Challenge of Coadministering Antiretroviral Therapy and Oral Anticoagulants in HIV-Positive Patients

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By AIDS Reader [1]

With an improved life expectancy, HIV-positive patients now face interactions between antiretroviral therapy and medications for chronic medical problems. One example is thromboembolism and its treatment with oral anticoagulants.

As the prognosis and life expectancy for patients with HIV/AIDS improves, clinicians are forced to manage the coexistence of HIV infection and common chronic medical problems. One potential complication is the existence of drug-drug interactions between antiretroviral agents and other medications commonly used in the primary care setting. These interactions are well described with medications such as statins, antiepileptic agents, and proton pump inhibitors. Another commonly required medication that has the potential for significant and dangerous drug-drug interactions is the anticoagulant warfarin.

The need for frequent coadministration of antiretroviral agents and warfarin can be predicted by the growing awareness of the increased risk of thrombosis in HIV-infected patients. An increased incidence of thromboembolism has been reported in the HIV-infected population, with an estimated incidence of 0.54% per patient-year and a standardized incidence ratio of 1.33 to 1.39. Risk of thromboembolism has been linked to younger age (under 50 years), recent hospitalization, and recent central venous catheter placement, and it has been variably associated with the degree of immunocompromise according to the CDC HIV classification and the person’s CD4 count. While the exact mechanism for increased thrombophilia in the HIV-infected population is uncertain, potential explanations include disruption of endothelial cells, disturbance of the fibrinolytic system and/or the coagulation cascade, variations in anticoagulation proteins, and hypercoaguability caused by an opportunistic infection. Others have reported an increased incidence of thrombotic events in patients treated with protease inhibitor (PI)-based therapy. There is also recent evidence of an elevated cardiovascular risk in patients with HIV/AIDS during acute viral replication, which suggests another manifestation of increased risk of thrombosis. Recent data presented by the Strategies for Management of Antiretroviral Therapy (SMART) study group showed that an elevation in interleukin-6 level was strongly associated with an elevated risk of cardiovascular mortality among HIV-infected patients following antiretroviral treatment interruption. Similarly, an association has been reported between plasma levels of VCAM-1 and ICAM-1 (soluble vascular cell adhesion molecule and intracellular adhesion molecule, respectively), which indicates endothelial dysfunction and acute viral replication following interruption of antiretroviral therapy.

There are at least 9 case reports in the literature demonstrating interactions between 5 separate antiretrovirals and oral anticoagulants. In most of these cases, a marked increase in oral anticoagulant dosage requirements to achieve therapeutic levels after changes in antiretroviral regimens is described. Complications of these interactions include recurrent thromboembolism, frequent dose manipulations of both anticoagulant and antiretroviral agents, frequent blood draws, and bleeding.

In our urban primary care clinic for HIV-positive patients, we noticed that patients receiving oral anticoagulants had highly variable anticoagulation levels despite their being perceived as adherent to treatment.

Given this clinical observation and the previously described interactions with antiretroviral agents and oral anticoagulants, we conducted a review of our clinic’s patient records to evaluate the variations in anticoagulant response among patients receiving antiretroviral therapy and warfarin in a real practice setting. We hypothesized that there would be documentation of difficulty in achieving and maintaining therapeutic anticoagulation in such patients.

METHODS
A retrospective chart review was conducted of all HIV-positive patients in an urban primary care clinic...
A clinic known to be currently taking warfarin for any reason or to have been treated with warfarin in the past 2 years. The patients were identified from records of individual providers from a total of approximately 1300 HIV-positive patients in the practice. Inclusion criteria were HIV-positive status, age over 18 years, and concomitant use of warfarin and antiretroviral therapy. Exclusion criteria included an international normalized ratio (INR) of blood clotting time greater than 1.5 at baseline, chronic liver disease with a Child-Turcotte-Pugh classification of B or C, nonadherence with scheduled clinic visits (defined as less than one clinical visit or laboratory test within a month after initiation of warfarin treatment), or a record of the patient not filling the warfarin prescription.

Charts of included patients were reviewed for the following characteristics: age, sex, current antiretroviral regimen at the initiation of warfarin therapy, CD4 count, viral load before and after warfarin therapy, all INR values during first 3 to 6 months of warfarin therapy, number of visits to a health care provider, other medical problems, other concomitant medications, and episodes of significant bleeding or clotting (defined as those requiring hospitalization, emergency department visits, or repeated imaging studies). Adherence to antiretroviral therapy was recorded as the percentage of time the patient was adherent to his or her drug regimen as estimated by the primary clinician.

