

# BÚSQUEDA DE INFORMACIÓN CIENTÍFICA

TALLER N° 01

Equipo del Centro  
Nacional de  
Documentación e  
Información de  
Medicamentos  
CENADIM



# ESCENARIO CLÍNICO

- Paciente varón de 34 años, natural de Lima, con infección por VIH desde el 2006, recibe tratamiento con didanosina, lamivudina e indinavir potenciado con ritonavir desde diciembre del 2012. Presenta carga viral < 20 copias/mL; CD4 924 células/mm<sup>3</sup>.
- Acude a emergencia por presentar dolor y parestesias, de inicio subagudo, las últimas 24 h, con marcado empeoramiento de la clínica en las últimas horas, a nivel de extremidades inferiores.
- Durante la anamnesis clínica refiere haber tomado un medicamento de venta sin receta médica que compró en la farmacia, para el dolor de cabeza, el cual contiene tartrato de ergotamina 1 mg + cafeína 100 mg por tableta.

# ESCENARIO CLÍNICO

- Al realizar una arteriografía se observa vasoconstricción arterial severa de miembros superiores e inferiores, con vascularización distal muy pobre, orientando el diagnóstico a un cuadro de isquemia aguda de las extremidades por vasoespasmo arterial. Se inicia tratamiento anticoagulante con heparina intravenosa y nitroglicerina, con resolución progresiva de la clínica, recuperando pulsos distales y buena perfusión de las extremidades a las 12 horas. Dada la buena evolución bajo tratamiento, se decide su alta hospitalaria.
- Antecedentes:
  - Se reporta herpes genital recurrente.
  - Sin alergias farmacológicas conocidas.

# IDENTIFICACIÓN DEL PROBLEMA

## Sospecha de Reacción adversa:

- Isquemia arterial aguda en las extremidades

## Medicamentos sospechosos:

- Tratamiento desde diciembre del 2012: didanosina, lamivudina, indinavir y ritonavir.
- Medicamento OTC para el dolor de cabeza, administrado en los últimos días: tartrato de ergotamina 1 mg + cafeína 100 mg por tableta.

