Boceprevir drug-drug interactions lead to priapism

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Priapism—prolonged erections lasting four hours or more—is uncommon. When this condition does occur, it requires prompt medical attention, as priapism can injure the delicate tissues of the penis. Subsequently, this can cause problems with getting and maintaining an erection.

There are two main types of priapism as follows:

**Ischemic priapism** – in this case, blood is not able to leave the penis; signs and symptoms include the following:

- unwanted erections that persist for more than four hours
- unwanted erections occurring intermittently over several hours (urologists call this “stuttering priapism”)
- the shaft of the penis is extremely hard but the tip is soft
- the erection hurts

**Nonischemic priapism** – in this case, too much blood has flowed into the penis; signs and symptoms include the following:

- unwanted erections persisting for more than four hours
- penis is erect but not extremely hard
- erection does not hurt

**Causes**

Here is a list of some medicines (and health conditions) that may, in rare cases, cause priapism (note that this list is not exhaustive):

- medicines for erectile dysfunction – including the oral drugs sildenafil (Viagra), tadalafil (Cialis) and vardenafil (Levitra) as well as injectable drugs such as alprostadil (Caverject)
- anti-psychotics – these drugs were originally designed for treating psychosis, but doctors sometimes find them useful for some other mental health conditions such as anxiety, depression, bipolar illness, obsessive-compulsive disorder and addiction. Examples of commonly used members of this class of drug are: aripiprazole (Ablify), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal) and ziprasidone (Zeldox, Geodon)
- drugs that interfere with a protein called alpha-1 adrenergic receptor, such as doxazosin (used to treat higher-than-normal blood pressure) and tamsulosin (used to treat enlarged prostate gland)
- street drugs – ecstasy and cocaine
- blood-related problems – sickle cell anemia and leukemia
- injury to nerves in the spine
- tumours in the penis

**Treatment of priapism**

Depending on the cause of priapism, treatment can involve one or more of the following interventions:

- drawing blood from the penis
- injecting drugs into the penis to help relax blood vessels
The case

Doctors in Denver, Colorado, reported details about a man with priapism who had multiple medical conditions when he sought care.

The 44-year-old man had been experiencing priapism for the past 72 hours when he came to the Emergency department of a hospital. His other medical conditions included the following:

- co-infection with HIV and hepatitis C virus (HCV)
- an enlarged prostate gland
- higher-than-normal blood pressure
- mood disorder
- excess stomach acid
- bone and muscle pain in his neck
- occasional diarrhea
- recent bronchitis

He did not have a history of priapism.

As a result of these co-morbidities, he was prescribed the following medicines:

- Atripla – a fixed-dose combination of three drugs in one pill: efavirenz, tenofovir and FTC
- boceprevir (Victrelis) – 800 mg three times daily
- peginterferon-alpha – one injection once weekly
- ribavirin – 1,000 mg/day
- doxazosin – 8 mg/day
- tamsulosin – 0.4 mg/day
- quetiapine – 100 to 300 mg/day
- testosterone cypionate – 200 mg injected every two weeks
- ondansetron – 4 mg every six hours
- esomeprazole – 40 mg/day
- lithium – 1,200 mg/day
- losartan – 50 mg/day
- naproxen – 1,000 mg/day
- a fixed-dose combination of 5 mg oxycodone and 325 mg acetaminophen taken every six hours as needed
- loperamide – 2 mg
- cyclobenzaprine – 10 mg every eight hours as needed

On questioning he did not disclose the use of supplements, herbs or medicines designed to treat impotence. Just prior to hospitalization he had taken a dose of pseudoephedrine in a failed attempt to relieve priapism.

Emergency procedures

Doctors attempted to relax the erection by injecting the drug phenylephrine into his penis but this did not have any effect. So surgeons intervened and placed a shunt into his penis to try to redirect the blood flow back into his body. This eventually worked.

Drug-drug interactions

In people who take multiple medications, sometimes drugs can interact or influence each other. Such effects are called drug-drug interactions and they can do the following:

- enhance the effect of a drug(s) – this can intensify pre-existing side effects of a drug or cause new side effects to appear
- weaken the action of a drug(s) – this can cause a drug(s) to lose its effectiveness and place a person at risk of
Pharmacologists who were advising the man’s care team in the Emergency department suggested that it was possible that drug-drug interactions could have been occurring between boceprevir and at least one of the following medicines:

- doxazosin
- tamsulosin
- quetiapine

These interactions, they surmised, may have led to priapism. Therefore, doctors advised the man to stop taking doxazosin and tamsulosin after surgery.

