainly of the facial skin, head and the upper part of thorax, due to vasoactive effects of serotonin. Carcinoid syndrome is also associated with difficulty of breathing and secondary restrictive cardiomyopathy that can be detected via ECG and imaging [3]. Laboratory diagnosis of carcinoid tumors relies on evaluations of serum and especially urine (24-hour collection) of serotonin and its metabolite 5-hydroxyindoleacetic acid (5-HIAA), and serum chromogranin A. Liver enzymes (ALT and AST) are often elevated as well [4]. Serum serotonin of this patient was within normal limits (122 ng/mL, reference range: 50–220 ng/mL) and her ALT and AST were within normal reference ranges as well. Therefore, abdominal carcinoid tumors were ruled out.

Niacin overdose can cause facial and upper body flushing as well as pruritus, nausea, vomiting, and palpitations, especially at high doses. The patient stated she ingested a few tablets of multivitamins in the morning of scheduled urine drugs testing. The concentration of niacin in the patient's blood was evaluated via HPLC and the result was 69.40 μg/ml or 563.71 nmol/ml (reference range: 0.50–8.45 μg/ml or 4.06–68.63 nmol/ml). Based on this finding, it was thought that severe hot flashes and other clinical symptoms were due to niacin overdose. The scores calculated based on the Naranjo algorithm [5] was 8, highly suggesting the probability of niacin induced adverse reaction in this patient. To our knowledge, this is the second case report that provides the concentration of plasma niacin metabolite as evidence of niacin overdose [6]. Within 24 h of hospitalization, the patient was released. At that time, all laboratory results were normal and none of the previous symptoms were still present.

Niacin is involved in the synthesis and metabolism of carbohydrates, fatty acids, and proteins and its deficiency causes pellagra. In moderate doses, supplements of niacin are often used as an anti-hyperlipidemic agent [7]. The use of niacin for nonmedical purposes has been increasing in prevalence in recent years, particularly in attempts to alter results of urine drug tests. Although there is no scientific evidence that niacin can alter a urine drug screen result, easily retrievable information exists online touting niacin as a potential way to prevent detection of tetrahydrocannabinol (THC) [8]. It is difficult to determine if the patient whose case is described herein intentionally consumed supplements containing high doses of niacin with the purpose of defying the drug test, or if this was an involuntary action. However, the possibility of niacin overdose being potentially used in an attempt to pass the drug test cannot be overlooked and clinicians should be aware of this phenomenon.

Many OTC supplements, vitamin mixtures (e.g. "Super B complex", "Stress complex") or other herbal supplements are poorly regulated and tested, and can contain various concentrations of niacin in every tablet. Combined, as in this case, these supplements can contain hundreds of milligrams of niacin and do not only lead to adverse effects, but they are toxic. The niacin flushing results from the stimulation of prostaglandins followed by cutaneous vasodilatation, redness and warm skin sensation, sometimes accompanied by tingling or itching. The onset of flushing can occur quickly after beginning of absorption and usually lasts for about 1–2 h (niacin elimination half-life is 45 min). It is a transient,

non-allergic response, but it may result in patient discomfort. Interestingly, for this patient, the relative longer duration of symptoms (a few hours) was puzzling, as this is not the regular pattern associated with niacin overdose [9]. It should be noted that there are various types of niacin supplements available on the market: Immediate-release (IR), Sustained-release (SR) and Extended-release (ER) preparations. Depending on the formulation, niacin can be released immediately or over time. IR niacin is released as soon as it is taken and is the form that causes the majority of niacin-induced side effects. Sustained-release (SR) and extended-release (ER) niacin formulations are designed to release niacin over a period of time, so it will take longer for the niacin to be cleared. As such, the side effects may also be longer, particularly in overdose cases. Many OTC supplements of niacin are not properly labeled, not stating what type of formulation they contain (e.g. IR or SR) and consumers might make inappropriate assumptions.

Since this patient's flushing lasted for a longer time, she might have ingested both IR and SR or ER niacin.

Episodes of flushing usually occur when niacin is consumed in doses of 500 mg or higher but according to CDC reports, they can actually occur at any dose [10]. Furthermore, some individuals can develop tolerance when high doses of niacin are used over time while others develop toxic reactions. Toxic reactions of niacin overdose can be associated with metabolic and lactic acidosis, nausea, vomiting, diarrhea, hypotension, myalgia, palpitations/tachycardia and hepatotoxicity [9]. SR preparations of niacin are implicated more often in more severe presentation of niacin intoxication, associated with metabolic acidosis and hepatic injury and dysfunction [11,12]. Mild hyperglycemia is a common complication of niacin overdose due to its concurrent induced insulin-resistance [11]. However, this patient had normal serum glucose level at presentation and during 24 h of hospitalization and no ketosis. Nevertheless, the patient had mildly elevated lactic acid (2.1 mmol/L, normal range: 0.5–2.0 mmol/l) and anion gap (AG) (17 mmol/l, normal range: 8–16 mmol/l), which are often associated with high-dose niacin intake, as described by Earthman *and colleagues* [12].

With increased numbers of drug abusers and an increase in the toxicology scrutiny (e.g. workplace testing, pain management, drugs compliance, etc.), abusers are constantly looking for modalities to masquerade their exposure.

In addition to niacin, a wide range of chemicals are used for adulteration of urine specimens, interfering with the analytical process of drugs detection [9]. The mandatory evaluation of specimen's integrity (temperature, color, pH, SG, creatinine, presence of oxidants, etc.) is meant to discourage the practice of specimen adulteration. A variety of supplements and methods have been used as innovative practices to "beat" the drug testing. A commonly used method is based on either overhydrating or use of diuretics which aim to "flush out the drugs", but also to dilute the urine to an extent that the concentration of the drug in the specimen will be below the established cutoffs [13].

4. Conclusion

This report presents a niacin overdose case with direct evidence of blood niacin concentration and demonstrates that niacin could be potentially used in an attempt to pass a drug test, although this may not be acknowledged by the patient. Many products (chemical adulterants or supplements) could be used to deceive urine drug testing. This is a continuing challenge to clinical laboratories. Laboratorians should use various tests to identify these adulterants for accurate drug testing results.

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