# PREGUNTA CLÍNICA

**¿Qué medicamento ocasionó la isquemia arterial aguda en las extremidades del paciente?**



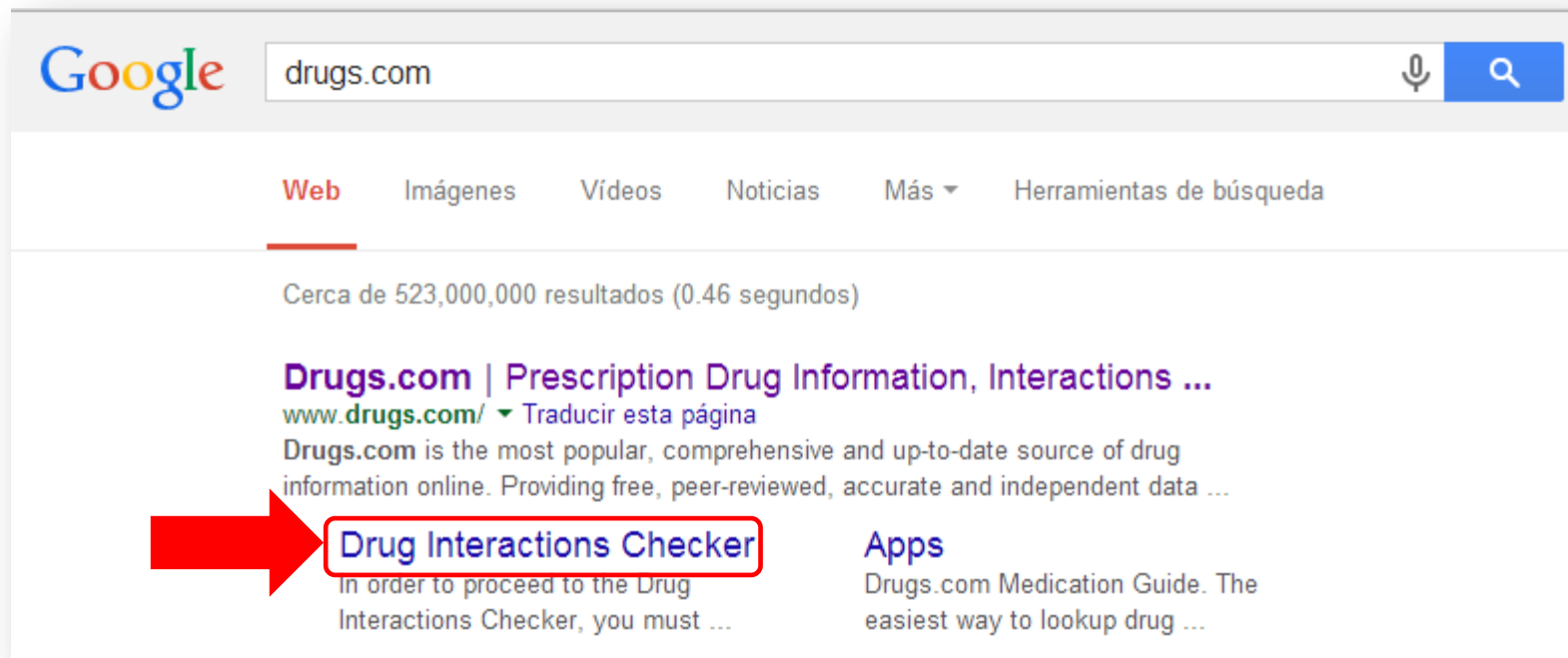


# **IDENTIFICAR Y SELECCIONAR LA FUENTES DE INFORMACIÓN A UTILIZAR EN LA BÚSQUEDA**



# BÚSQUEDA EN FUENTES ESPECIALIZADAS

- Consultar la base de interacciones medicamentosas disponible en Drugs.com



The image shows a Google search interface. The search bar contains 'drugs.com'. Below the search bar, there are tabs for 'Web', 'Imágenes', 'Vídeos', 'Noticias', 'Más', and 'Herramientas de búsqueda'. The search results show 'Cerca de 523,000,000 resultados (0.46 segundos)'. The first result is for 'Drugs.com | Prescription Drug Information, Interactions ...' with the URL 'www.drugs.com/'. Below this, there is a red arrow pointing to a link labeled 'Drug Interactions Checker'. The text below the arrow says 'In order to proceed to the Drug Interactions Checker, you must ...'. To the right of this link, there is a section for 'Apps' with the text 'Drugs.com Medication Guide. The easiest way to lookup drug ...'.

Google

drugs.com

Web Imágenes Vídeos Noticias Más Herramientas de búsqueda

Cerca de 523,000,000 resultados (0.46 segundos)

**Drugs.com | Prescription Drug Information, Interactions ...**  
www.drugs.com/ Traducir esta página  
Drugs.com is the most popular, comprehensive and up-to-date source of drug information online. Providing free, peer-reviewed, accurate and independent data ...

**Drug Interactions Checker**  
In order to proceed to the Drug Interactions Checker, you must ...

**Apps**  
Drugs.com Medication Guide. The easiest way to lookup drug ...

## Drug Interactions Checker

Drug interactions occurs when the effect of a particular drug is altered when it is taken with another drug, or with food.

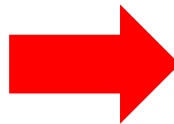
The Drug Interaction Checker explains the mechanism of each drug interaction, the level of significance of the interaction (major, moderate or minor), and in certain cases, can provide the recommended course of action to manage the interaction. The Drug Interaction Checker will also display any interactions between your chosen drug(s) and food.

**In order to proceed to the Drug Interactions Checker, you must read and agree to the following terms:**

The Service is a service provided to you by Cerner Multum, Inc. ("Multum"). The Service and the Drugs.com internet website are separate products provided by separate entities. The Service is intended for use by consumers in the United States.

Your use of this product acknowledges acceptance of these restrictions, disclaimers,

and limitations. You expressly acknowledge and agree that Multum is not responsible for



I Agree

Aceptar (dar clic en “**I Agree**”) los términos de restricciones, renuncias y limitaciones relacionadas a la información disponible en Drug Interactions Checker



# Drug Interactions Checker


Type in a drug name and select a result from the list. Repeat the process to add multiple drugs. When complete, save your list for future reference or check for interactions immediately.

Suggestions...

**didanosine**

Escribir en Inglés el nombre de cada medicamento, y agregar a la caja de búsqueda

 To view your previously saved lists, please [sign in](#).

# Drug Interactions Checker


Type in a drug name and select a result from the list. Repeat the process to add multiple drugs. When complete, save your list for future reference or check for interactions immediately.

Unsaved Drug List

[Save](#) | [New list](#)

caffeine / ergotamine 


X

didanosine 

X

indinavir 

X


lamivudine 

X

ritonavir 

X



 To view your previously saved lists, please [sign in](#).

Después de ingresar el nombre de todos los medicamentos sospechosos, dar clic en “**check for interactions**” para verificar si existen interacciones medicamentosas.

# Resultados:

## Interactions between your selected drugs



ergotamine ↔ ritonavir

Applies to: caffeine / ergotamine, ritonavir

Using ergotamine together with ritonavir is not recommended. Combining these medications may significantly increase the blood levels and effects of ergotamine, which in some cases can lead to excessive narrowing of blood vessels in the body. This can reduce blood flow to vital organs and increase the risk of rare but serious side effects such as high blood pressure, heart attack, stroke, and gangrene (death of tissues, usually in the arm or leg, that may require surgical amputation). You should seek immediate medical attention if you experience severe abdominal pain, nausea, vomiting, numbness or tingling, muscle pain or weakness, blue or purple discoloration of fingers or toes, pale or cold skin, chest pain or tightness, irregular heartbeat, severe headache, shortness of breath, blurred vision, confusion, and/or slurred speech during treatment with ergotamine. Do not take larger doses or use the drug more frequently than prescribed. It is important to tell your doctor about all other medications you use, including vitamins and herbs. Do not stop using any medications without first talking to your doctor.



