

Appearance of Anaphylactic Shock after Long-Term Intravenous Itraconazole Treatment

Jie Chen, Xianmin Song, Peng Yang, and Jianmin Wang

Acute lymphoblastic leukemia (ALL), a malignant disorder of lymphoid progenitor cells, affects both children and adults. The high complete remission (CR) rate of chemotherapy in patients with ALL makes it a main strategy for ALL treatment. However, the immune system of these patients is weakened by the disease and further suppressed by intensive chemotherapy and prolonged periods of severe neutropenia; thus, patients with ALL are more vulnerable to fungal infections.¹

Itraconazole is a widely used antifungal drug with broad-spectrum antifungal activity and mostly minor and reversible adverse effects. Common adverse effects of itraconazole include gastrointestinal upset such as nausea, vomiting, diarrhea, and abdominal pain; mild and transient elevation in transaminase levels; skin rash; headache; and mild-to-severe hypokalemia.²⁻⁴ Documented rare, serious adverse effects include premature ventricular contractions, cholestasis, and pancreatitis.⁵⁻⁸ A recent report showed that long-term pulse itraconazole treatment may lead to fatal hepatitis.⁹ Here, we report on a patient with ALL who developed hypotension and hypoxemia shock during intravenous itraconazole treatment for invasive and disseminated lung fungal infection.

OBJECTIVE: To report a rare but severe adverse effect of intravenous itraconazole, anaphylactic shock with hypotension and hypoxemia, in a female patient with acute lymphoblastic leukemia (ALL).

CASE SUMMARY: A 36-year-old woman with ALL received antifungal therapy for pulmonary fungal infections. On day 17 of itraconazole treatment, she developed hypotension and hypoxemia shock after intravenous administration of itraconazole 200 mg, which was eventually reversed by steroid treatment. On days 18 and 19, the patient developed the same type of shock 2 more times in the course of itraconazole administration. These 2 episodes of shock occurred more quickly after intravenous itraconazole administration (100 mg on day 18, 40 mg on day 19), and were reversed by stopping itraconazole and applying steroid treatment. In the modified antifungal therapy, intravenous administration of itraconazole was replaced by oral administration of voriconazole 200 mg twice daily. Shock did not recur after discontinuation of itraconazole treatment. The Naranjo probability scale showed a probable relationship between itraconazole treatment and shock occurrence.

DISCUSSION: Itraconazole is a widely used antifungal drug and is well tolerated. However, long-term itraconazole treatment might lead to serious and even life-threatening adverse effects such as anaphylactic shock, as seen in our patient. T cell reduction caused by immunosuppression and itraconazole accumulation in patients with ALL are considered to be important causal factors for this delayed-type hypersensitivity reaction.

CONCLUSIONS: Anaphylactic shock represents a previously undocumented severe adverse effect associated with long-term itraconazole treatment; patients receiving this therapy and should be monitored closely.

KEY WORDS: anaphylactic shock, itraconazole, steroid.

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Case Report

A 36-year-old woman was admitted to the hospital with a 2-week history of fatigue, fever, malaise, anorexia, gum bleeding, and petechial rash. She was given hydroxyurea 1.5 g 3 times daily for 2 days in a regional hospital because of her high white blood cell (WBC) count (174,500/ μ L). Physical examination on admission revealed only petechia over her lower limbs. She was diagnosed as having

Author information provided at the end of the text.

CD19+CD20+ ALL. After 3 sequential chemotherapy regimens, the patient achieved CR of the neoplastic ALL. However, during antifungal therapy, long-term administration of itraconazole led to unexpected episodes of anaphylactic shock. The detailed timeline for the chemotherapy and antifungal therapy is shown in Table 1.

