Fluconazole-associated Stevens-Johnson syndrome following single-dose use in an HIV-negative patient

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ABSTRACT:

We describe a case of fluconazole-associated Stevens-Johnson syndrome (SJS) in a healthy, young woman following single-dose treatment for presumed vaginal candidiasis. After several ambulatory consultations, she was hospitalized with worsening dysphagia, odynophagia, conjunctivitis, mucosal ulcers and reduced oral intake. Over her two-week stay, cutaneous and mucosal involvement worsened, with esophageal lesions identified on endoscopy. Investigations did not reveal an alternative cause for her presentation, and subspecialty consultants supported the diagnosis of fluconazole-associated SJS. She required parenteral nutrition and analgesia for six days in hospital before discharge. We provide a review of the literature on all cases of fluconazole-associated SJS and toxic epidermal necrolysis (TEN), and apply the Naranjo probability scale for drug-induced adverse reaction to each case. Given the wide availability of fluconazole, this is a rarely reported adverse reaction with only 13 other case reports rated as 'probable' and only two other cases following a single dose exposure.

CASE:

A 26-year-old Caucasian woman took a single, oral dose of fluconazole 150 mg, obtained over the counter, for self-diagnosed vaginal candidiasis. Three days later, bilateral ocular erythema and pruritus with exudate developed. One day after ocular involvement, she developed buccal ulcers and odynophagia. She attended a walk-in clinic and was prescribed a chlorhexidine oral rinse and amoxicillin and tobramycin eye drops for presumed conjunctivitis. The following day, she presented to an Urgent Care Clinic (UCC) due to lack of improvement in symptoms and was prescribed Valacyclovir for presumed stomatitis. Four days after, she

returned to the UCC with worsening oral ulcers, and increased ocular pruritus. She was prescribed Benzydamine mouthwash, and instructed to discontinue her eye drops. Later the same day, she returned with new dysphagia, worsening odynophagia, and nausea. She was prescribed oral analgesics, and referred to see Ophthalmology the following day. The possibility of Stevens-Johnson syndrome (SJS) was considered by Ophthalmology, so the patient presented to the Emergency Department with now severe odynophagia, chest pain radiating to her back, and intermittent dysuria. In response to worsening symptoms and reduced oral intake, the patient was referred to Internal Medicine and admitted to hospital.

On admission, her vitals were: blood pressure 131/79 mmHg, heart rate 97 bpm, oxygen saturation of 99% on room air and temperature 38.1°C. She had superficial ulcers in the oral mucosa, lesions on her edematous lips and bilateral conjunctivitis (Figure 1).

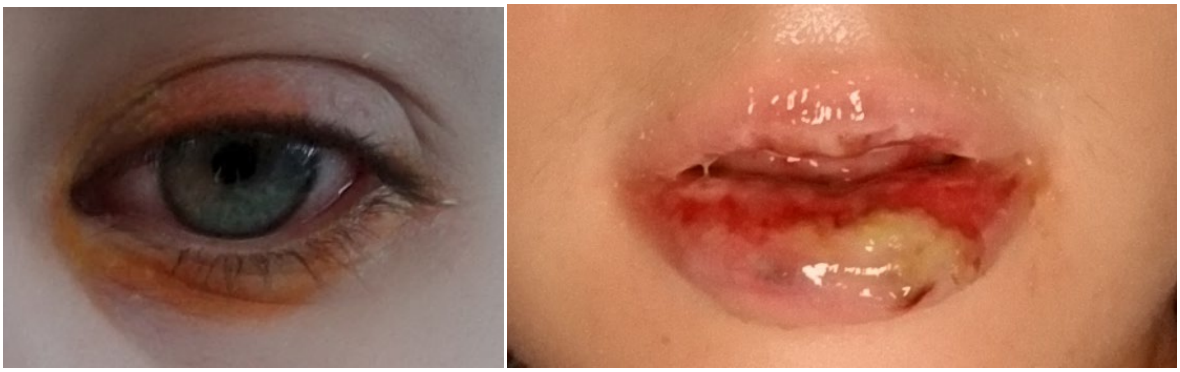

Figure 1. Lip lesions and conjunctivitis on our patient

She had target lesions on her hand, arm, and foot; however, Nikolsky's sign was negative. A vaginal exam was negative for vaginal lesions. Overall, skin involvement was <10% and she was diagnosed with SJS.[1] Given that it only involved two mucosal surfaces, the calculated SCORTEN score was 0, which has an expected mortality of 3%.[2] On further history, the patient did not report a family or personal history of malignancy, autoimmune conditions, constitutional

symptoms, or joint pain. She had normal, prior pap smears and a remote, prior Epstein-Barr infection. Social history did not reveal risk factors for Human Immunodeficiency Virus (HIV) infection.