## ergotamine ↔ indinavir

Applies to: caffeine / ergotamine, indinavir

**CONTRAINDICATED:** Coadministration with protease inhibitors (PIs), particularly ritonavir, may significantly increase the plasma concentrations of ergot derivatives. The mechanism is PI inhibition of CYP450 3A4, the isoenzyme responsible for the metabolic clearance of ergotamine and related drugs. Clinical ergotism, occasionally resulting in surgical amputation or death, has been reported in patients receiving ergotamine tartrate with ritonavir, indinavir, and/or nelfinavir. Even small, single doses of ergotamine have been involved in clinically significant interactions.

**MANAGEMENT:** Given the potential for ergot toxicity characterized by peripheral vasospasm, ischemia, thrombosis, tachycardia and hypertension, concomitant use of ergot derivatives with protease inhibitors is considered contraindicated.

### References

1. Eadie MJ "Clinically significant drug interactions with agents specific for migraine attacks." *Cns Drugs* 15 (2001): 105-18
2. Liaudet L, Buclin T, Jaccard C, Eckert P "Severe ergotism associated with interaction between ritonavir and ergotamine." *Br Med J* 318 (1999): 771
3. "Product Information. Viracept (nelfinavir)." Agouron Pharma Inc, La Jolla, CA.
4. Baldwin ZK, Ceraldi CC "Ergotism associated with HIV antiviral protease inhibitor therapy." *J Vasc Surg* 37 (2003): 676-8
5. "Product Information. Victrelis (boceprevir)." Schering-Plough Corporation, Kenilworth, NJ.
6. "Product Information. Cafergot (caffeine-ergotamine)." Novartis Pharmaceuticals, East Hanover, NJ.
7. Liaudet L "Severe ergotism associated with interaction between ritonavir and ergotamine." *BMJ* 318 (1999): 771
8. Rosenthal E, Sala F, Chichmanian RM, Batt M, Cassuto JP "Ergotism related to concurrent administration of ergotamine tartrate and indinavir." *JAMA* 281 (1999): 987
9. "Product Information. Lexiva (fosamprenavir)." GlaxoSmithKline, Research Triangle Park, NC.
10. "Product Information. Agenerase (amprenavir)." Glaxo Wellcome, Research Triangle Pk, NC.
11. Mortier E, Pouchet J, Vinceneux P, Lalande M "Ergotism related to interaction between nelfinavir and ergotamine." *Am J Med* 110 (2001): 594



### didanosine ↔ indinavir

Applies to: didanosine, indinavir

Using didanosine together with indinavir may decrease the effects of indinavir. Contact your doctor if your condition changes. If your doctor does prescribe these medications together, you may need a dose adjustment or special test to safely use both medications. It is important to tell your doctor about all other medications you use, including vitamins and herbs. Do not stop using any medications without first talking to your doctor.

