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CASE REPORT

Postoperative Bleeding After Administration of a Single Dose of Rivaroxaban to a Patient Receiving Antiretroviral Therapy

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Abstract A 62-year-old man was admitted to hospital for elective revision of a left total hip arthroplasty. His history was significant for human immunodeficiency virus (HIV) infection for which he was taking the following antiretroviral agents (ARVs): etravirine, ritonavir, darunavir, raltegravir and tenofovir/emtricitabine. Rivaroxaban 10 mg daily was commenced on the second postoperative day for venous thromboembolism (VTE) prophylaxis. Approximately 24 h later, the patient developed hypotension and anaemia, accompanied by thigh swelling due to bleeding at the surgical site. Fluid resuscitation was commenced with red cell transfusion. The prothrombin time (PT) was prolonged at 24.3 (10.6–15.3) s, and a rivaroxaban level taken 24 h after administration was 75 ng/mL. Rivaroxaban was ceased, the PT normalised within 24 h of stopping the drug, and the patient made an uneventful recovery. None of the other coadministered drugs are known to interact with rivaroxaban, or are likely to, based on their metabolic pathways. Rivaroxaban, a substrate for cytochrome P450 (CYP) 3A4 and P-glycoprotein (P-gp), is contraindicated in patients concomitantly treated with strong inhibitors of both these systems, e.g. protease inhibitors (PIs) such as ritonavir (based on in vitro data and a pharmacokinetic study in healthy volunteers). No published data are available on the PI darunavir, a moderate inhibitor; however, concomitant use with rivaroxaban should also be avoided. A prolonged PT and a rivaroxaban trough level greater than eight times that predicted from pharmacokinetic modelling suggests that bleeding was due to increased exposure to rivaroxaban, probably due to an interaction with ritonavir and darunavir. This is supported by a Drug Interaction Probability Scale (DIPS) score of 8. An interaction between a single dose of rivaroxaban and ARVs may be clinically significant; therefore, the patient's medication history should be extensively evaluated to identify any potential interactions.

Key Points

Drug interactions with rivaroxaban are a potential cause for serious adverse effects.

An interaction between a single dose of rivaroxaban and protease inhibitors may result in bleeding.

Extensive evaluation of the interaction profile is essential prior to adding rivaroxaban to antiretroviral therapy.

Introduction

A recent study by McDonald et al. showed that a large proportion of spontaneous reports of adverse events with rivaroxaban were associated with concomitant medicines, which may have increased the risk [1]. The authors concluded that there is a need for ongoing postmarketing surveillance of rivaroxaban, together with an increased awareness of the potential for drug interactions as a cause

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for serious adverse events. However, there was no mention of reports of interactions with antiretroviral agents (ARVs). We would like to describe a case report that illustrates the rapid effect of an interaction between the target-specific oral anticoagulant (TSOAC) rivaroxaban and ARVs.

Case Report

A 62-year-old male orthopedic surgical patient receiving long-term ARVs was commenced on enoxaparin 40 mg subcutaneously daily for venous thromboembolism (VTE) prophylaxis 3 weeks preoperatively. Preadmission medications that were continued postoperatively included the ARVs, etravirine 200 mg twice daily, ritonavir 100 mg twice daily, darunavir 600 mg twice daily, raltegravir 400 mg twice daily and emtricitabine/tenofovir 300/200 mg daily; mirtazapine 45 mg at night, aspirin 100 mg in the morning, esomeprazole 20 mg daily, valaciclovir 500 mg daily, and oxycodone sustained-release 60 mg twice daily. New medications that were commenced postoperatively included intravenous prophylactic antibiotics, meropenem 1000 mg three times daily and linezolid 600 mg twice daily for 1 week, and a single dose of antifungal therapy, oral fluconazole 400 mg. Pain was managed with pregabalin 75 mg twice daily, ketamine intravenous infusion up to 16 mg/h and morphine patient-controlled analgesia. Postoperatively, enoxaparin was replaced with rivaroxaban 10 mg daily. Twenty-four hours after concomitant administration of rivaroxaban with ARVs, the patient experienced profound hypotension and bleeding at the surgical site. At the time of bleeding, laboratory results showed a prolonged prothrombin time (PT) of 24.3 (10.6–15.3) s and a significantly elevated rivaroxaban trough level of 75 ng/mL (median plasma concentration 24 h after a 10 mg dose has been reported to be 9 ng/mL) [2]. Renal function was normal. Rivaroxaban was ceased and the patient was managed with fluid resuscitation, packed red blood cells, fresh frozen plasma and human prothrombin complex (Prothrombinex-VF®). No further bleeding occurred and 24 h later PT had normalized and the rivaroxaban level had decreased to 11 ng/mL. Enoxaparin for VTE prophylaxis was commenced 1 week later.

Discussion

Rivaroxaban, a substrate for cytochrome P450 (CYP) 3A4 and P-glycoprotein (P-gp), is contraindicated in patients concomitantly treated with strong inhibitors of both these systems, e.g. protease inhibitors (PIs) such as ritonavir [3]. The PI darunavir, a moderate CYP3A4 inhibitor, should also be avoided in patients receiving rivaroxaban [4, 5].