Despite the man’s use of the powerful anti-nausea drug ondansetron, doctors found that the man was experiencing “excessive nausea and vomiting” while taking boceprevir as part of treatment for HCV. Therefore, he also discontinued taking boceprevir and other anti-HCV drugs (peginterferon and ribavirin).

**Recovery**

The man continued to take quetiapine to help manage his mood disorder and two months since his hospitalization for priapism has not had a recurrence of this latter condition. The doctors noted that the man’s “[sensitivity in his penis] has returned, and sexual functioning is slowly improving though it is not yet back to baseline.”

**Avoiding danger in cases of multiple meds**

The Denver report underscores the complex issues faced by people who have to deal with multiple medical conditions, including co-infection with HIV and HCV.

Boceprevir and telaprevir (Incivek, Incivo) are protease inhibitors designed to attack HCV. They will continue to be part of combination therapy for some cases of HCV infection in high-income countries for at least the next 12 months. As both of these drugs have the potential for drug-drug interactions with other medicines, we may receive further reports of other drug-drug interactions.

People taking several or more medicines may find, in addition to meeting with their doctors and nurses, that regular consultation with their pharmacists may be useful in helping to predict and prevent potential drug-drug interactions, particularly when new drugs are added or some drug(s) are taken away from a regimen.

The Denver team has alerted the U.S. Food and Drug Administration (FDA) about its findings and conclusions. The team now strongly suggests that doctors treating patients who use alpha-1a receptor inhibitors do not also prescribe boceprevir as part of their HCV treatment. Furthermore, they suggest that doctors not prescribe quetiapine to patients while they are taking boceprevir.

**Technical notes**

Read this section if you are interested in more complex information about the molecular events that may have led to the man’s priapism.

Doxazosin works by interfering with proteins on the surface of cells; these proteins are called alpha-1 adrenergic receptors (alpha-1a). These particular receptors are found on smooth muscles, which are found in arteries, and muscles that help to control the bladder and that are around the prostate gland, the intestines and genital tract. Alpha-1a receptors are also found on nerves in the penis.

Doxazosin is used to help treat elevated blood pressure and/or enlargement of the prostate gland.

Tamsulosin interferes with alpha-1a receptors in the urinary tract and is also used to treat enlargement of the prostate gland.

The Denver team noted that it is unusual for doctors to prescribe both doxazosin and tamsulosin for men with enlarged prostate glands. Furthermore, the use of either of these drugs has been associated with rare cases of
priapism. When such cases of priapism occur, they tend to do so within one to 15 days of commencing therapy with either of these drugs.

The man had been taking doxazosin for 10 months and tamsulosin for two years prior to seeking care for priapism. Therefore, it seems unusual that these drugs by themselves would cause this problem. Note that the enzyme CYP3A4 breaks down both drugs.

Boceprevir moderately impairs the activity of CYP3A4 enzymes, which suggests that boceprevir may have elevated levels of both doxazosin and tamsulosin in the man’s blood.

Quetiapine interferes with multiple receptors, including alpha-1a and alpha-2a. This drug is broken down by CYP3A4. The Denver team suggests that the use of boceprevir “may significantly increase the concentration of quetiapine” when both drugs are used by the same person. Published reports suggest that quetiapine can in rare cases cause priapism.

The Denver team suggests that this is what likely happened:

Boceprevir impaired the activity of the enzyme CYP3A4, leading to elevated “concentrations of doxazosin, tamsulosin and/or quetiapine. These elevated concentrations then likely resulted in increased inhibition of [alpha-1a and other receptors], leading to priapism in our patient.”

The Denver team points out that another case of priapism was reported in the literature in a 50-year-old man who was taking Kaletra (lopinavir-ritonavir), an inhibitor of CYP3A4. Within hours of the man initiating therapy with quetiapine, he developed priapism.

—Sean R. Hosein

REFERENCES:
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