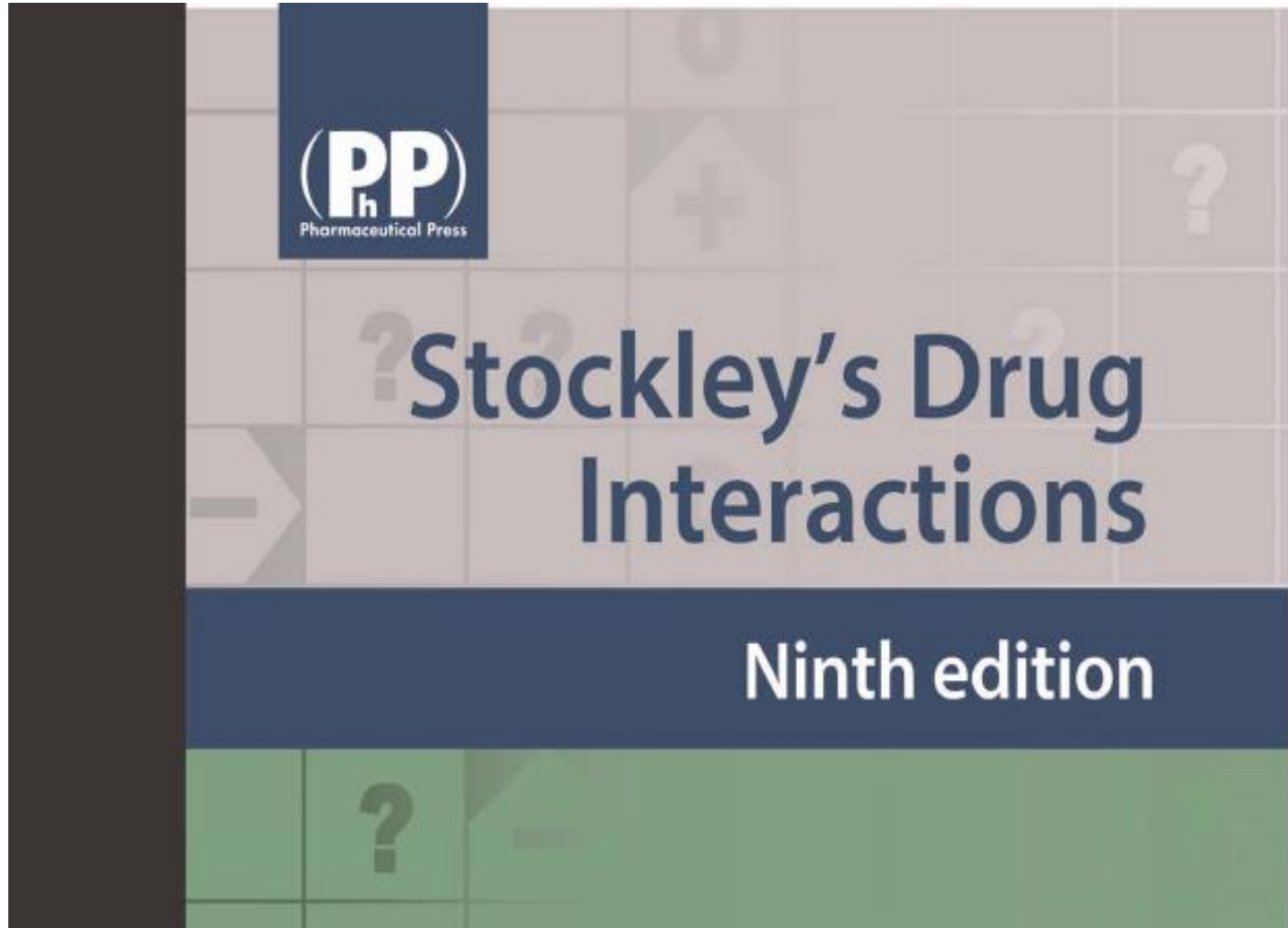


### didanosine ↔ ritonavir

Applies to: didanosine, ritonavir

Consumer information for this minor interaction is not currently available. Some minor drug interactions may not be clinically relevant in all patients. Minor drug interactions do not usually cause harm or require a change in therapy. However, your healthcare provider can determine if adjustments to your medications are needed.

# Texto especializado de interacciones medicamentosas





## Ergot derivatives + Protease inhibitors

A patient receiving indinavir rapidly developed ergotism after taking normal doses of ergotamine. Several other patients taking ritonavir (sometimes with another protease inhibitor) and ergotamine have developed the same interaction. A patient taking nelfinavir developed peripheral arterial vasoconstriction after also taking ergotamine. Other ergot derivatives and protease inhibitors are expected to interact similarly.

### Clinical evidence

#### (a) Indinavir

An HIV-positive man who had been taking lamivudine, stavudine, co-trimoxazole and indinavir (2.4 g daily) for more than a year was given *Gyn-ergene caféiné* (ergotamine tartrate 1 mg with caffeine 100 mg) for migraine. He took two doses on two consecutive days, and 5 days later presented with numbness and cyanosis of the toes of his left foot. The next day he complained of intermittent claudication of his left leg, and 6 days later was admitted to hospital because of worsening symptoms and night cramps. Examination showed a typical picture of ergotism, with vasospasm and reduced blood flow in the popliteal, tibial and femoral arteries. He was given heparin and buflomedil (a vasodilator), and recovered after 3 days.<sup>1</sup>

See *Ritonavir with other protease inhibitors*, below, for details regarding a fatality involving the use of indinavir and ritonavir with ergotamine.

#### (c) Ritonavir

A 63-year-old man with AIDS, who had taken ergotamine tartrate 1 to 2 mg daily for migraine headaches over the last 5 years, had his treatment with zidovudine, zalcitabine and co-trimoxazole changed to zidovudine, didanosine and ritonavir 600 mg every 12 hours. Within 10 days he developed paraesthesias, coldness, cyanosis and skin paleness of both arms, and when admitted to hospital his axillary, brachial, radial and ulnar pulses were found to be absent. An arterial doppler test showed the absence of blood flow in both his radial and ulnar arteries and he was diagnosed as having ergotism. The ergotamine and ritonavir were stopped, and he recovered when given prostaglandin E1 and calcium nadroparin.<sup>3</sup>

A case report describes irreversible coma in a 34-year-old woman who was taking ritonavir 600 mg twice daily, lamivudine and stavudine. She presented with dizziness, loss of vision, headache, vomiting, diarrhoea and a feeling of cold in her left foot after having taken three tablets of ergotamine 1 mg in the preceding 4 days. Peripheral pulses were absent in her extremities. After an initial period of recovery she again experienced a loss of consciousness, with signs of stenosis and vasospasm with cerebral hypoperfusion. Despite treatment with alprostadil, and discontinuation of ritonavir her condition deteriorated, and 2 years after the initial presentation, she remained in coma vigil (a state of altered consciousness).<sup>4</sup>