In hospital, the patient continued to be febrile for the subsequent four days, with her maximum temperature reaching 39.6°C. A conjunctival virology culture was negative for Herpes simplex 1&2, varicella zoster, and adenovirus all by PCR. Her initial investigations revealed a Hemoglobin of 135 g/L (115 – 165 g/L), Leukocytes 10.8 $x10^9$/L (4-11 x 10^9/L) with no eosinophilia, Platelets 361 x 10^9/L (150-400 x 10^9/L), Creatinine 69 umol/L (50 – 98 umol/L), normal electrolyte panel and normal liver enzymes. Her CRP was elevated at 59.9 mg/L (<5 mg/L). A throat culture was negative for *Streptococcus pyogenes* Group A. Serology testing revealed negative mono screen, negative CMV IgG, and a reactive Epstein Barr Virus VCA, EA, and EBNA due to a past infection. Blood cultures were negative x 2. She declined HIV testing in hospital and was deemed to be low risk given history. A chest X-Ray completed during her admission was normal. An endoscopy was performed which revealed multiple small, partial thickness ulcerations without perforation in the patient's esophagus.

Due to the nature of the patient's symptoms and endoscopy findings, the patient was given intravenous fluids, intravenous hydromorphone, oral analgesic rinses, intravenous antacids, antiemetics, and steroidal eye drops. Given the patient's 10 day history of reduced oral intake, total parenteral nutrition was begun. Thoracic surgery, Allergy and Immunology, Clinical Pharmacology and Toxicology, and Ophthalmology consultants were involved in her care over the course in hospital. The patient was able to tolerate oral intake and discharged by day 13 post-admission. A repeat scope three months post-discharge revealed healed proximal esophageal

ulcers. Skin allergy testing was completed in follow-up, and was normal. No specific antifungal sensitivity testing was completed. The patient has remained symptom free one year after her initial event.

DISCUSSION

Fluconazole is an antifungal medication indicated in the treatment of oropharyngeal and esophageal candidiasis, serious systemic candidal infections, cryptococcal meningitis, and prevention of the recurrence of cryptococcal meningitis in patients with acquired immunodeficiency syndrome.[3] The drug is available over-the-counter without prescription in several developed countries including Canada, United Kingdom and Australia. It is prescription-only in the United States where more than 3 million prescriptions were dispensed in 2017.[4]

Adverse effects associated with single dose fluconazole for vaginal candidiasis include, in order of decreasing frequency: headache, nausea, and abdominal pain.[3] The two most serious adverse clinical events noted during clinical trials with fluconazole were: exfoliative skin disorders, such as SJS, and hepatic necrosis.[3] These reactions were more commonly noted in patients with underlying disease such as AIDS and malignancy.[3] Stevens-Johnson syndrome (SJS) is a rare and severe mucocutaneous adverse reaction associated with a high mortality rate.[5] There are many agents associated with SJS, the most common including: antibiotics, allopurinol, antiepileptics, and nonsteroidal anti-inflammatory agents.[6] Fluconazole's product monogram identifies exfoliative skin disorders, such as SJS, as one of its most serious adverse clinical events.

