Memoranda
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Memoranda are statements concerning the conclusions or recommendations of certain WHO scientific meetings; they are signed by the participants in the meeting.

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Current status of amantadine and rimantadine as anti-influenza-A agents: Memorandum from a WHO Meeting*

Amantadine (1-adamantanamine hydrochloride), an anti-influenza drug, effectively inhibits the replication of all human subtypes of influenza A virus (H1N1, H2N2 and H3N2) both in laboratory studies and in a variety of clinical situations in young and old persons. So far, it has been used on a relatively limited scale by community and hospital clinicians, partly because of concern over mild side-effects in approximately 6% of persons. The related compound, rimantadine (α-methyl-1-adamantane-methylamine hydrochloride), shows comparable antiviral activity with few or no side-effects. Although the mode of antiviral action is considered to be similar, the two drugs differ in their metabolic and pharmacological properties.

Both amantadine and rimantadine have therapeutic uses and shorten the duration of influenza-A-induced fever, malaise, and virus shedding. A dosage of 200 mg of either drug for a 3–5-day period is effective but treatment has to commence on the first day of symptoms. Prophylaxis, particularly using rimantadine, could be usefully initiated in elderly and other high-risk individuals living in institutions and in the general community.

Influenza A and B viruses are responsible for epidemics of disease throughout the world. Besides causing deaths, these epidemics lead to increased demands on health resources and services, particularly when there is a need for hospitalization (*21, 45*). The highest mortality during an epidemic occurs among certain high-risk groups in the population (*1, 38, 39*), such as old people (generally over 65 years of age), infants under 18 months, and persons with diabetes or chronic heart, kidney and respiratory ailments.

Because of limitations in the efficacy of influenza vaccines (*4, 11, 45*), there has been considerable interest in the development of specific antiviral compounds that could be used to supplement the use of vaccines. Amantadine and related compounds, such as rimantadine, which were discovered in the early 1960s (*5*), are antiviral agents that have been extensively investigated in the laboratory and clinic over the past two decades (*7, 8, 16, 20, 29, 47*). Although there is evidence of antiviral activity against all antigenic subtypes of influenza A virus (H1N1, H2N2 and H3N2) in laboratory and clinical studies, neither amantadine nor rimantadine has been used widely to date.

The present article summarizes recent laboratory and clinical work with this group of antiviral agents. After the 1980 report on amantadine (*27*), new data have appeared which make a re-evaluation of the status of antiviral drugs against influenza pertinent. Recent work presents comparisons of the antiviral efficacy of amantadine and rimantadine in field trials, precise comparisons of their pharmacology and

* This Memorandum was drafted by the signatories listed on page 54 on the occasion of a WHO consultation meeting held in Vienna on 26–28 August 1983. Requests for reprints should be addressed to Chief, Virus Diseases, World Health Organization, 1211 Geneva 27, Switzerland. A French translation will appear in a later issue of the *Bulletin*.

toxicology, and clinical data on their use in persons in old people's homes (*4*).

CURRENT SITUATION

Amantadine, a stable, water-soluble primary amine with a low relative molecular mass, inhibits replication of all known human influenza A strains by blocking an early stage of virus replication (*3*) although the exact mechanism is unknown. Rimantadine (α-methyl-l-adamantane-methylamine hydrochloride) is a molecular derivative of amantadine, which has been reported to be as active in the laboratory and clinic as amantadine, but is less toxic (*47*).

In vitro *and* in vivo *studies*

Considerable inhibition (⩾ 99%) of the replication of influenza A viruses of all three subtypes (H1N1, H2N2, and H3N2) occurs in the presence of subtoxic concentrations of amantadine or rimantadine in tissue cultures or eggs (*5,16*). Inhibition of the growth of clinical isolates of influenza A virus has been observed with amantadine (0.5 μg/ml) using a plaque reduction assay, although quantitative studies of the virus yield with different doses of amantadine revealed considerable variations in sensitivity among different influenza A viruses within the tested range (*34*). However, most field influenza A viruses are probably sensitive to clinically achievable levels of the drug.