At least 4 other cases of ergotism have been reported in patients taking ritonavir after taking ergot derivatives:<sup>5-8</sup> one required surgical amputation of the toes.<sup>6</sup> Ergotism developed in two of the patients within a few hours to 24 hours of taking a single 1- or 2-mg dose of ergotamine tartrate,<sup>5,7</sup> and in the others within about 4 to 15 days.<sup>6,8</sup> One was taking a combination drug (ergotamine tartrate 300 micrograms, belladonna extract 200 micrograms and phenobarbital 20 mg) twice daily for gastric discomfort,<sup>6</sup> and another received 10 mg of ergotamine rectally over 4 days.<sup>8</sup>

## (c) Ritonavir

A 63-year-old man with AIDS, who had taken **ergotamine tartrate** 1 to 2 mg daily for migraine headaches over the last 5 years, had his treatment with zidovudine, zalcitabine and co-trimoxazole changed to zidovudine, didanosine and ritonavir (600 mg every 12 hours). Within 10 days he developed paraesthesias, coldness, cyanosis and skin paleness of both arms, and when admitted to hospital his axillary, brachial, radial and ulnar pulses were found to be absent. An arterial doppler test showed the absence of blood flow in both his radial and ulnar arteries and he was diagnosed as having ergotism. The **ergotamine** and ritonavir were stopped, and he recovered when treated with prostaglandin E1 and calcium nadroparin.<sup>3</sup>

Another man, aged 31 years, taking ritonavir 400 mg twice daily (also taking pizotifen, nelfinavir, stavudine, lamivudine, co-trimoxazole and venlafaxine) developed severe burning and numbness in both hands and paraesthesias in his hands after taking 4 tablets of **ergotamine tartrate** 1 mg and caffeine 100 mg, over 10 days. He was diagnosed as having ergotism. The **ergotamine** and caffeine were stopped and he was treated effectively with intravenous alprostadil and heparin.<sup>4</sup>

A case report describes irreversible coma in a 34-year-old woman who was taking ritonavir 600 mg twice daily, lamivudine and stavudine. She presented with dizziness, loss of vision, headache, vomiting, and a feeling of cold in her left foot after having taken three tablets of **ergotamine tartrate** 1 mg in the preceding 4 days. Peripheral pulses were absent in her extremities. After an initial period of recovery she again experienced a loss of consciousness, with signs of stenosis and vasospasm

of the cerebral hypoperfusion. Despite treatment with alprostadil, and discontinuation of ritonavir her condition deteriorated, and 2 years after the initial presentation, she remained in coma vigil (a state of altered consciousness).<sup>5</sup>

A fatality has been reported in a 49-year-old man taking ritonavir 200 mg twice daily and indinavir 800 mg twice daily in addition to stavudine and lamivudine. After taking three tablets of **Cafergot (ergotamine tartrate 1 mg and caffeine 100 mg)** his headache worsened, he developed progressive lower extremity weakness, severe peripheral vasoconstriction, labile hypertension and livedo reticularis (skin discolouration due to underlying capillary changes). He lapsed into coma and on day 5 was declared "brain dead".<sup>6</sup>

At least 6 other cases of ergotism have been reported in patients taking ritonavir after taking ergot derivatives,<sup>7-12</sup> and one required surgical amputation of the toes.<sup>8</sup> The ergotism developed in three of the patients within a few hours to 24 hours of taking a single 1- or 2-mg dose of **ergotamine tartrate**,<sup>7,9,11</sup> and in the others within about 4 to 15 days.<sup>8,10,12</sup> One was taking a combination drug (**ergotamine tartrate** 300 micrograms, belladonna extract 200 micrograms and phenobarbital 20 mg) twice daily for gastric discomfort,<sup>8</sup> another took up to 2 mg of **ergotamine** daily,<sup>10</sup> and a third received 10 mg of ergotamine rectally over 4 consecutive days.<sup>12</sup>



**Texto  
especializado en  
Reacciones  
Adversas  
Medicamentosas**



# MEYLER'S Side Effects of Drugs

The International Encyclopedia of Adverse  
Drug Reactions and Interactions

Fifteenth Edition  
J.K. ARONSON



## Drug–Drug Interactions

### Clarithromycin

Clarithromycin has been reported to potentiate the effects of ergotamine.

- A 41-year-old woman presented with pain and pallor in the leg and a sensation of coolness exacerbated by exercise (34). For many years she had been taking a formulation containing ergotamine 1 mg plus caffeine 100 mg, at a dose of one or two tablets daily, for both prophylaxis and treatment of migraine. For 7 days she had also taken clarithromycin (dose is not stated) for a chest infection. Her legs were cool and cyanosed, with no palpable popliteal or foot pulses and an ankle–brachial index of only 0.6 (normal >0.8).

The authors concluded that her symptoms had been precipitated by the introduction of clarithromycin, an inhibitor of CYP isozymes like the other macrolide antibiotics. However, she was also taking omeprazole, another inhibitor, which may have contributed to the problem. All drugs were withdrawn and nifedipine was given, with full recovery within a couple of days.

### Ritonavir

Ritonavir has been reported to potentiate the effects of ergotamine.

- A 28-year-old woman was taking triple therapy for HIV infection, including the protease inhibitor ritonavir (35).