On day 1 of admission, the patient began a classic MOAPL induction regimen (mitoxantrone 8 mg on days 1–3, cytarabine 200 mg on days 1–7, vinorelbine 40 mg on days 4 and 11, plus dexamethasone 15 mg on days 1–15, L-asparaginase on days 8–17). However, the patient did not achieve hematologic CR, with 44% leukemic blasts on bone marrow aspiration on day 28. During the period of neutropenia caused by the chemotherapy regimen, the patient was administered granulocyte colony-stimulating factor (G-CSF) for severe granulocytopenia (WBC 40/ μ L) and broad-spectrum antibiotics for episodes of febrile neutropenia (temperature $>40^{\circ}\text{C}$). On day 24, the patient developed a dry cough. A chest computed tomography (CT) scan showed bilateral pulmonary infiltrates and *Aspergillus fumigatus* was identified in phlegm. Amphotericin B 0.65

mg/kg daily, which is used frequently against a wide range of fungi, including *A. fumigatus*,¹⁰ was prescribed as the initial antifungal therapy and dexamethasone 1 mg was coadministered to reduce the adverse effects of amphotericin B. The fever disappeared within 48 hours, and a chest CT scan showed improvement in pulmonary infiltrates on day 38.

On day 48, the patient received the second induction therapy using the typical hyper-CVAD regimen (cyclophosphamide 1 g on days 1–3, vinorelbine 40 mg on day 4, doxorubicin 80 mg on day 4, and dexamethasone 40 mg on days 1–4 and days 11–14). G-CSF was administered for the second episode of neutropenia, which was severe and lasted for 20 days. On day 72, a chest CT scan revealed progression of infiltrates, with new condensation, and several cavitary lesions of 1 cm or smaller in diameter appeared at the apex of both lungs. Micafungin 200 mg daily was coadministered with amphotericin B for 2 weeks and then discontinued because no significant improvement was observed. On day 100, a chest CT scan showed no obvious improvement in pulmonary infiltrates, and itraconazole, in a 400-mg loading dose followed by 200 mg daily, was administered with amphotericin B.

On day 103, the patient received the third induction therapy using the MTX/Ara-C regimen (methotrexate 2 g on day 1, cytarabine 5 g on days 2–3). During the third episode of febrile neutropenia, the result of a blood culture for *Klebsiella pneumoniae* was positive; thus, piperacillin 0.5 g 3 times daily was administered intravenously for 2 weeks. The fever disappeared within 72 hours and the blood culture no longer showed *K. pneumoniae*. On day 114, a chest CT scan demonstrated progressive resolution of lung nodules.

On day 117, the patient reported dyspnea, nausea, vomiting, and palpitations after administration of itraconazole 200 mg. Temperature was 37°C , heart rate was 110–130 beats/min, and respiratory rate was 25 breaths/min; blood pressure was too low to be detected. The patient was lethargic, and no pruritus or urticaria was found. Examination of the cardiovascular and abdominal systems was unremarkable. Blood examination showed WBC 230/ μ L, γ -glutamyltransferase (γ -GT) 41 U/L, and urea nitrogen 81.6 mg/dL. Arterial blood gas analysis showed pO_2 47 mm Hg, pCO_2 23 mm Hg, and SO_2 83%. A 12-lead electrocardiogram revealed only nodal tachycardia.

High-dose oxygen therapy was initiated. The blood pressure became stable with administration of dopamine 20 μ g/kg/min, but the

Table 1. Timeline of Chemotherapy and Antifungal Treatment and the Occurrence of Febrile Neutropenia and Shock

Day	Chemotherapy	Antifungal	Comments
1	MOAPL ^a		MOAPL finished on day 17
16			first episode of neutropenia; lasted for 10 days
24		amphotericin B	
48	hyper-CVAD ^b	amphotericin B	hyper-CVAD finished on day 61
62		amphotericin B	second episode of neutropenia; lasted for 20 days
72		amphotericin B plus micafungin	
87		amphotericin B	
100		amphotericin B plus itraconazole	
103	MTX/Ara-C ^c	amphotericin B plus itraconazole	MTX/Ara-C finished on day 105
113		amphotericin B plus itraconazole	third episode of neutropenia; lasted for 10 days
117		amphotericin B plus itraconazole	first episode of shock; reversed by steroid
118		amphotericin B plus itraconazole	second episode of shock; reversed by steroid
119		amphotericin B plus itraconazole	third episode of shock; reversed by steroid
120		amphotericin B	
124		voriconazole	

^aMitoxantrone 8 mg on days 1–3, cytarabine 200 mg on days 1–7, vinorelbine 40 mg on days 4 and 11, plus dexamethasone 15 mg on days 1–15, L-asparaginase on days 8–17.

