Hepatic Safety and Postexposure Prophylaxis

Sir—In the March supplement of Clinical Infectious Diseases [1] dedicated to hepatic safety and antiretroviral agents, the issue of postexposure prophylaxis (PEP) was not considered. However, concerns about PEP safety should arise because of its wide and increasing use following occupational and nonoccupational exposures to human immunodeficiency virus (HIV). Moreover, information derived from antiretroviral use in uninfected healthy individuals can provide further insights into direct drug toxicity not confounded by underlying diseases, use of illicit substances, or other causes of liver injury.

In patients receiving PEP, indirect hyperbilirubinemia is frequent but not clinically relevant when indinavir-including regimens are used; 2 cases of nelfinavir-associated acute hepatitis with cholestatic features were also reported [2]. The Italian Registry of Antiretroviral Post-Exposure Prophylaxis, using the AIDS Clinical Trial Group toxicity grading, did not find any instances of severe transaminase elevations in 207 individuals receiving 2 nucleoside reverse-transcriptase inhibitors (NRTIs), and found grade three elevation in 2 (0.5%) of 429 individuals receiving 2 NRTI plus a protease inhibitor [3].

However, treatment with nevirapine was associated with cases of life-threatening hepatitis [4] in uninfected individuals and with a frequency of severe, mostly rash-associated, hepatotoxicity that was significantly higher than that observed among HIV-infected patients [3, 5].

Recently, Patel et al. [5] described 30 cases of hepatotoxicity—including 14 severe cases and 1 case of fulminant hepatic necrosis—associated with nevirapine-including PEP, although they concluded that attributing the cause of hepatotoxicity to nevirapine could be problematic because of the concomitant exposure to other antiretrovirals.

Similarly, Dieterich et al. [6] reviewed available cohort studies on the risk of nevirapine-associated hepatotoxicity among HIV-infected patients and concluded that the overall rate of transaminase elevations is similar for all antiretrovirals, although the frequency of symptomatic hepatic events is significantly higher in nevirapine-treated individuals. These data, already presented elsewhere [6], were criticized by US Food and Drug Administration representatives [7], who, taking into account a possible bias in selection of the study population, found that the frequency of asymptomatic transaminase elevations was significantly higher in the nevirapine group (6% of subjects) than in control group (3%).

In an updated review of the above-mentioned Italian Registry data [3], we identified 1 grade three and 2 rash-associated grade four transaminase elevations among 10 women and 8 men receiving nevirapine-including PEP, for an incidence of 25 cases per 100 person-months. All cases occurred in female health care workers, none of whom had concurrent viral hepatitis. Although a selection bias caused by reporting of “positive” cases cannot be ruled out, these findings clearly suggest a prevalent role of nevirapine in causing hepatotoxicity.

Finally, female sex and high pretreatment CD4+ cell count are independent risk factors for developing hepatotoxicity among HIV-infected patients [6–8].

PEP data support these associations, suggestive of an immune-mediated basis for nevirapine rash-associated hepatotoxicity, and suggest a yet unexplained relationship between this adverse reaction and the level of immunocompetence.

In conclusion, available data suggest that antiretroviral-induced hepatotoxicity during PEP is rare, often mild to moderate in severity, and always reversible; in fact, nevirapine is the only antiretroviral whose inclusion in a PEP regimen is discouraged [9–10].

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References

7. Stern JO, Robinson PA, Love J, Lanes S, Im-

Reply to Puro et al.

Sir—In response to Puro et al. [1], we remind readers that nevirapine should only be used for the indications found on the product label. The product label clearly states nevirapine should not be used in the context of postexposure prophylaxis. The use of nevirapine, like the use of any antiretroviral drug, should be based on a risk-benefit assessment. We believe that antiretroviral drug, should be based on a risk-benefit assessment. We believe that the risk for patients who are not infected with HIV outweighs the benefit, especially since there are other treatment options available. Empirical observation of several spontaneous cases of liver failure, which may make liver transplantation necessary or result in death, has led the manufacturer, Boehringer-Ingelheim, to conclude that nevirapine should not be used as postexposure prophylaxis in HIV-negative patients.

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Broadened Definition for Hospital-Acquired Infective Endocarditis

Sir—In their article on hospital-acquired infective endocarditis (IE), Ben-Ami et al. [1] suggest that the traditional definition of hospital-acquired IE should be modified to include cases in recently hospitalized patients (i.e., those discharged from the hospital within 6 months before the onset of symptoms). Indeed, recently hospitalized patients with IE in their cohort are similar, with respect to in-hospital mortality and distribution of bacterial isolates, to patients who have traditionally defined hospital-acquired IE. Both of these groups significantly differ from patients with community-acquired IE [1].

To test the proposed new definition, we reviewed data on IE episodes observed at National Institute for Infectious Diseases “Lazzaro Spallanzani” (Rome, Italy) during 2000–2003. Injection drug users were excluded from the analysis because of the peculiar clinical and microbiological pattern of IE in this population [2].

Thirty patients with community-acquired definite IE (on the basis of the Duke criteria [3]) were observed; 24 had native valve IE, 5 had late prosthetic valve IE, and 1 had cardiac pacemaker infection. The mean age (±SD) of patients was 56.6 ± 16.3 years, and 21 patients (70%) were male. In 17 cases, a known valvular disease preexisted; comorbid conditions were present in 5 patients, including diabetes (3 patients), arterial hypertension, and chronic renal insufficiency. The in-hospital mortality rate was 22% (2 patients).

Nine episodes (30%) of IE fulfilled the broadened definition of hospital-acquired IE proposed by Ben-Ami et al. [1]: during the 6 months prior to hospital admission, 4 patients had been hospitalized, 2 had undergone surgical operations, 1 had been undergoing dialysis, 1 had undergone dental treatment, and 1 had undergone gastric endoscopy. Seven patients had native valve IE, and 2 had late prosthetic valve IE. In 3 episodes, no pathogens were isolated from blood cultures; in the remaining 6 episodes, blood cultures yielded viridians group streptococci (2 episodes), group B Streptococcus species (1 episode), methicillin-susceptible Staphylococcus aureus (2 episodes), and Enterococcus faecalis (1 episode).

No statistically significant differences were found between the remaining 21 patients with community-acquired IE with regard to age, sex, preexisting comorbidity, native or prosthetic valve localization, blood culture isolates, and in-hospital mortality (P = .08, by Fisher’s exact test).

Thus, the proportion of recently hospitalized patients with IE in our cohort was similar to that observed by Ben-Ami et al. [1]. Conversely, the distribution of bacterial isolates was different. This may be a result of different study populations or different epidemiological patterns in Italy than in Israel. Indeed, our patients were younger and had fewer comorbid conditions—findings that could also account for the lower mortality rate we observed.

Moreover, the epidemiology of pathogens traditionally considered to be associated with health care is changing. For example, the nosocomial incidence of community-acquired, methicillin-resistant S. aureus (MRSA) infection is increasing, and MRSA can no longer be considered an exclusively nosocomial pathogen [4–6]. Moreover, community-associated and health care–associated MRSA isolates have distinct resistance profiles and microbiological characteristics [6] that could be used to distinguish them.

According to Ben-Ami et al. [1], sus-