### 1234 Ergot derivatives

---

She had also started to take a combined formulation containing ergotamine (0.6 mg/day), phenobarbital (40 mg/day), and belladonna extract (0.4 mg/day). Four days later she noted pain in both legs and all her extremities were cold, pale, and pulseless. She had diffuse arterial spasm in the aorta and all four limbs. Despite intensive vasodilator therapy, she developed bilateral gangrene of the toes, requiring transmetatarsal amputations.

- A 37-year-old woman with AIDS who had been taking ritonavir developed acute dysphasia and right-sided weakness having taken a total of 10 mg of ergotamine in suppository form for severe headaches that were presumed to be migraine (36). Transcranial Doppler and angiography showed multiple stenoses in vessels in the circle of Willis, and an MRI scan showed watershed infarcts in the right and left hemispheres. It was presumed that she had had ergotamine-induced vasospasm due to inhibition of ergotamine metabolism by ritonavir. She was treated with “hemodilution, hypertension and hypervolemia”; the cerebral flow velocities normalized over the next 18 days and the angiographic appearances by day 90. She was left with a slight right expressive dysphasia and weakness in the right leg.

Ritonavir is a very potent inhibitor of CYP3A4, which is responsible for the metabolism of ergotamine, and this interaction obviously led to toxic plasma concentrations of the alkaloid.

# BÚSQUEDA EN FUENTES SECUNDARIAS

- Identificación y selección de términos de búsqueda

	<b>Español</b>	<b>Inglés</b>
Problema	Isquemia	Ischemia
Medicamentos sospechosos	Ergotamina Ritonavir Indinavir	Ergotamine Ritonavir Indinavir

PubMed ischemia ergotamine (ritonavir OR indinavir OR HIV Protease Inhibitors)

RSS Save search Advanced

ischemia ergotamine (ritonavir OR indinavir OR Protease Inhibitors)

Show additional filters

Display Settings: Summary, 20 per page

Article types

More ...

Text availability

- Abstract
- Free full text
- Full text



Results: 7

[\[Arterial occlusion associated with interaction between ritonavir and ergotamine in HIV patient\].](#)

1. Collado Borrell R, Sanz Márquez S, Pérez Encinas M. Farm Hosp. 2013 Sep-Oct;37(5):426-7. doi: 10.7399/FH.2013.37.5.735. Spanish. No abstract available. PMID: 24128109 [PubMed - indexed for MEDLINE] Free Article  
[Related citations](#)

[\[Splenic infarction. Ergotism induced by ritonavir?\].](#)

2. Dal Verme A, López E, Grinspon S, Fernández Pardal R, Mengia M, Mazzocchi O. Medicina (B Aires). 2012;72(6):475-7. Spanish. PMID: 23241290 [PubMed - indexed for MEDLINE] Free Article  
[Related citations](#)

Publication dates

- 5 years
- 10 years
- Custom range...

Species

Humans

Clear all



[Four-limb acute ischemia induced by ergotamine in an AIDS patient treated with protease inhibitors.](#)

3. Marine L, Castro P, Enriquez A, Greig D, Sanhueza LM, Mertens R, Bergoening M, Kramer A, Valdes F, Serri M. Circulation. 2011 Sep 20;124(12):1395-7. doi: 10.1161/CIRCULATIONAHA.111.020586. No abstract available. PMID: 21931103 [PubMed - indexed for MEDLINE] Free Article  
[Related citations](#)

Show additional filters



[Ergotism caused by concurrent use of ritonavir and ergot alkaloids: a case report.](#)

4. Cagatay A, Guler O, Guven K. Acta Chir Belg. 2009 Oct;109(5):639-40. No abstract available. PMID: 19994812 [PubMed - indexed for MEDLINE]  
[Related citations](#)



PubMed

Search

US National Library of Medicine  
National Institutes of Health

Advanced

Help



Display Settings: Abstract

Send to:

Circulation. 2011 Sep 20;124(12):1395-7. doi: 10.1161/CIRCULATIONAHA.111.020586.

### Four-limb acute ischemia induced by ergotamine in an AIDS patient treated with protease inhibitors.

Marine L<sup>1</sup>, Castro P, Enriquez A, Greig D, Sanhueza LM, Mertens R, Bergoeing M, Kramer A, Valdes F, Serri M.

#### Author information

PMID: 21931103 [PubMed - indexed for MEDLINE] **Free full text**



Publication Types, MeSH Terms, Substances

LinkOut - more resources

PubMed Commons

[PubMed Commons home](#)

0 comments

[How to join PubMed Commons](#)

Save items

Add to Favorites

Related citations in PubMed

Ergotism associated with HIV antiviral protease inhibitor therapy. [J Vasc Surg. 2003]

[Arterial occlusion associated with interaction between ritonavir and ergota [Farm Hosp. 2013]

Ergotism caused by concurrent use of ritonavir and ergot alkaloids: a cas [Acta Chir Belg. 2009]

**Review** Side effects of ergotamine. [Cephalalgia. 1996]

**Review** Acute treatment of migraine. [Neurol Clin. 2009]

See reviews...