**RESULTS**

Twelve patients who had been taking both warfarin and antiretrovirals during the previous 2 years were identified. Two patients were excluded because they had abnormal INRs and were being monitored at a separate clinic, and a third patient was excluded because her anticoagulation therapy was discontinued as a result of long-term nonadherence. Of the 9 remaining patients, the mean age was 47 years. All but one were receiving PI-based antiretroviral therapy, with 3 receiving a ritonavir-boosted regimen. All patients had a goal INR of 2.0 to 3.0. Indications for anticoagulation included antiphospholipid antibody (1 patient), pulmonary embolism (1 patient), deep venous thrombosis (6 patients), and pulmonary embolism and deep venous thrombosis (1 patient). The complexity of the clinical situation for each of these patients is illustrated in Table 1, which provides the patients’ medical histories and concurrent medications.

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Most patients’ HIV disease was well controlled, with 7 of the 9 patients having undetectable viral loads at the start of their anticoagulation therapy. In 5 of the 9 patients, adherence to the antiretroviral regimen was documented as “100%” as assessed by their clinician. Six of the patients had a CD4+ cell count above 300/µL. There was no clinically significant change in the patients’ CD4 counts or viral loads during the first 6 months of anticoagulation treatment.
Median percentage of INR measurements within the therapeutic range was 27.7% for the 9 patients, with the highest at 71.4% and the lowest at 0.07%. If only the INRs after the first 2 months of warfarin therapy are considered, then the median percentage of therapeutic INR measurements becomes 30.1%, with the highest at 72.7% and the lowest at 0%. Of the values outside the therapeutic range, 50.5% were subtherapeutic and 21.2% were supratherapeutic. The mean number of INR values per patient per month was 2.5, and the average number of clinic visits during a 4- to 6-month period was 6.9 (median 7.2) (Table 2).

One patient experienced excessive vaginal bleeding during the 2-year study period and another was hospitalized for lower extremity swelling and bruising. No patient developed new episodes of thrombosis during the study period.

The records for 1 of the 9 patients (patient 9) were further reviewed. This patient presented to the clinic while already receiving 15 mg/d of warfarin for recurrent deep venous thrombosis. His antiretroviral therapy included nelfinavir plus lamivudine/zidovudine. His INR was 0.9, and his warfarin dosage was increased to 20 mg/d. During the following few months, his INR could not be maintained in the therapeutic range and remained persistently subtherapeutic, ranging from 1.0 to 1.1. His adherence to both his antiretroviral and warfarin regimens was repeatedly verified and encouraged. His antiretroviral regimen was switched after 10 months to emtricitabine/tenofovir fixed-dose combination and the integrase inhibitor raltegravir in order to avoid potential drug-drug interactions between the PI class and warfarin. Despite several initial subtherapeutic measurements (1.5 to 1.7), he has since achieved therapeutic INRs while receiving warfarin at dosages of only 5 to 7.5 mg/d. His CD4 count and HIV RNA level were stable throughout the transition in his treatment.

**DISCUSSION**

Because of an increased risk of thromboembolism in patients with HIV/AIDS and the increasing longevity of the HIV-infected population receiving effective antiretroviral therapy, it can be safely assumed that there will be more HIV-positive patients receiving concomitant oral anticoagulant and antiretroviral therapy. This retrospective case series highlights the experience of 9 patients who had therapeutic INRs less than half of the time while receiving both warfarin and antiretroviral therapy. The only patient who had therapeutic INRs more than 70% of the time was not being treated with a PI-containing regimen. While a causal relationship cannot be established by this small study, it does suggest the difficulty of the “real world” experience of achieving therapeutic INRs in antiretroviral-treated patients who also require anticoagulation therapy.

This difficult clinical situation is consistent with previously published case reports. Five separate antiretroviral agents were implicated: saquinavir, indinavir, nevirapine, nelfinavir, and ritonavir. In most of these cases, an increase in oral anticoagulant dosage was required after changes in the antiretroviral regimen involving the addition of one of the above-mentioned agents. One case report noted a marked decrease dosage requirement. Another described widely varying anticoagulant dosage requirements because of the patient’s intermittent adherence to ritonavir therapy. It is worth noting that in the cases in which exposure to ritonavir was reported, all patients but one were taking full-dose ritonavir (400 mg/d or more) rather than the lower dose used in current boosted PI regimens (ie, 100 mg once or twice daily depending on the PI being used).

That this drug-drug interaction occurs should not be surprising, since PIs interact with the cytochrome P-450 (CYP450) system. PIs specifically inhibit the isoenzymes CYP2C9, the enzyme responsible for the metabolism of the more active S-enantiomer of warfarin, and CYP3A4, which contributes to the metabolism of the less active R-enantiomer. Ritonavir in particular is a potent inhibitor of these enzymes, the basis for its use as a pharmacokinetic “booster” of other PIs in many
current antiretroviral regimens. Furthermore, ritonavir has potential for drug-drug interaction through inhibition of P-glycoprotein, a protein involved in the transport of drugs at the level of the intestine, liver, and kidney. Although to a lesser extent, NNRTIs, such as nevirapine, also inhibit metabolism of some medications in this way. It is important to describe and further explore the occurrence of such interactions with medications, such as warfarin, that are increasingly and commonly being used so that clinicians can better anticipate and manage potentially dangerous drug-drug interactions in their aging HIV-infected patients.

