at the B. P. Koirala Institute of Health Sciences (Dharan, Nepal), a policy was instituted of performing baseline and weekly electrocardiograms (ECGs) for all patients receiving sodium stibogluconate, with temporary suspension of treatment if the corrected QT interval (QTc) exceeded 0.5 s. In the several months that followed the institution of this policy, there were no sudden deaths of patients treated with sodium stibogluconate. Interestingly, our experience was that, in most patients, the QTc increased until the second week and then decreased. Thus, checking the ECG at the end of treatment, as has been reported in some studies, underestimates the ECG changes associated with sodium stibogluconate toxicity and clearly misses those who die because of arrhythmia. In Ritmeijer et al. [1], the median time to death was 13 days after initiation of treatment, which certainly raises the possibility that the deaths resulted from ventricular arrhythmias caused by prolongation of the QTc. I am interested in knowing if the deaths of patients who were receiving sodium stibogluconate were sudden deaths and if ECGs were monitored on a weekly basis. The study provides useful data on the treatment of a neglected disease, but a true measure of the safety of sodium stibogluconate treatment cannot be established in the absence of at least weekly ECG monitoring and a protocol that defines how a prolonged QTc is handled.

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Amantadine May Be Lifesaving In Severe Influenza A

To the Editor—Both amantadine and rimantadine have been used for prophylaxis and therapy for influenza A, and both are ineffective against influenza B. Resistance to amantadine or rimantadine may occur during treatment if a single amino acid point mutation occurs in the M2 protein. Because of widespread resistance in 2006, some have suggested that amantadine and rimantadine should not be used for prophylaxis or therapy for influenza A [1].

The great concern, of course, is the possibility of a highly virulent strain of influenza virus A causing the next influenza pandemic. Recently, in Asia, infection with a highly virulent strain of influenza virus A, avian influenza virus (H5N1), was often lethal. Many deaths occurred in patients receiving oseltamivir, a neuraminidase inhibitor. Without amantadine, rimantadine, or oseltamivir, therapeutic options in an avian influenza pandemic are limited, and mortality could be exceedingly high.

It is commonly believed that, if an avian influenza or severe influenza A pandemic occurs, fewer mortalities would result than in the 1918 pandemic because of better medical support capabilities (e.g., ventilators and antibiotics). However, it is not appreciated that the most of the fatalities during the 1918 influenza pandemic were caused by the effects of viral influenza alone and not by secondary bacterial pneumonia. Although young persons and elderly persons were affected in the 1918 influenza pandemic, peak mortality was among healthy young adults. Young adults with influenza died rapidly of hemorrhagic tracheobronchitis/pneumonitis and hypoxemia secondary to influenza. Severe influenza pneumonia results from an oxygen diffusion defect, manifested by severe hypoxemia and an increased A–a gradient (>30). Patients with influenza are unable to oxygenate adequately, become cyanotic, and die a hypoxic death—often within 48–72 h after onset of the infection. The main determinant of mortality in influenza A is the severity of hemorrhagic tracheobronchitis/pneumonitis and hypoxemia [2–4]. Even in recent experience with influenza virus infection, most deaths were not due to superimposed bacterial pneumonia, but to influenza alone [5–8]. Some influenza-related deaths were due to encephalitis or myocarditis.

Most clinicians are unaware that amantadine has 2 mechanisms of action against influenza A. Amantadine’s antiviral properties are well known, but emerging resistance limits its antiviral effects. However, it should be remembered that the pharmacologic action of amantadine, independent of its antiviral activity, increases peripheral airway dilatation with resultant improved oxygenation [9]. Because hypoxemia is the main determinant of mortality in influenza A, amantadine is the only antiviral medication available that is known to improve oxygenation. Amantadine’s effect on peripheral airway dilatation and improved oxygenation may be lifesaving in cases of severe influenza A [10].

In the event of an avian influenza pandemic, some have suggested stockpiling oseltamivir and not amantadine because of potential amantadine resistance. From experience, oseltamivir has had limited effectiveness against avian influenza in 2005–2006 in Asia. Until an avian influenza vaccine is available, oseltamivir should continue to be administered in the usual or high doses, but it may be ine-
fective [7]. Because the pharmacological effects of amantadine on peripheral airway function and oxygenation are independent of its antiviral properties (and thus unaffected by antiviral resistance), amantadine should be used in adults to increase distal airway function and oxygenation; this effect may be lifesaving in cases of severe avian influenza and influenza A.

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