^bCyclophosphamide 1 g on days 1–3, vinorelbine 40 mg on day 4, doxorubicin 80 mg on day 4, and dexamethasone 40 mg on days 1–4 and days 11–14.

^cMethotrexate 2 g on day 1, cytarabine 5 g on days 2–3.

hypoxemia was unresponsive to high-dose oxygen therapy. Methylprednisolone 40 mg was then administered intravenously. The patient's vital signs gradually stabilized over 5 hours, and the oxygen and dopamine treatment were then withdrawn. Her heart rate dropped to 85–90 beats/min and blood pressure increased to 110/70 mm Hg. Arterial blood gas analysis showed pO_2 82.3 mm Hg, pCO_2 24 mm Hg, and SO_2 96.3%.

On day 118, after administration of itraconazole 100 mg, the patient developed dyspnea and a cough, with white or pink foam phlegm. Her heart rate was 110–130 beats/min and blood pressure was 70/50 mm Hg; oxygen saturation was 70% on room air. On auscultation, bilateral crackles were discovered at both bases of the chest. γ -GT and urea nitrogen levels increased dramatically to 537 U/L and 97.8 mg/dL, respectively. The patient was administered deslanoside 0.2 mg and furosemide 20 mg immediately for treatment of heart failure, but her symptoms were not alleviated until methylprednisolone 40 mg was administered. On day 119, hypotension and hypoxemia occurred for the third time after intravenous administration of only 40 mg of itraconazole. After immediate termination of itraconazole administration and simultaneous initiation of hydrocortisone infusion, the patient's vital signs stabilized. A chest CT scan showed bilateral disseminated infection, with a little amount of pleural and pericardial effusion. Itraconazole treatment was permanently discontinued and amphotericin B treatment was continued.

On day 124, the patient was in CR of ALL and amphotericin B treatment was replaced by intravenous voriconazole treatment (6-mg/kg loading dose followed by 4 mg/kg daily). One week later, a chest CT scan demonstrated progressive resolution of lung nodules, and γ -GT and urea nitrogen levels gradually dropped to normal levels, 34 U/L and 37.2 mg/dL, respectively. Intravenous voriconazole treatment was replaced by suppressive therapy with oral voriconazole 200 mg twice daily. Noticeably, shock did not recur after discontinuation of intravenous itraconazole, indicating a direct relationship between its use and shock. The Naranjo probability scale showed a probable causal relationship between administration of itraconazole and development of shock.¹¹

Discussion

It is believed that about 20% of adverse drug reactions are unpredictable, uncommon, and usually not related to the pharmacologic actions of drugs. These types of reactions often do not appear until a drug is widely marketed and used.¹² Itraconazole has been in use for a long time, and some of its adverse effects have been discovered.^{2–9} In this report, we found that a patient with ALL developed serious hypotension and hypoxemia on 3 occasions after or during intravenous itraconazole administration. Of particular note is

that the initial shock occurred after 2 weeks of itraconazole treatment at the recommended safe dose.

Other drugs that the patient had taken were considered to be unlikely culprits, because she had been receiving them during and, for several months, before and after the adverse events developed. She manifested a lower blood pressure and oxygen saturation only 15 minutes to about 1 hour after being exposed to itraconazole and the symptoms were eventually reversed by steroid treatment. Moreover, after discontinuation of itraconazole treatment, shock did not recur. As stated above, the Naranjo probability scale supports a probable association between shock and itraconazole treatment.¹¹ In addition, although numerous drug interactions involving itraconazole are known, itraconazole itself (ie, not its interactions with other drugs) seemed to be the cause of the shock, because the shock did not occur during administration of itraconazole and other drugs for the first 2 weeks. The effect of hydroxypropyl- β -cyclodextrin (HP- β -CD), the solubilizing excipient used in itraconazole injection, should be minor if not completely excluded. This is because HP- β -CD is also the solubilizing excipient for voriconazole, and shock did not occur when voriconazole was administered.