Occasional drug-resistant influenza A viruses have been isolated from the community (*15*) but have not been reported from persons undergoing prophylaxis or treatment with amantadine or rimantadine. Drug-resistant variants can be produced by serial passage of virus in the presence of amantadine in either eggs or animal tissue cultures (*30*). In laboratory experiments, amantadine-resistant mutants have been reported to revert to sensitivity when cultivated in the absence of the drug (Hoffman, unpublished data). Genetic reassortment studies have indicated that the genes coding for the virus matrix and haemagglutinin proteins may be involved in drug resistance (*23, 35*).

Rimantadine possesses a similar antiviral spectrum *in vitro* and *in vivo* to amantadine (*18, 24*). However, it is more active than amantadine on a molar concentration basis. Thus, nearly all influenza A virus strains of the H1N1, H2N2 and H3N2 subtypes are inhibited by a 2–4 times lower concentration of rimantadine when compared with amantadine (*13*). *In vivo* studies in animal models have indicated significant prophylactic and therapeutic effects of amantadine and rimantadine against influenza infection (*5, 12, 33*).

Human studies

Pharmacokinetics. Amantadine is readily absorbed from the gastrointestinal tract and is not metabolized, more than 99% being excreted in the urine (*2*). Its half-life in serum is approximately 20 hours, and consequently administration once or twice per day is adequate. In contrast to amantadine, rimantadine is completely metabolized prior to excretion. Rimantadine has a longer half-life than amantadine (33.4 hours v. 20.4 hours), but the mean plasma drug levels are lower (301 ng v. 633 ng/ml) with the same oral dose (200 mg/day) owing to pharmacological differences between the two compounds (*14*).

Side-effects. At the usual dosage of amantadine of 200 mg/day (2.5 mg/kg), mild dose-related side-effects involving the central nervous system occur in a small proportion of subjects (*25*). The most frequently observed side-effects are nervousness, light-headedness, difficulty in concentrating, insomnia, and fatigue. However, it should be noted that other trials have failed to show important side-effects of amantadine involving the nervous system (*9, 31*). Also, amantadine has been administered to patients with Parkinson's disease (*36*) for periods in excess of four years (*40*) without serious effects attributed to the drug.

In contrast, with rimantadine (200 mg/day) there was no increase in side-effects compared with a placebo (*14, 47*);[a] with a 300 mg/day dosage, only mild and infrequent gastrointestinal, but not central nervous system complaints were observed. These differences may, in part, be explained by the differences in pharmacokinetics between the two compounds referred to above, since, with equal doses, the blood levels of amantadine are approximately twice those of rimantadine (*14*).

Prophylactic activity. Numerous double-blind placebo controlled studies, carried out over the past 20 years, have demonstrated the prophylactic efficacy of amantadine (200 mg/day) against infection caused by a number of different subtypes of influenza A virus (*29*). These trials included natural and experimental infection with influenza A (H2N2), (H3N2) and (H1N1) viruses (*6, 19, 26, 32, 41, 47*). The protective efficacy demonstrated in clinical trials has ranged from 70% to 90%, although in an early trial in volunteers (*43*) and in the community against

[a] PATRIARCA, P. A. ET AL. *Safety of prolonged administration of rimantadine hydrochloride in the prophylaxis of influenza A infections in nursing homes.* Paper presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy, Las Vegas, NV, October 1983.

the new Hong Kong virus (*10*) no antiviral activity was detected. The greatest antiviral efficacy has been shown in studies of natural infection with high attack rates. For the most part, the above clinical studies have been performed using healthy young adults in family groups, the army, university campuses or in working situations, but recent studies have confirmed and extended these earlier findings in other population groups such as old persons in institutional homes (see below).

Rimantadine appears to be as effective as amantadine when used prophylactically and, moreover, some studies indicate that it may be effective at a dose of 100 mg/day, besides the usual dose of 200 mg per day (*37, 47*).