See all...



[« Prev Article](#) | [Next Article »](#)  
[Table of Contents](#)

## Images in Cardiovascular Medicine

### Four-Limb Acute Ischemia Induced by Ergotamine in an AIDS Patient Treated With Protease Inhibitors

Leopoldo Marine, MD; Pablo Castro, MD; Andres Enriquez, MD; Douglas Greig, MD; Luis Manuel Sanhueza, MD; Renato Mertens, MD; Michel Bergoeing, MD; Albrecht Kramer, MD; Francisco Valdes, MSCCh, FACS; Michel Serri, MD

[Author Affiliations](#)

Correspondence to Pablo Castro, MD, Department of Cardiology and Cardiovascular Diseases, Pontificia Universidad Católica de Chile, Santiago 8320000, Chile. E-mail [pcastroenator@yahoo.es](mailto:pcastroenator@yahoo.es)

A 32-year-old man infected with HIV presented to the emergency department of our hospital reporting pain, coldness, paresthesias, and cyanosis in both feet and hands. The symptoms had started 3 days before, with lower extremities claudication at 200 m, which progressed to rest pain the day of admission; it was worse on the right foot. He was on chronic antiretroviral therapy with 300 mg QID tenofovir (Viread), 300 mg BID abacavir (Ziagen), and two 200/50 mg BID lopinavir/ritonavir (Kaletra). His CD4 cell count was 245 cells/mm and his HIV viral load was 45 copies/mL. When directly interviewed, the patient remembered that he

### This Article

Circulation.  
2011;124:1395-1397  
doi:  
10.1161/CIRCULATIONAHA.110.20586

- 
- [Extract Free](#)
  - [Figures Only Free](#)
  - [» Full Text Free](#)
  - [PDF Free](#)
  - [PPT Slides of All Figures](#)

### Classifications

Images in Cardiovascular Medicine

### Services

- [Article Usage Statistics](#)
- [E-mail this article to a friend](#)
- [Alert me when this article is cited](#)
- [Alert me if a correction is posted](#)
- [Similar articles in this journal](#)
- [Similar articles in PubMed](#)

### Current Issue

September 23, 2014



[Alert me to new issues of Circulation »](#)

[About Circulation](#)

[Instructions for Authors](#)

[Online Submission/Peer Review](#)

[Editorial Board](#)

Follow us on:  

[Advertiser Information](#)



Most Read

Most Cited

1. 2013 ACC/AHA Guideline on the

## Four-Limb Acute Ischemia Induced by Ergotamine in an AIDS Patient Treated With Protease Inhibitors

Leopoldo Marine, MD; Pablo Castro, MD; Andres Enriquez, MD; Douglas Greig, MD; Luis Manuel Sanhueza, MD; Renato Mertens, MD; Michel Bergoeing, MD; Albrecht Kramer, MD; Francisco Valdes, MSCCh, FACS; Michel Serri, MD

A 32-year-old man infected with HIV presented to the emergency department of our hospital reporting pain, coldness, paresthesias, and cyanosis in both feet and hands. The symptoms had started 3 days before, with lower extremities claudication at 200 m, which progressed to rest pain the day of admission; it was worse on the right foot. He was on chronic antiretroviral therapy with 300 mg QID tenofovir (Viread), 300 mg BID abacavir (Ziagen), and two 200/50 mg BID lopinavir/ritonavir (Kaletra). His CD4 cell count was 245 cells/mm and his HIV viral load was 45 copies/mL. When directly interviewed, the patient remembered that he had taken a single dose of ergotamine (1 mg) for migraine 24 hours before the onset of symptoms. He denied any recent drug intake. On examination, his 4 extremities were cold, cyanotic, and pulseless (Figure 1A). Only femoral pulses were weakly palpable. Plethysmography revealed bilateral multilevel ischemia, with severe proximal disease and flat curves at popliteal and distal levels (Figure 2A). Lower limb computed tomographic angiography showed diffuse arterial narrowing from the external iliac arteries to the distal, consistent with severe and diffuse spasm (Figure 3A). A similar pattern was seen in the upper extremities.

Antiretroviral drugs were withdrawn, and the patient was started on therapeutic intravenous administration of heparin, morphine, and sodium nitroprusside infusion, with no evident response. An arteriography was then performed, confirming the presence of diffuse arterial spasm, with no images of



**Figure 1.** Right foot perfusion. **A**, Severe forefoot ischemia on admission. **B**, Improvement of perfusion after treatment, residual mild ischemia on first toe that recovered later.



# **RESUMIR LA EVIDENCIA**





# ELABORACIÓN DE LA RESPUESTA

## Pregunta

¿Qué medicamento ocasionó la isquemia arterial aguda en las extremidades del paciente?

