

Drug Interaction Incident with HIV Post-exposure Prophylaxis

The regimens for post-exposure prophylaxis (PEP) against human immunodeficiency virus (HIV) consist of combinations of antiretroviral medications. These medications are taken for a period of 4 weeks to reduce the risk of HIV infection in people who may have been exposed to the virus, either through occupational exposure (e.g., needle-stick injuries) or non-occupational exposures (e.g., sexual assault).^{1,2} They must be started as soon as possible (preferably within hours of exposure);^{1,2,3} therefore, if the person is deemed a suitable candidate for prophylaxis, an HIV PEP “starter kit” is often provided in the emergency department or other ambulatory setting to ensure prompt initiation. The process for supplying the balance of the HIV PEP medication varies. The medications may be dispensed by a community pharmacy or may be provided during follow-up clinic visits. When providing HIV PEP, a systematic approach for identifying possible drug interactions may be lacking.

Certain antiretroviral medications are known to be involved in numerous drug interactions through their inhibition of the cytochrome P450 system.^{4,5} As illustrated by the following case, these interactions can have severe consequences if not promptly identified and resolved.

Case Report

A 46-year-old patient was provided with a “starter” medication kit for HIV PEP, containing Kaletra (lopinavir and ritonavir) and Combivir (zidovudine and lamivudine), by a hospital emergency department. The patient’s regular medications were noted as venlafaxine, amitriptyline, bupropion, hormone replacement therapy, and fentanyl patch 100 mcg/h. Approximately 4 days after initiation of PEP, the patient was noted to be very drowsy and needed to be frequently wakened. The patient went to lie down and some time later that evening was found unresponsive. Resuscitation attempts were not successful. Based on post-mortem examination and serum drug levels, the cause of death was determined to be fentanyl toxicity due to an interaction with Kaletra.

Contributing Factor

The following factor was identified as possibly contributing to the sentinel event described in the case report:

- The clinically significant drug interaction between ritonavir and fentanyl was not identified.

Ritonavir is a potent inhibitor of the CYP 3A4 enzyme which is responsible for metabolizing fentanyl.⁶ A study evaluating the interaction between ritonavir and intravenous fentanyl found that fentanyl clearance was reduced to one third when ritonavir 200 mg, given three times per day, was added. The authors conclude that ritonavir treatment results in an approximately three-fold increase in fentanyl concentrations,⁷ an interaction of major clinical significance.⁸ Administration of Kaletra for HIV PEP delivers a ritonavir dose of 100 mg twice per day. Studies of the increase in fentanyl concentration occurring as a result of an interaction with a lower dose of ritonavir (as in the HIV PEP protocol) have not been published. Of interest, the product monographs for the fentanyl patch (e.g., Duragesic)⁹ do list ritonavir as an interacting drug. However, the ritonavir product monographs (Kaletra,¹⁰ Norvir,¹¹ and Norvir SEC¹¹), do not include fentanyl in the list of interacting medications.

Recommendations

ISMP Canada suggests the following steps to reduce the potential for harm due to drug interactions with HIV PEP.

Facilities and Treatment Centres Providing HIV PEP: (e.g., emergency departments, occupational health departments, sexual assault treatment centres)

- Develop and use a systematic approach (e.g. predefined electronic or printed order sets) for HIV PEP, that includes documentation of any medications that patients are currently taking.
- For patients taking any other medications, require an evaluation of the potential drug interactions using an electronic medication information database (e.g., pharmacy information system, MicroMedex), preferably by a pharmacist. This evaluation should be done either before the HIV PEP medications are provided, or as soon as possible after the first dose.
- For treatment centres and clinics without access to an on-site or on-call pharmacist, arrange a consultation service with a local community pharmacy.
- If the concomitant use of ritonavir and transdermal fentanyl is required, the fentanyl dosage, pain management, and monitoring need to be reassessed.

- Counsel the patient regarding any potential adverse effects, including those that might arise from possible drug interactions, and provide advice about when to seek immediate medical attention.
- Provide written information, including the complete medication list and HIV PEP prescribed, and advise that the information should be taken to the health care provider(s) who will be seeing the patient in follow-up.

Pharmaceutical Manufacturers:

- Modify ritonavir product monographs to include information about the fentanyl interaction and the need for close monitoring and reduction in the fentanyl dose if the two medications are used together.

With the ever-growing number of available drugs and potential drug interactions, an electronic check for drug interactions is an important safeguard. The provision of HIV PEP medications directly to patients is an example of a process that may bypass drug-interaction screening. Since patients receiving HIV PEP rarely need to be admitted to hospital, their medications are not routinely entered into the hospital pharmacy information system, which means there

may be no opportunity for an automated drug interaction check. Although some treatment centres have developed their own lists of important drug interactions involving HIV PEP, manual checks may be less reliable and are prone to human error.¹² Because of the high potential for clinically significant drug interactions associated with HIV PEP medications, health care professionals involved in the management of patients requiring HIV PEP should ensure that their processes include electronic drug interaction screening.

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