SJS involves keratinocyte death resulting in dermal-epidermal junction area separation secondary to a causative agent or process.[7] SJS is viewed on a spectrum along with toxic

epidermal necrolysis (TEN). A specific cause of SJS/TEN has yet to be identified, but is believed to result from a cumulative effect of aligned risk factors, such as drug structure, and genetic predisposition. The immune component of SJS/TEN involves a delayed-type drug hypersensitivity reaction with the drug acting as a foreign antigen recognized by T-cell receptors, activating the adaptive immune response resulting in SJS/TEN.[6] SJS/TEN can be triggered by drugs, infections and malignancies, with infections being the leading cause in children versus drugs and malignancies in adults (Table 1).[7]

Table 1. Drugs and Conditions Associated with Stevens-Johnson syndrome and toxic epidermal necrolysis[6,7,8,9]

Drugs	**Infections and Malignancies**
More Frequently Associated: Allopurinol Antiepileptic agents (Carbamazepine, Hydantoins, Barbiturates, Phenylbutazone, Lamotrigine, Phenobarbital, Phenytoin) Antibacterial sulfonamides (Sulphadoxine, Sulphadiazine, Sulphasalazine, Cotrimoxazole) Lamotragine Nevirapine Oxicam-derived NSAIDs (Meloxicam, Piroxicam)	**Viral:** Herpes simplex virus HIV Coxsackievirus Influenza Hepatitis Lymphogranuloma venereum Smallpox Enterovirus Epstein-Barr virus
Phenobarbital Phenytoin Amithiozone Aminopenicillins	**Bacterial:** Group A beta-hemolytic streptococcus Diphtheria bacilli Brucellosis Typhoid fever Tularemia Mycobacteria Mycoplasma
Less Frequently Associated: Cephalosporins Macrolides Fluoroquinolones Tetracyclines Vancomycin Rifampin Ethambutol Acetic acid-derivative NSAIDs (Diclofenac) Beta-blockers ACE inhibitors Calcium channel inhibitors Thiazide diuretics	**Fungal:** Paracoccidiodomycosis Dermatophytosis Histoplasmosis
	Protozoan: Malaria parasites Trichomonas
	Malignancies: Carcinomas Lymphomas

Sulfonylurea antidiabteics Insulin Propionic acid-derivative NSAIDs (Fenbufen, Ketoprofen, Naproxen, Ibuprofen)	

The classic manifestation of SJS and TEN involves an initial "flu-like" prodromal phase involving malaise, fever, sore throat, coughing, eye burning, myalgia, arthralgia and anorexia, which can last up to a week.[6] This phase is followed by cutaneous and mucous membrane inflammation, pain, and other systemic involvement with symptoms usually showing 4-28 days after initial drug intake.[6] In our case, the patient showed symptoms of conjunctivitis and oral lesions within 3 days after initial dose, with symptomatic progression over the following 10 days.

The types of lesions include atypical target lesions, consisting of two concentric rings, and macular lesions, which ultimately lead to sloughing of necrotic skin and a positive Nikolsky's sign.[7] Nikolsky's sign describes detachment of the full surface of the epidermis when light lateral pressure is applied.[8] The rash typically begins on the trunk, gradually spreading, often sparing the palmoplantar surfaces.[7] SJS is differentiated from TEN by the degree of skin involvement, with TEN having >30% involvement and SJS having <10% involvement; 10-30% is defined as an overlap between SJS and TEN.[1] In SJS/TEN, mucosal involvement occurs in two or more distinct mucosal surfaces, and this may precede or follow skin involvement.[7] About 10-30% of cases occur with fever and lesions in the gastrointestinal and respiratory tracts, and 39-61% of cases involve ocular symptoms.[7] Complications may include: corneal ulcers, anterior uveitis, panophthalmitis, gastrointestinal adhesions, urinary incontinence, vaginal stenosis, renal tubular necrosis, renal failure, skin ulceration with re-infection and scarring.[7] The risk of secondary bacterial infection,

electrolyte imbalances, and thermoregulation issues increases with lesions and loss of skin integrity.[7]

Although SJS is well reported in the literature, there are very few case reports of fluconazole-associated SJS/TEN, particularly after single doses. We analyzed case reports on fluconazole-associated SJS and TEN (Table 2). Nine of the 15 cases were fluconazole-associated SJS, and seven were fluconazole-associated TEN. We applied the Naranjo nomogram which uses rules of causation to measure the likelihood that the adverse event was related to the drug in question rather than other potential causes.[10] Fourteen of the cases were probable, and two were possible fluconazole-associated SJS/TEN (Table 3).