The interaction between antiretroviral agents, in particular PIs, and other medications has been described in controlled experiments. Yeh and colleagues reported a decreased INR response to warfarin in healthy volunteers who had been given a lopinavir/ritonavir coformulation. Von Moltke and colleagues found that ritonavir and indinavir were potent CYP3A4 inhibitors and that ritonavir was a particularly potent inhibitor of CYP2C9, CYP2C19, and CYP2D6 through in vitro metabolic models. These models predicted a high potential for dangerous drug interactions with other drug substrates of these cytochrome enzymes, including warfarin. Serious interactions between PI regimens containing ritonavir and other commonly used medications, including phenytoin, methadone, and other drugs, have also been well documented. Ritonavir has been shown to increase tissue exposure to digoxin by decreasing digoxin’s clearance by the liver.

Even in the general population, achieving ideal patient adherence to treatment and sustained therapeutic INRs is challenging. A recent article by Kimmel and colleagues explored the effects of poor treatment adherence on control of anticoagulation. The International Normalized Ratio Adherence and Genetics (IN-RANGE) Study was a prospective cohort study that followed 136 persons for a mean of 32 weeks and found that 40.4% of INRs were out of range, with 25.8% being below and 14.6% above range. Participants who had poor adherence were significantly more likely to be underanticoagulated. This contrasts with our case series of HIV-positive persons in which 71.6% of INR measurements were out of range, with 50.5% of the out-of-range measurements being below the therapeutic range and 21.2% being above. It is also clear that risk of serious bleeding or thrombotic complications occur with INRs significantly above or below, respectively, the therapeutic range.

It cannot be assumed that if a patient is adherent to his HIV medication, then he is similarly adherent to other prescribed concomitant medications. It is not clear, however, whether the patients in our case series were poorly anticoagulated because of poor adherence to warfarin therapy. While adherence to antiretroviral therapy is regularly monitored in patients with HIV infection, adherence to warfarin therapy is not as routinely followed in any patient population. The results from a recent study by Parker and colleagues showed that even in clinics that specialize in anticoagulation, clinicians and patients tend to overestimate patient adherence to warfarin. Specifically, patients treated with warfarin take their medication incorrectly 20% of the time.

Potential solutions to this increasingly important drug-drug interaction can be found in the patient (patient 9) described in more detail above (end of the “Results” section). In that patient, with abnormal INRs despite increasing his warfarin dosage, once his nelfinavir-containing antiretroviral regimen was switched to a PI-sparing regimen with an in-tegrase inhibitor, his INRs were markedly improved and he required much lower dosages of warfarin. As new classes of antiretrovirals become available, it is possible that preferentially choosing a newer agent, such as an integrase inhibitor or a CCR5 coreceptor inhibitor, may spare patients from this potentially dangerous drug-drug interaction. Anecdotally, another potential solution that has improved anticoagulation (in patients not described here) is to administer warfarin and the PI (particularly ritonavir) at different times over the course of the day.

As with any small study, this one has its limitations. First, because this is an uncontrolled study, we cannot draw any conclusions, but we can use the findings as hypothesis-generating. Second, since this clinic population from which these cases were drawn does not have a computerized, searchable database, we cannot be assured that all appropriate cases were included. Furthermore, all of the included patients were also receiving numerous other medications, such as antibiotics and steroid-based appetite stimulants, that can affect the pharmacology of warfarin. Given the small number of patients who were receiving ritonavir-boosted PI regimens in this clinic population, it is possible that we saw a reduced effect of the potential drug-drug interaction; other clinicians with patients on boosted-PI regimens and who are also receiving warfarin may observe more dramatic variations.

Despite the amount of time the patients spent with a nontherapeutic INR, there were few significant clinical outcomes. This could be due to the small number of patients in this study and the relatively
short duration of follow-up. Finally, this is a retrospective case series describing the experience of patients in a real practice setting, and the findings cannot be used to establish causality. Interactions between antiretroviral therapy and other medications will become more problematic in the coming years with the growing recognition of the importance of treating coexistent diseases in the aging HIV-positive population. This drug-drug interaction is of particular concern for HIV providers who are not comfortable with treating the common comorbidities of an aging population and who may be co-managing patients with another provider. Currently available reference resources recommend caution and close monitoring when coadministering warfarin and PIs, specifically ritonavir.

Health care providers should be alert to the potential for dangerously high or low INRs when they are giving anticoagulants to patients with HIV infection who are undergoing antiretroviral therapy. Perhaps alternative forms of anticoagulation, such as low-molecular-weight heparin, should be considered in the HIV-infected population receiving antiretroviral therapy or the timing of administration of warfarin and certain antiretroviral agents should be staggered. Future research efforts should address the exact interaction of antiretroviral agents and oral anticoagulants and explore mechanisms to overcome these drug-drug interactions to preserve the most treatment options for HIV-infected patients requiring both antiretroviral and anticoagulation therapy.

References:

REFERENCES


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