To explore the mechanism of itraconazole-associated shock in our patient, several potential causal factors were considered. Initially, septic shock was evaluated because the patient had neutropenia and was treated with itraconazole for pulmonary fungal infection and antibiotics for *K. pneumoniae* infection. However, chest CT scan showed that the pulmonary lesions had improved significantly, a blood culture was negative for *K. pneumoniae*, and the patient's temperature was normal. Then, congestive heart failure was suspected, mainly due to the fact that the patient coughed with white or pink foam phlegm and pulmonary rales were heard during lung examination in the course of the second episode of shock. However, the possibility of heart failure was excluded since she had no history of heart disease and no symptoms of orthopnea or diaphoresis; in addition, blood pressure should not decline so rapidly with heart failure. Moreover, steroid treatment, not deslanoside and furosemide, eventually reversed the second episode of shock. This patient had never received antiarrhythmics; thus, premature ventricular contractions⁶ or refractory shock^{13,14} caused by an interaction between azole antifungal drugs and calcium-channel blockers were also excluded. Finally, the shock was diagnosed as a delayed-type hypersensitivity (DTH) reaction, an anaphylactic shock episode caused by long-term itraconazole administration. This diagnosis was also supported by the fact that the subsequent 2 episodes of shock occurred more quickly and aggressively than the first one.

Drug-initiated immune reactions can cause a variety of diseases affecting skin, liver, kidney, lungs, and other organs. Besides the immediate immunoglobulin E-mediated reactions, the initial appearance of many drug-induced hy-

persensitivity reactions is delayed. Recent studies revealed that in these delayed reactions, memory T cells and drug-specific CD4+ and CD8+ T cells are of vital importance. In addition to their cytotoxic functions, drug-specific T cells may release certain cytokines and chemokines to activate and recruit monocytes, eosinophils, or neutrophils during DTH reactions.¹² Immunosuppression is a major adverse effect of chemotherapy for ALL. During maintenance therapy of ALL, both CD4+ and CD8+ T cell levels decreased, and this decrease has been found to be correlated with infection.¹⁵ The decrease of CD4+ and CD8+ T cells may also be the reason for itraconazole-associated DTH in this case. This is probably true if we consider that anaphylactic shock associated with ketoconazole, another azole antifungal agent, occurred only after 4 days of ketoconazole therapy in a corneal ulcer patient who did not receive immunosuppressive therapy.¹³

The half-life of itraconazole varies with its concentration in blood, but is typically 34–42 hours, and it takes 2 weeks for blood concentrations to stabilize.^{16,17} Moreover, the elimination rate of itraconazole decreases with the increase in its blood concentration. We speculated that long-term intravenous administration may lead to itraconazole accumulation in vivo and that this accumulation may be responsible for triggering the DTH reaction. Our speculation is supported by the facts that high doses of itraconazole are known to result in liver and renal toxicity⁴ and that serum γ -GT and urea nitrogen levels of our patient increased from 34 U/L to 537 U/L and from 37.2 mg/dL to 97.8 mg/dL, respectively, after 2 weeks of itraconazole treatment.

As shown in this case, long-term intravenous itraconazole treatment could lead to serious and even life-threatening adverse effects such as anaphylactic shock in patients with ALL. The occurrence of this DTH reaction may be related to the immunosuppression associated with chemotherapy and high accumulation of itraconazole in vivo. To our knowledge, this is the first report on the induction of anaphylactic shock by itraconazole. Awareness of this rare but life-threatening adverse effect of long-term itraconazole treatment is important to ensure patient safety.

Jie Chen MD PhD, Attending Physician, Department of Hematology, Changhai Hospital, The Second Military Medical University, Shanghai, China

Xianmin Song MD, Associate Professor, Department of Hematology, Changhai Hospital, The Second Military Medical University

Peng Yang MD, Resident, Department of Hematology, Changhai Hospital, The Second Military Medical University

Jianmin Wang MD, Professor, Director, Department of Hematology, Changhai Hospital, The Second Military Medical University

Reprints: Dr. Wang, Department of Hematology, Changhai Hospital, The Second Military Medical University, Shanghai 200433, China, fax 86-21-25070545, jmwang@medmail.com.cn

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Aparente Choque Anafilático Luego de un Tratamiento Prolongado de Itraconazol Intravenoso

