Amantadine and Rimantadine Prophylaxis of Influenza A in Nursing Homes
A Tolerability Perspective

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Summary

Amantadine and rimantadine are recommended for the treatment and prophylaxis of influenza A infections, and constitute an integral component of influenza control measures in the nursing home setting. However, optimal use necessitates a thorough understanding of the toxicity profiles of these agents, as well as strategies to reduce the risk of adverse reactions.

Adverse reactions of these compounds predominantly involve the gastrointestinal tract and the central nervous system (CNS), including hyperexcitability, slurred speech, tremors, insomnia, dizziness, mood disturbance, ataxia, psychosis and fatigue.

Based on data from comparative trials, rimantadine appears to exhibit a lesser propensity to cause adverse CNS reactions than amantadine, but a similar propensity to cause adverse gastrointestinal reactions. Factors enhancing the risk of adverse reactions to these agents include reduced renal function (especially for amantadine), drug-drug interactions with cationic drugs, which inhibit amantadine renal tubular secretion (e.g. trimethoprim, triamterene, and possibly cimetidine and procainamide), elevated peak and trough plasma concentrations, and a history of seizures.

Careful attention to published dosage adjustment guidelines for these com-
Adverse Reactions to Amantadine/Rimantadine

Influenza remains an important epidemic viral pathogen in the nursing home setting because it escapes host immune control through antigenic variation, is highly contagious, and can cause pneumonia and death in susceptible hosts. Approximately 80 to 90% of those who die from influenza are 65 years of age or older and death is due to pneumonia and/or the exacerbation of cardiopulmonary or other comorbidities. Influenza C is relatively nonvirulent while influenza B is most virulent in children. The antigenic stability of the latter agent presumably allows the adult population to acquire immunity. Influenza A is virulent in people of all ages, especially those at the extremes of age and those immunocompromised by drugs or disease. In fact, the attack rate of influenza A is 4-fold higher in persons over 70 years of age than that in adults under 40 years of age. A major factor accounting for recurrent influenza A epidemics is change in the virus (antigenic drift and shift) that renders the vaccine less effective. The annual financial and human toll due to influenza is substantial.

Based upon the above, chemoprophylaxis and chemotherapy of influenza A infection with amantadine and rimantadine potentially assumes an important role in the management of outbreaks in nursing homes. However, appropriate use of these agents necessitates a thorough understanding of their toxicity potential and means to reduce this, these aspects being the focus of this paper.

1. Overview of Amantadine and Rimantadine

Amantadine, a primary symmetric amine with a unique tricyclic structure, was discovered in the early 1960s and licensed for use against influenza A in 1966 in the US. At clinically-achievable concentrations, amantadine exerts activity against influenza A virus. Amantadine interferes with viral uncoating, preventing release of viral nucleic acid into the cell and thus prevents replication. Prophylactic use of amantadine reduces disease spread. Furthermore, amantadine used within 48 hours of developing symptoms, reduces influenza morbidity and mortality. Amantadine does not interfere with antibody production, whether due to natural infection or vaccination.

Rimantadine, a close structural congener of amantadine, was discovered in the 1960s, but only became licensed for use against influenza A in 1993 in the US. Rimantadine is similar to amantadine in antiviral spectrum and mechanism of action although somewhat more potent than amantadine in plaque assays and organ cultures. Rimantadine and amantadine appear to be equally effective in the prophylaxis and treatment of influenza A infections.

2. Clinical Pharmacokinetics

2.1 Amantadine

Amantadine is essentially completely absorbed after oral administration with a time to peak plasma concentration ranging from 2 to 4 hours. Multiple-dose administration of 100mg oral amantadine twice daily to healthy young volunteers resulted in steady-state peak plasma concentrations ranging from 500 to 800 μg/L (ng/ml). Adults over the age of 65 years require only 50% of the bodyweight-adjusted dose administered to healthy young adults to achieve equivalent plasma concentrations.