## Resumen y análisis

La ergotamina es un agonista de los receptores alfa-adrenérgicos, que es utilizada en el tratamiento de las cefaleas vasculares de tipo migraña. Actúa por vasoconstricción periférica del músculo liso de los vasos sanguíneos y se metaboliza a través del citocromo P450. Tiene múltiples efectos secundarios, a pesar de lo cual, y favorecido por su bajo coste y venta libre, tiene un uso muy extendido, siendo uno de los fármacos con que más se automedican los pacientes que sufren de cefaleas. <sup>1,2</sup>

El ritonavir es un inhibidor selectivo de la proteasa para tratamiento del VIH junto con otros antirretrovirales. Se utiliza principalmente como *booster* (potenciador) de otros inhibidores de la proteasa. Se metaboliza a nivel hepático presentando una alta afinidad por algunas formas isoméricas del citocromo P450, fundamentalmente por la isoenzima CYP3A. <sup>1,2</sup>

Indinavir, es otro medicamento inhibidor de la proteasa que se usa junto con otros medicamentos para tratar la infección por el virus de la inmunodeficiencia humana (VIH). Indinavir al igual que ritonavir se metaboliza a nivel hepático por la isoenzima CYP3A. <sup>1,2</sup>

Existen numerosas interacciones medicamentosas entre los ergotamínicos y otros fármacos, siendo de particular importancia aquellas sustancias capaces de aumentar la toxicidad de la ergotamina y por consiguiente, la probabilidad e intensidad de vasoespasmo. Los fármacos inhibidores del citocromo P450 son los que más se relacionan con esta interacción, entre los que se encuentran los macrólidos, los antifúngicos azólicos y los inhibidores de la proteasa como el ritonavir e indinavir, arsenal terapéutico usado en los pacientes con infección VIH. <sup>1,2,3,4</sup>

# ELABORACIÓN DE LA RESPUESTA

La interacción ergotamina-ritonavir y ergotamina-indinavir se da por una unión competitiva reversible a la isoenzima CYP3A, generando una elevación de las concentraciones plasmáticas de la ergotamina hasta niveles tóxicos, produciendo así mayor vasoespasmo.<sup>2,3,4</sup>

En los pacientes con infección VIH, que reciben tratamiento con antirretrovirales, se debe considerar las potenciales interacciones medicamentosas al administrar concomitantemente otros medicamentos, en especial cuando alguno de los medicamentos se metaboliza en el citocromo P-450.<sup>5</sup>

La intoxicación por derivados ergotamínicos debe sospecharse ante manifestaciones clínicas compatibles con isquemia arterial aguda en las extremidades y el antecedente de ingesta de la ergotamina junto a un fármaco que inhiba su metabolismo o no.<sup>5,6</sup>

El elemento central del tratamiento es el retiro de los fármacos y sin importar el sitio que afecte, se deben asociar vasodilatadores arteriales y anticoagulación profiláctica. Los casos clínicos que se han presentado sugieren que ritonavir e indinavir puede asociarse con el desarrollo de ergotismo severo en pacientes tratados con derivados ergotamínicos. Los médicos clínicos deben estar al tanto de esta interacción y la administración de ergóticos debe interrumpirse cuando se inicia el tratamiento antirretroviral con el objetivo de prevenir la aparición de cuadros graves asociados a la vasoconstricción periférica.<sup>4,5,6</sup>

## **Conclusión**

La ergotamina es el medicamento responsable de isquemia arterial aguda que afectó las extremidades del paciente, por lo cual no debe indicarse o usarse en forma indiscriminada ya que la intoxicación producida por ésta, puede ocasionar graves consecuencias si no se diagnostica y trata a tiempo.

# ELABORACIÓN DE LA RESPUESTA

## Referencias bibliográficas

1. Aronson JK. Meyler's Side Effects of Drugs. Fifteenth Edition. Ed. Elsevier. 2006;p.1233-1234
2. Karen Baxter. Stockley's Drug Interactions. Eighth edition. Ed. Pharmaceutical Press. 2008; p.600-601
3. Drug Interactions Checker. Drugs.com. c2000-2014 [acceso 24 mayo 2014] Disponible en: [http://www.drugs.com/drug\\_interactions.html](http://www.drugs.com/drug_interactions.html)
4. Rosenthal E, Sala F, Chichmanian RM, Batt M, Cassuto JP. Ergotism related to concurrent administration of ergotamine tartrate and indinavir. JAMA. 1999 Mar 17;281(11):987.
5. Collado Borrell R, Sanz Márquez S, Pérez Encinas M. [Arterial occlusion associated with interaction between ritonavir and ergotamine in HIV patient]. *Farm Hosp.* 2013 Sep-Oct;37(5):426-7. doi: 10.7399/FH.2013.37.5.735.
6. Acle S, Roca F, Vacarezza M, Álvarez RA. Ergotismo secundario a la asociación ergotamina-ritonavir: A propósito de 3 casos. Rev. méd. Chile [revista en la Internet]. 2011 [citado 2014 Ago 17]; 139(12): 1597-1600. Disponible en: [http://www.scielo.cl/scielo.php?script=sci\\_arttext&pid=S0034-98872011001200010&lng=es](http://www.scielo.cl/scielo.php?script=sci_arttext&pid=S0034-98872011001200010&lng=es)