Pharmacokinetics of the Treatment Switch from Efavirenz to Nevirapine

To the Editor—Because of its potency, easy dosing (1 tablet per day), and relatively favorable adverse-effect profile, efavirenz (EFV) is one of the most widely studied antiretroviral agents for the treatment of human immunodeficiency virus infection. The most common symptoms after initiating EFV include neuropsychiatric adverse effects. Other adverse effects include rash, gynecomastia, teratogenicity, fat redistribution, and dyslipidemia. EFV toxicity may require a switch to nevirapine (NVP), a safe and effective alternative [1–4], but whether NVP should be started at 200 or 400 mg per day remains unclear [5]. EFV increases the metabolism of other coadministered drugs that are metabolized by the cytochrome P450, such as methadone, voriconazole, and NVP. Consequently, the NVP dose escalation may not be justified in the presence of EFV. The dose-effect relationship between steady-state plasma EFV levels and subsequent enzyme induction has not been studied. The study by Parienti et al [3] was a prospective randomized controlled trial evaluating the impact on low-density lipoprotein cholesterol of switching from EFV to NVP in case of EFV-associated dyslipidemia. This post hoc analysis aimed to describe the pharmacokinetics of the steady-state plasma NVP level during the switch from EFV and identify factors associated with suboptimal NVP plasma levels.

EFV was randomly switched to NVP in 18 of 37 white patients. NVP was introduced at 200 mg per day for 14 days, followed by 400 mg twice per day with intense pharmacokinetic sampling. The drugs’ steady-state plasma levels were determined in a central laboratory at the end of the study. The steady-state plasma EFV level at week 0 and the steady-state plasma NVP levels at weeks 2, 4, 6, 8, and 12 were plotted by use of box plots. First, we used linear regression to assess the correlation between the steady-state plasma EFV level at week 0 and the steady-state plasma NVP level at week 2. Second, we modeled the steady-state plasma NVP level using a mixed model, including age, sex, weight, baseline steady-state plasma EFV level, NVP dosage (200 mg per day vs 400 mg per day), and time as potential predictors.

A higher steady-state plasma NVP level at week 2 was significantly and positively correlated with a higher steady-state plasma EFV level at week 0 ($r = 0.54; P < .03$). As shown in Figure 1, there were 7 of 18 patients who had a steady-state plasma NVP level below 3000 ng/mL at week 2 (lower than the recommended limit for antiviral activity), and 5 of these 7 patients subsequently regained a therapeutic steady-state plasma NVP level when treated with an NVP dosage of 400 mg per day. Only baseline steady-state plasma

Figure 1. Efavirenz (week 0) and nevirapine (weeks 2–12) plasma concentrations during the switch from efavirenz to nevirapine (for 18 patients). The box plot shows a comparison of the plasma concentrations, with the upper and lower edges of the boxes representing upper and lower quartiles, respectively. Lines extending above and below the boxes represent the highest and lowest values, respectively. Circles represent outliers. Plus signs represent the mean values of the nevirapine plasma levels, and the small white square inside the first interquartile range (IQR) box represents the mean value of the efavirenz plasma level. The horizontal line within each IQR box represents the median value of the nevirapine or efavirenz plasma level.
EFV levels ($P = .008$) and NVP dosage ($P < .001$) were independently and positively associated with the steady-state plasma NVP levels in multivariate analysis.

The switch from EFV to NVP can lead to a time-limited subtherapeutic steady-state plasma NVP level. In this context, genetic variability may be responsible for the low steady-state plasma NVP levels among patients with previous low steady-state plasma EFV levels. Although the virologic consequences of a time-limited subtherapeutic steady-state plasma NVP level are unknown, subtherapeutic steady-state plasma NVP levels have been associated with virologic failure after a switch from protease inhibitor–based therapy [6].

To limit exposure to subtherapeutic steady-state plasma NVP levels, we suggest that determining the steady-state plasma EFV level before the switch to NVP may be helpful for deciding whether to start NVP at 200 mg per day (patients with high baseline EFV levels) or 400 mg per day (patients with low baseline EFV levels).

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References


Risk of Fatal Adverse Events after H1N1 Influenza Vaccination

To the Editor—The safety of the H1N1 influenza vaccine is controversial. Some fatal cases were reported after receipt of H1N1 influenza vaccine. A recent study shows that no patterns in age, sex, or type of underlying medical condition were observed that might lead investigators to suspect a causal link with H1N1 influenza vaccination [1]. However, the situation is different in Japan.

Some patients died immediately after H1N1 influenza vaccination in Japan. Severe adverse events following receipt of H1N1 influenza vaccine may occur in pregnant women, patients with underlying diseases, and young children, who have been preferentially vaccinated since October 2009 in Japan.

We investigated clinical features of patients who died immediately after H1N1 influenza vaccination, using the information on adverse events announced by the Ministry of Health, Labor, and Welfare. Physicians are required to report severe adverse events after H1N1 influenza vaccination to the Ministry of Health, Labor, and Welfare.

From 19 October to 21 December 2009, an estimated 15 million doses of monovalent, inactivated H1N1 influenza vaccine without an adjuvant were distributed in Japan. As of 7 January 2010, 107 fatal cases were reported, including 2 autopsied cases. Of the 107 cases, 98 (91.6%) involved persons aged $\geq$60 years. All the deceased individuals had underlying diseases, including respiratory disease ($n = 39$), cardiovascular disease ($n = 31$), and neurologic disorders ($n = 19$). Exacerbation of underlying diseases was the ma-

Figure 1. Number of fatal cases. Most of the fatal cases, which peaked in number within 24 h after H1N1 influenza vaccination, occurred within 4 days after vaccination.