Levofoxacin and Hypoglycemia

To the Editor—Levofoxacin has been previously reported to cause hypoglycemia in 4 patients [1–4]. In 2 of these instances, delays in recognizing the etiology of the hypoglycemia led to unfortunate consequences [1, 3]. An elderly surgical patient in our care recently died of recurrent hypoglycemia induced by levofoxacin. This prompted us to undertake a questionnaire survey of clinicians in our hospital, which is a university-affiliated teaching hospital. We queried them on the frequency of prescriptions for levofloxacin and gatifloxacin, the indications for their use, whether they were aware of its hypoglycemic adverse effects, and whether they could recall any unexplained hypoglycemic events in patients receiving levofoxacin or gatifloxacin in the previous 6 months.

Ninety-seven completed questionnaires were obtained from 138 clinicians. Most (37 of 97) were received from clinicians in internal medicine and its allied specialties. Others were from specialists in surgery (26), gynecology (13), critical care (9), orthopedics (8), and otolaryngology (4). More than 58% of respondents prescribed levofoxacin at least once in the preceding month, and ~19% were considered heavy prescribers (>3 prescriptions/week). Gatifloxacin had been prescribed by 72% of respondents in the previous month, and 14% were considered heavy prescribers. The most common reason for prescribing levofoxacin and gatifloxacin was lower respiratory infection (42%) and urinary tract infection (30%), respectively. Seventy-nine respondents (80.4%) were unaware that levofoxacin could cause hypoglycemia. More strikingly, 17 (94.4%) of the 18 heavy prescribers of levofoxacin were unaware that it could cause hypoglycemia. There was a better awareness about the potential adverse effect of gatifloxacin for levofoxacin among surgical colleagues because of the recent death of a surgical patient caused by levofoxacin-induced hypoglycemia. With regard to gatifloxacin, the 14 heavy prescribers were distributed across all departments, and 8 (57.1%) of the 14 were aware of the possibility of hypoglycemia. Six respondents (6.2%) could recall unexplained hypoglycemia in patients receiving levofoxacin, and 14 (14.4%) of 97 could recall hypoglycemic episodes in patients receiving gatifloxacin in the preceding 6 months.

This survey reveals that both levofoxacin and gatifloxacin are commonly prescribed antibiotics in our hospital. Despite their frequent use, awareness about the potential hypoglycemic effect is poor. On the basis of physician recall of unexplained hypoglycemia over the previous 6 months, it appears that hypoglycemia due to levofoxacin use is much more common than is reported in literature. There is better documentation of the dysglycemic adverse effects of gatifloxacin, and thus, better awareness. Improved awareness about hypoglycemia associated with levofoxacin use is essential to prevent further unfortunate consequences.

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Risk of Early Viral Failure of Once-Daily Tenofovir-Emtricitabine plus Twice-Daily Nevirapine in Antiretroviral Therapy-Naive HIV-Infected Patients

To the Editor—The combination of tenofovir, emtricitabine, and nevirapine is recommended as first-line treatment for
antiretroviral-naive patients in some guidelines [1, 2], although it has never been evaluated in randomized, controlled trials. By contrast, other guidelines recommend this combination only as an alternative [3].

We conducted an open-label, randomized, controlled trial to compare elevations in the plasma cholesterol and triglyceride levels after receipt of coformulated tenofovir-emtricitabine plus either nevirapine (200 mg twice daily after a 14-day course of 200 mg once daily) or atazanavir (300 mg once daily) plus ritonavir (100 mg once daily; ATV/r). Antiretroviral-naive HIV-1–infected adults with a CD4+ T cell count \!<\! 250 cells/mm³ (for women) or \!<\! 400 cells/mm³ (for men) were enrolled in the study.

In light of unexpected virological failure and evidence from the DAUFIN study [4], an unplanned ad interim analysis was conducted in April 2007, when 7 patients had been enrolled in each arm. Virological failure was defined as a reduction in the HIV RNA level of \!<\! 1 log₁₀ copies/mL at week 4 or viral rebound at week 12 after an initial decrease.

Three women and 2 former injection drug users were randomized to the nevirapine arm, whereas only men and no injection drug users were randomized to the ATV/r arm. The median ages of patients were 36 years (range, 28–44 years) and 43 years (range, 33–75 years) for the nevirapine and ATV/r arms, respectively. Three patients in the nevirapine arm and 2 patients in the ATV/r arm had HIV RNA levels \!<\! 5 log₁₀ copies/mL and CD4+ T cell counts \!<\! 200 cells/mm³.

Two premature treatment discontinuations occurred in the nevirapine arm (because of severe hypertransaminasemia for one patient and generalized rash for the other). All patients experienced a \!<\! 1-log₁₀ reduction in the HIV RNA level after 4 weeks. However, 3 patients (all of whom were in the nevirapine arm) experienced virological rebound at week 12, despite an initial decrease in the HIV RNA level. Viral genotypes noted at the time of virological rebound were K65R, Y181C, and G190A; T69N, K101E, Y181C, and M184V; and K103N, Y181C, and M184V. None of these mutations were present at baseline (figure 1). The remaining 2 patients in the nevirapine arm and all 7 patients in the ATV/r arm achieved an HIV RNA level \!<\! 1000 copies/mL at week 12. Self-reported adherence to treatment was 100% for all patients but 1, who reported an adherence rate of 93% at visual analogue scale at week 12 and subsequently developed virological failure, even though they had trough plasma concentrations of nevirapine that were greater than the threshold of 3.0 mg/dL [5]. In addition, the remaining patients who experienced virological failure had nevirapine concentrations that always exceeded the efficacy threshold. All 3 patients who experienced virological failure had high HIV RNA levels \!<\! 5 log₁₀ copies/mL and low CD4+ T cell counts \!<\! 200 cells/mm³ at baseline. Risk of early virological failure was sig-

Figure 1. HIV RNA levels and resistance profiles for the 3 patients who experienced early virological failure by week 12 of treatment with tenofovir-emtricitabine plus nevirapine. Pro, protease gene; RT, reverse-transcriptase gene.
significantly higher in the nevirapine arm than in the ATV/r arm for both the intent-to-treat \( (P = .021, \text{ by Fisher’s exact test}) \) and on-treatment \( (P = .045, \text{ by Fisher’s exact test}) \) analyses. The trial was prematurely stopped.

In our small population of antiretroviral-naïve patients, use of tenofovir-emtricitabine plus nevirapine was associated with unexplained early virological failure. This observation supports a similar finding by Rey et al. [4]. Although some guidelines are more rigorous in suggesting preferred treatment regimens that have been validated by randomized, controlled trials [3], other guidelines are more permissive [1, 2]. Our results appear to support the former approach, suggesting that tenofovir-emtricitabine plus nevirapine should be avoided if antiretroviral combinations that have been “validated” by randomized, controlled trials are available. We await more information from ongoing, randomized, controlled trials of tenofovir-emtricitabine plus nevirapine, and intensive ad interim monitoring should be performed to assess the risk of premature virological failure.

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