144 **Table 2.** Summary of existing case reports of fluconazole-associated SJS and TEN†
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Reference	Demographics	Surfaces Involved	Relevant Comorbidities	Diagnosis	Dose of Fluconazole	Treatment*
Ofama UR et al.[9]	52 F Caucasian	D, L, OM	HZ & ?HIV	TEN	Fluconazole 150 mg/day (5 doses prior to admission)	Pain control, skin, mouth and eye care, IV fluids
Craythorne E et al.[11]	40 F	GM, O, OM	AH	SJS	Fluconazole 100 mg/day (13 doses prior to admission)	Prednisolone 20mg OD for hepatitis, continued for treatment
	23 F	D, GM, L, O, OM	AuH	SJS	Fluconazole 100 mg/day (16 doses prior to admission)	Prednisolone 20mg OD for hepatitis, continued for treatment
Monastirli A et al.[12]	50 F Caucasian	D, L, O, OM	None	SJS	Fluconazole 200 mg/day (7 doses prior to admission)	Antiseptic eye drops, oral and skin washings, IV methylprednisone 120 mg/day for 3 days with decreasing dose over 3 weeks, topical amphotericin suspension for vaginal candidiasis
Azón-Masoliver A et al [13]	33 M	D, OP, O, GM	HIV	TEN	Fluconazole 50mg q12h (7 doses prior to admission)	IV fluids, antihistamines, IV methylprednisone 40 mg/day, skin soakings, antiseptic eye drops, oral antiseptic washes
Gussenhoven MJ et al.[14]	30 M	D, OM,	HIV	SJS	Fluconazole 150 mg twice monthly (7 doses prior to admission)	Antibiotics
Lester LJU et al.[15]	30 F	D	AIDS	TEN	Fluconazole unknown **single dose**	IV Methylprednisone sodium succinate for 3 days, amphotericin B (for thrush), antibiotics, Diphenhydramine hydrochloride,

						Acetaminophen, Topical triamcinolone 0.1% cream for lesions
Pasmatzi E et al.[16]	32 F Caucasian	T, E, OM, L, O	None	SJS	100-200 mg/day Fluconazole (1-4 doses prior to admission)⁋	IV Methylprednisone 80-160 mg/day for 3-6 days, oral and skin washings, antiseptic eye drops
	42 F Caucasian	T, E, OM, L, O	None	SJS	100-200 mg/day Fluconazole (1-4 doses prior to admission) ⁋	IV Methylprednisone 80-160 mg/day for 3-6 days, oral and skin washings, antiseptic eye drops
	59 M Caucasian	T, E, OM, L	None	SJS	100 mg/day Fluconazole (1-4 doses prior to admission) ⁋	IV Methylprednisone 80-160 mg/day for 3-6 days, oral and skin washings
George J et al.[17]	28 M	D, O	HIV	TEN	Fluconazole 150 mg daily (2 doses prior to presentation)	Analgesics, Azithromycin, Antihistamines, eye care, and parenteral hydration
Islam S et al.[18]	Neonate F (21 DOL)	D, O, OM, OP	NH?	TEN	Fluconazole first loading dose, then 10g per kg/daily IV (9 doses prior to presentation)	Vancomycin and cefepime (Sepsis)
Lewerenz V et al.[19]	43 F Caucasian	D, L, GM, OM	T1DM, Mult-iple sclerosis	TEN	Fluconazole **single**, unknown dose	Oral prednisone, antibiotics, triamcinolone acetonide cream
Tseng J et al.[20]	49 M, Asian	Unknown, SCORTEN Score of 3	HIV, Late latent syphilis	TEN	Fluconazole unknown dose/frequency	IVIG 1g/kg/day x 4 days

Thiyanaratnam J et al.[21]	23 M Indian	D, GP, L, OM	None	SJS	Fluconazole 400 mg (2 doses, 20 days apart, prior to admission)	Oral prednisone, Diphenhydramine, Viscous lidocaine, Topical mupirocin
Our Case	26 F Caucasian	D, OM, Es, O, L	None	SJS	Fluconazole 150 mg, **single dose**	IV fluids, pain medication, oral antiseptic wash, eye drops

† Abbreviations: AH, alcoholic hepatitis; AuH, autoimmune hepatitis; CR, current report; D, dermis; Es, esophageal; GM, genital mucosa; GP, glans penis; L, lips; NH, neonatal hemochromatosis; O, ocular; OM, oral mucosa; OP, oropharyngeal; HIV, human immunodeficiency virus; HZ, herpes zoster; SLE, systemic lupus erythematous; SLN, secondary lupus nephritis; T1DM, type 1 diabetes mellitus

*In all treatments, fluconazole was stopped.