This recommendation is based on in vitro data and a pharmacokinetic study in healthy volunteers of rivaroxaban coadministered with drugs that share its metabolic pathway, e.g. ritonavir, midazolam [6]. Our patient was taking six ARVs, including the two PIs ritonavir and darunavir, and one non-nucleoside reverse-transcriptase inhibitor (NNRTI), etravirine (a moderate CYP3A4 inducer) [4]. No clinically significant interactions were expected to occur with the other ARVs, i.e. the integrase inhibitor, raltegravir and the nucleoside reverse-transcriptase inhibitors (NRTIs) emtricitabine/tenofovir [5].

After oral administration of a CYP3A4 inhibitor such as ritonavir, there is a rapid increase in the substrate plasma level, which is reversible, typically within 2–3 days of stopping the inhibitor [7]. Ritonavir is used as a pharmacokinetic booster and is included in most PI-based regimens at the lower dose of 100 mg twice daily compared with the 600 mg twice-daily regimen when used for its antiviral activity [4]. In this setting, ritonavir is a pharmacologic enhancer because it inhibits the metabolism of coadministered PIs, resulting in an increase in blood and tissue levels. Administration of a single dose of rivaroxaban 10 mg to healthy volunteers taking steady-state ritonavir 600 mg twice daily has been shown to increase the area under the curve (AUC) by 153 % and the mean maximum concentration (C_{max}) by 55 % [6]. No pharmacokinetic data are available on the impact of lower doses of ritonavir, i.e. 100 mg twice daily coadministered with rivaroxaban. In addition, no published data are available on the clinical significance of the interaction potential of darunavir, but the recommendation to avoid concomitant administration with rivaroxaban is similar to ritonavir [5].

Since the registration of rivaroxaban in Australia, in 2008 to November 2014 no reports, in addition to the one presented here, have been submitted to the Australian regulatory authority for therapeutic goods—the Therapeutics Goods Administration (TGA)—on adverse effects resulting from an interaction between rivaroxaban and ARVs [8]. To our knowledge, there is only one published case describing clinically significant bleeding possibly associated with an interaction between rivaroxaban and ARVs, including ritonavir, darunavir and etravirine [9]; however, a causal relationship between the adverse event and the drug interaction is unclear.

The clinical significance of an interaction between rivaroxaban and etravirine, a moderate CYP3A4 inducer, is not known. Induction of CYP3A4 is not an instantaneous process and may take 2–3 weeks to reach steady state [10]. Our patient had been taking etravirine for a number of years, therefore maximal induction was already present. The concomitant administration of rivaroxaban and etravirine may have decreased rivaroxaban levels to some extent and may have attenuated its effect.

Other drugs such as fluconazole may interact with rivaroxaban; however, it is a moderate inhibitor of CYP3A4 and, potentially, Bcrp (ABCG2). In the study by Mueck et al., only a modest increase in rivaroxaban blood level was observed after 4 days of pretreatment with fluconazole [6]. Our patient had only received one dose of fluconazole, therefore it is not likely to have had an impact on rivaroxaban levels.

None of the other coadministered drugs are known to, or are likely to, interact with rivaroxaban based on their metabolic pathway, i.e. ketamine, morphine.

For TSOACs, routine coagulation tests can be useful as screening tests to determine residual anticoagulant effect in certain clinical situations, such as the presence of bleeding [11]. The PT is the most sensitive assay for detecting rivaroxaban; however, it can be influenced by a number of factors, including hepatic impairment, sepsis, trauma with significant blood loss and laboratory PT reagent (thromboplastin) sensitivity [12].

The clinical relevance of TSOAC drug levels is unknown and should not be used to improve effectiveness [13]. However, in the presence of TSOAC-associated bleeding, specific drug levels should be performed, in conjunction with appropriate coagulation testing, to assess the contribution of excess drug to the bleeding event and to guide the need for intervention. In patients undergoing hip replacement surgery, the median rivaroxaban plasma concentration after a 10 mg once-daily dose was 9 ng/ml 24 h after the dose, i.e. trough level [2].

In our patient, the presence of a trough rivaroxaban level more than eight times higher than that expected from published data, together with a prolonged PT, suggests that bleeding may have been associated with increased exposure to the anticoagulant [2]. The rapid onset of bleeding and subsequent normalization of PT upon discontinuation of rivaroxaban is consistent with the pharmacokinetics of the drug and an interaction with ritonavir, which has been described in vitro and in healthy volunteers, and also with darunavir, based on its metabolic pathway. This is supported by a Drug Interaction Probability Scale (DIPS) score of 8, indicating a probable association [14].

Conclusions

Prescribers and pharmacists need to be alert to the potential for this clinically significant interaction to occur and to use the combination of TSOACs and ARV regimens containing PIs with caution. Due to the potentially serious consequences, for patients on ARVs it may be prudent to consider alternative agents for VTE prophylaxis, such as low-molecular-weight heparin, until an extensive evaluation of the interaction profile has been performed. Specialized resources for checking interactions with ARVs are readily available [5].

Written informed consent was obtained from the patient prior to publication of this case report.

Compliance with Ethical Standards

Conflicts of interest Carmela Corallo, Louise Grannell and Huyen Tran declare they have no conflicts of interest.

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