J Chen, X Song, P Yang, y J Wang

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EXTRACTO

OBJETIVO: Informar de un efecto adverso raro, pero severo, de itraconazol intravenoso, choque anafilático con hipotensión e hipoxemia en una paciente femenina con leucemia limfoblástica aguda (ALL)

RESUMEN DEL CASO: Una mujer de 36 años de edad con diagnóstico de ALL; recibió terapia antifungal para una infección pulmonar causada

por hongo. En el día 17 de tratamiento con itraconazol, ella desarrolló hipotensión e hipoxemia luego de una administración intravenosa de 200 mg de itraconazol, la cual finalmente se controló con tratamiento de esteroides. En el día 18 y 19, la paciente desarrolló el mismo tipo de reacción en dos ocasiones adicionales en el curso de la administración de itraconazol. Estas 2 reacciones ocurrieron más rápido luego de la administración intravenosa (100 mg en el día 18 y 40 mg en el día 19) y se controló deteniendo el itraconazol y administrando tratamiento con esteroides. En la terapia antifungal modificada, la administración intravenosa de itraconazol se reemplazó por una administración oral de voriconazol, en dosis de 200 mg 2 veces al día. La reacción no volvió a ocurrir una vez discontinuado el tratamiento con itraconazol. El análisis de la escala de probabilidad de Naranjo reflejó una puntuación de 7, indicando una relación probable entre el tratamiento de itraconazol y el desarrollo de la reacción.

DISCUSIÓN: Itraconazol es una de las drogas antifungales ampliamente utilizadas y es bien tolerado. Sin embargo, el tratamiento prolongado con itraconazol puede llevar a efectos adversos serios y hasta atentar contra la vida del paciente, como lo es el choque anafilático en este caso. La reducción en células T causadas por inmunosupresión y la acumulación de itraconazol en pacientes con ALL son consideradas como factores causales importantes para esta reacción de hipersensitividad de tipo tardío (DTH)

CONCLUSIONES: El choque anafilático representa un efecto adverso severo no revelado previamente con el tratamiento prolongado de itraconazol y se le debe prestar más atención al mismo.

Traducido por Jennifer Guzmán

Choc Anaphylactique Après un Traitement Intraveineux d'Itraconazole à Long Terme

J Chen, X Song, P Yang, et J Wang

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RÉSUMÉ

OBJECTIF: Rapporter un effet indésirable rare mais sévère d'un choc anaphylactique avec hypotension et hypoxie chez une femme atteinte d'une leucémie lymphoblastique aiguë (LLA).

RÉSUMÉ DU CAS: Une femme de 36 ans avec une LLA a reçu une thérapie antifongique pour une infection pulmonaire. Au jour 17 du traitement, elle a développé une hypotension et un choc hypoxique après l'administration intraveineuse de 200 mg d'itraconazole qui a été renversé avec un traitement avec des stéroïdes. Aux jours 18 et 19, la patiente a développé des épisodes identiques durant l'administration d'itraconazole. Ces 2 épisodes sont apparus plus rapidement (100 mg au jour 18 et 40 mg au jour 19) et ont été renversés avec l'arrêt de l'itraconazole et un traitement aux stéroïdes. Le traitement antifongique a été changé par l'administration orale de voriconazole 200 mg 2 fois par jour. Le choc n'a pas été observé après l'arrêt de l'itraconazole. L'analyse avec l'algorithme de Naranjo a démontré un score de 7, indiquant une relation probable entre l'incidence du choc et le traitement avec l'itraconazole.

DISCUSSION: L'itraconazole est l'un des antifongiques les plus utilisés et est généralement bien toléré. Cependant, un traitement à long terme peut mener à des effets indésirables menaçant la vie tel qu'un choc anaphylactique comme dans ce cas. La réduction des cellules T causée par l'immunosuppression et une accumulation d'itraconazole chez les patients atteints de LLA peuvent être la cause d'une réaction retardée d'hyper-sensitivité.

CONCLUSIONS: Le choc anaphylactique représente un effet indésirable non rapporté précédemment avec l'administration à long terme d'itraconazole et ce risque devrait être communiqué aux cliniciens.

Traduit par Nicolas Paquette-Lamontagne