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Short Communication

The importance of virus drug-resistance in the treatment of influenza with rimantadine

O.I. Kubar, E.A. Brjantseva, L.E. Nikitina and D.M. Zlydnikov

Leningrad Scientific Research Institute of Epidemiology and Microbiology, Leningrad, U.S.S.R.

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Summary

Rimantadine is the first specific antiviral agent widely used in the Soviet Union for the treatment and prophylaxis of influenza A in adults. Development of resistance of influenza A virus to rimantadine has been observed. Concern has been expressed about the development of resistance during treatment of large populations with the antiviral. The efficacy of rimantadine in the treatment of various outbreaks caused by different serotypes of influenza virus has been followed over a period of 20 years in 142227 patients with influenza. No diminution in efficacy that could be contributed to the development of drug-resistant virus strains was observed.

Rimantadine; Influenza A; Virus drug-resistance

Because of the antigenic variability of the influenza virus and its ability to develop resistance to its inhibitors, particularly rimantadine, it is important to study the efficacy of anti-influenza drugs in the control of the disease, particularly when caused by drug-resistant virus strains (Chizhov, 1985). The long-term use of rimantadine in the U.S.S.R. and of amantadine in the U.S.A. and some western European countries has apparently not led to a change in drug efficacy in the period from 1969 to date (La Montagne and Galasso, 1978; Sabin, 1978; Zlydnikov et al., 1981a,b; Galasso, 1981, 1984). During this period, 142227 patients in the U.S.S.R. were treated with rimantadine for various outbreaks which included Hong

Correspondence to: O.I. Kubar, Leningrad Scientific Research Institute of Epidemiology and Microbiology, Leningrad, U.S.S.R.

Kong influenza A (H_3N_2) followed by various serotypes of H_3N_2 such as A/Victoria 72–73, A/Port Chalmers/I/75, A/Victoria 3/76, A/Texas/I/77, A/Bangkok/I/79, and A/Philippines/2/82. During the 1977/78 season we witnessed the return of influenza A (H_1N_1), followed by a decade of co-incidence of both epidemic variants of H_1N_1 and H_3N_2. We also witnessed the circulation of influenza B virus in 1980–81, 1984 and 1986.

During the outbreaks of influenza A (H_1N_1), 120678 patients were examined; during outbreaks of H_3N_2, 9081 patients; and during the outbreaks where influenza A predominated, 12506 patients. The efficacy of rimantadine was studied in these patients as outpatients. The numbers include patients with additional pathologies, including chronic disease. During the 20-year course of the study, the prescription for rimantadine was changed. The 24-h dose was increased from 150 to 300 mg.

These studies have led to the following conclusions:

1. Rimantadine is effective in the treatment of patients with influenza A (H_1N_1) and influenza A (H_3N_2).
2. The effect of rimantadine on recovery from the disease may vary depending on when treatment is initiated, on whether additional therapies are followed, and on whether the infection is based on one or several viruses.
3. Efficacy of rimantadine in influenza patients may vary during a given epidemic depending on the severity of the disease and the dose and frequency of drug administration.
4. Use of rimantadine in patients with influenza B confirmed by laboratory diagnosis is efficacious.

On the whole, rimantadine seems to be effective against influenza A regardless of the serotype. Attempts were made to isolate rimantadine-resistant virus in the German Democratic Republic and Bulgaria where rimantadine is not used for the treatment of influenza. Resistant variants appear to the same extent regardless of whether rimantadine is used or not (Heider et al., 1981; Hils et al., 1983; Bailowitz and Kaslow, 1985).

The development of resistant viruses could be a potential problem. To determine the clinical importance of drug-resistant influenza virus, we have since 1982 attempted at isolating rimantadine-resistant virus strains from patients who were treated or not treated with rimantadine. The percentage of rimantadine-resistant influenza A (H_1N_1) variants was 4.7%. For H_3N_2 it was 40.1% (Iljenko et al., 1987). The therapeutic effect of rimantadine was similar in both groups of patients (infected with influenza A H_1N_1 or H_3N_2) (Zlydnikov et al., 1986). Although all virus strains that were isolated were highly sensitive to ribavirin, and a high percent of the strains was resistant to rimantadine, the therapeutic effect of rimantadine on influenza A H_3N_2 mono-infection was much greater than that of ribavirin (Leonov et al., 1985; Golubev et al., 1987).

To obtain specific data on the interference of virus drug-resistance with the clinical efficacy of rimantadine, we compared the efficacy of rimantadine in the prophylaxis and therapy of influenza in family settings during the epidemic of 1985. In 23 family units, the therapeutic dose presented for patients was 100 mg riman-

tadine three times a day on the first day and 100 mg twice a day on the second and third days. For prophylaxis in other family members of the contact case, 100 mg once a day was prescribed for 5 consecutive days. Among the index cases, 3 sensitive influenza virus strains were isolated from 4 patients and 4 resistant strains were isolated from 4 patients. The therapeutic response to rimantadine was independent on whether the virus strain isolated from the patients was sensitive to the drug or not. Actually, the morbidity was higher in family units from which drug-sensitive virus was isolated.

In conclusion, the development of rimantadine-resistant influenza virus strains does not seem to be a matter of great concern. There was no decrease in the efficacy of rimantadine as a result of the development resistance.

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