

HIV Postexposure Prophylaxis and the Need for Drug Interaction Screening

Roger Cheng, Julie Greenall, Christine Koczmara, and Sylvia Hyland

Contributions to this column are prepared by the Institute for Safe Medication Practices Canada (ISMP Canada), a key partner in the Canadian Medication Incident and Prevention System, and include, with permission, material from the *ISMP Canada Safety Bulletin*. The present article is based on "Drug interaction incident with HIV post-exposure prophylaxis", *ISMP Can Saf Bull* 2008;8(3):1-2. From time to time, ISMP Canada invites others to share learning based on local initiatives.

INTRODUCTION

Certain antiretroviral medications are known to be involved in numerous drug interactions through their inhibition of the cytochrome P450 system.^{1,2} One of the uses of antiretroviral medications is postexposure prophylaxis (PEP) against HIV, to reduce the risk of infection among people who may have been exposed to the virus, either through occupational exposure (e.g., needlestick injuries) or non-occupational exposure (e.g., sexual assault).^{3,4} To maximize effectiveness in this situation, antiretroviral therapy must be started as soon as possible (preferably within hours of exposure)^{3,5}; therefore, if a person is deemed a suitable candidate for prophylaxis, an HIV PEP "starter kit" is often given to the patient in the emergency department or other ambulatory setting to ensure prompt initiation. When providing HIV PEP in this setting, a systematic approach for identifying possible drug interactions may be lacking. 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 given 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. About 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. On the basis

of postmortem examination and serum drug levels, the cause of death was determined to be fentanyl toxicity due to an interaction with Kaletra.

CONTRIBUTING FACTOR

Failure to identify the clinically significant drug interaction between ritonavir and fentanyl was identified as possibly contributing to the sentinel event described in the case report.

Ritonavir is a potent inhibitor of the CYP 3A4 enzyme, which is responsible for metabolizing fentanyl.⁶ In a study evaluating the interaction between ritonavir and IV fentanyl,⁷ the authors found that fentanyl clearance was reduced to one-third when ritonavir 200 mg, given 3 times per day, was added to the drug regimen. The authors concluded that ritonavir treatment results in an approximately 3-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 (about one-third the dose in the study by Olkkola and others⁷). Studies of the effect on fentanyl concentration as a result of an interaction with a lower dose of ritonavir (as in the HIV PEP protocol) have not been published. Of interest, product monographs for the fentanyl patch (e.g., Duragesic[®]) list ritonavir as an interacting drug. However, the ritonavir product monographs (for Kaletra,¹⁰ Norvir,¹¹ and Norvir SEC¹¹) do not include fentanyl in the list of interacting medications.

SELECTED RECOMMENDATIONS OF HIGH RELEVANCE TO PHARMACISTS

Identification and resolution of drug interactions is an important component of pharmacists' patient care responsibil-

ities. The following recommendations highlight key areas where pharmacists can assist in the implementation of processes to reduce the potential for harm due to drug interactions with HIV PEP.

- 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. (This approach provides additional support for medication reconciliation in the ambulatory setting.)
- 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 or Micromedex), preferably by a pharmacist. This evaluation should be done either before the HIV PEP medications are given to the patient 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, reassess the fentanyl dosage, overall pain management, and monitoring.
- 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 the patient to take this written information to the health care provider(s) who will be seeing the patient in follow-up.

CONCLUSION

With the ever-growing numbers 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 processes 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 check for drug interactions. 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 Given the high potential for clinically significant drug interactions associated with HIV PEP medications, pharmacists have an important role to play in ensuring that processes for provision of HIV PEP include electronic drug-interaction screening.

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Roger Cheng, RPh, BScPhm, Pharm D, is an Analyst with ISMP Canada, Toronto, Ontario.

Julie Greenall, RPh, BScPhm, MHSc, FISMPC, is a Project Leader with ISMP Canada, Toronto, Ontario.

Christine Koczmar, RN, BSc, is a Senior Analyst with ISMP Canada, Toronto, Ontario.

Sylvia Hyland, RPh, BScPhm, MHSc, is Vice-President, ISMP Canada, Toronto, Ontario.

ISMP Canada homepage: <http://www.ismp-canada.org>

e-mail: info@ismp-canada.org

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