‖ Case reports with incomplete information.

Table 3. Probability Score for all 16 cases using the Naranjo Scale*

NARANJO SCALE ALGORITHM[10]				CASE REPORTS⁋														
Question	**Yes**	**No**	**Do Not know**	**OU**	**CEa**	**CEb**	**MA**	**AM**	**GM**	**LL**	**PEa**	**PEb**	**PEc**	**GJ**	**IS**	**LV**	**TsJ**	**TJ**	**Case**
Are there previous conclusive reports on this reaction?	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**
Did the adverse event appear after the suspected drug was administered?	2	-1	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	**2**
Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	1	0	0	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	**1**
Did the adverse event reappear when the drug was re-administered?	2	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**
Are there alternative causes that could on their own have caused the reaction?	-1	2	0	2	2	2	2	2	2	2	2	2	2	2	-1	2	0	2	**2**
Did the reaction reappear when a placebo was given?	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**
Was the drug detected in blood or other fluids in concentrations known to be toxic?	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	1	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	1	**0**
Was the adverse event confirmed by any objective evidence?	1	0	0	1	1	1	1	1	0	0	0	1	0	0	0	1	1	0	**0**
	TOTAL SCORE:			**6**	**6**	**6**	**6**	**6**	**6**	**6**	**5**	**6**	**5**	**5**	**1**	**6**	**4**	**6**	**5**

*Total score of ≥ 9 is **Definite** (The reaction followed a reasonable temporal sequence after drug exposure had been established in body fluids or tissues, followed a recognized response to the suspected drug, was confirmed by improvement on withdrawing the drug and reappeared on re-exposure); Total score of 5-8 is **Probable** (The reaction followed a reasonable temporal sequence after a drug exposure, followed a recognized response to the suspected drug, was confirmed by withdrawal but not by exposure to the drug, and could not be reasonably explained by the known characteristics of the patient's clinical state); Total score of 1-4 is **Possible** (The reaction followed a temporal sequence after a drug exposure, possibly followed a recognized pattern to the suspected drug, and could be explained by characteristics of the patient's disease); Total score of ≤ 0 is **Doubtful** (The reaction was likely related to factors other than the drug)

⁋ OU: Ofoma UR et al[9]; CEa: Craythorne E et al[11a]; CEb: Craythorne E et al[11b]; MA: Monastirli A et al[12]; AM: Azón-Masoliver A et al[13]; GM: Gussenhoven MJ et al[14]; LL: Lester LJU et al[15]; PEa: Pasmatzi E et al.[16a]; PEb: Pasmatzi E et al.[16b]; PEc: Pasmatzi E et al.[16c;] GJ: George J et al.[17]; IS: Islam S et al.[18]; LV: Lewerenz V et al[19] ; TsJ : Tseng J et al.[20;] TJ : Thiyanaratnam J et al.[21]; Case : our case report.

Six of the cases involved individuals with known or presumed HIV infection. Our patient declined HIV testing, but was presumed negative based on absence of risk factors. Single dose fluconazole has only been reported in two previous cases. Management most often involved the use of IV corticosteroids, IV rehydration, antiseptic eye drops, and pain management. Many of the cases noted the use of antibiotics, often for prophylaxis against sepsis or localized infection at the site of ulcers. Depending on the extent of skin involvement, burn-style skin care regimes were enacted to improve overall healing and prevent against infection.

In summary, our case adds to the small, yet growing literature of fluconazole-associated SJS after single-dose use in an otherwise healthy, young adult. This case has implications for regulation of fluconazole, given the serious nature of SJS.

TAKE HOME POINTS:

1. Fluconazole, currently an over-the-counter medication not requiring a prescription, is reported here as the probable cause of Stevens-Johnson syndrome in a young, otherwise healthy patient.
2. Our case is only the third reported case of fluconazole-associated Stevens-Johnson syndrome following single dose ingestion.
3. Stevens-Johnson syndrome is a difficult diagnosis to make, and in combination with less commonly associated medications, this can lead to prolongation in diagnosis and increased risk of morbidity and mortality.

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