Of particular interest are comparative trials where both amantadine and rimantadine have been evaluated together. In a recent double-blind, placebo controlled trial, 200 mg/day each of amantadine and rimantadine were compared (*6*). A high attack rate (41% clinical influenza, 21% laboratory confirmed influenza) by concurrent influenza A/Bangkok/1/79(H3N2) and A/Brazil/11/78(H1N1) viruses was observed. A 78% reduction in the incidence of influenza-like illness and a 91% reduction in laboratory documented influenza was detected in persons given amantadine, and the respective frequencies in students given rimantadine were 65% and 85% (*6*). In this trial there were significant differences in the rates of side-effects among the recipients of placebo, rimantadine or amantadine: 22% of amantadine recipients withdrew from the study, compared with 10% of rimantadine and 11% of placebo recipients. The greater number of withdrawals among amantadine recipients were a result of central nervous system side-effects, which occurred in 13% compared with 6% among rimantadine recipients and 4% among placebo recipients (*6*).

A similar study was performed in 105 elderly residents of a nursing home (mean age, 83 years) in a double-blind, randomized trial.[b] Influenza-like illness occurred in 27.3% of placebo recipients compared to 10.3% of rimantadine recipients ($P < 0.05$). The efficacy rate of rimantadine for prevention of influenza-like illness was 62.7%. Laboratory confirmed influenza occurred in 22.7% of placebo subjects but only in 10.3% of those receiving rimantadine. Of particular interest was the observation that, when the rates of influenza-like illness in the treatment groups were analysed according to previous influenza vaccination status, it became clear that the effect of rimantadine was additive to the effect of inactivated influenza vaccine. Placebo recipients who had received inactivated influenza vaccine had rates of influenza-like illness of 30.3% compared with 6.1% among vaccinated rimantadine recipients ($P \leqslant 0.015$), giving an overall efficacy rate for rimantadine among vaccinated individuals of 79.9%. This additive protective effect with rimantadine and influenza vaccine was also reported previously (*47*).

Another selected aspect of amantadine and rimantadine prophylaxis is the proven efficacy of these drugs in patients hospitalized during an outbreak of nosocomial influenza A infection (*28*). Since many hospitalized patients are elderly or have a chronic underlying disease, they are at high risk for the serious complications of influenza, and prevention of influenza A is thus highly desirable in such populations.

In summary, a considerable body of evidence now exists indicating that amantadine and rimantadine are effective in the prevention of influenza A infection and illness caused by all known human serotypes of human influenza A virus in all age groups. The reported antiviral efficacy is comparable to that induced by influenza vaccines, although these two antiviral compounds, unlike vaccine, have no effect against influenza B viruses. Moreover, the prophylactic efficacy induced by these drugs appears to be additive to any vaccine-induced effect. The antiviral efficacy of the two compounds is comparable at a dosage of 200 mg/day, but amantadine appears to cause more side-effects at this dosage. Studies in the USSR indicate that a lower dose of rimantadine (100 mg, but not 50 mg/day) would appear to be fully efficacious. Moreover a recent study in a boarding school in the United Kingdom indicates that 100 mg/day of amantadine is effective as a prophylactic (*32*).

Therapeutic activity. A number of studies have indicated that amantadine possesses moderate therapeutic effectiveness in uncomplicated influenza A virus infection in healthy young adults (*17, 42, 44, 46*). A rapid antipyretic action (mean time for the fever to come down to less than 37.7°C was 23 hours, compared with 45 hours for subjects receiving placebo) and an accelerated disappearance of other signs and symptoms have been a consistent finding in studies with amantadine. Other studies have shown, in addition to the clinical effects, an effect on the frequency or quantity of virus shedding (*44*). Most of these therapeutic studies employed 200 mg/day of amantadine for a short duration such as five days and, possibly because of the short duration of therapy, side-effects were not so evident.

[b] DOLIN, R. ET AL. *Rimantadine prophylaxis of influenza A in the elderly*. Paper presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy, Las Vegas, NV, October 1983.

Some studies have focused also on the abnormalities in pulmonary function that occur in even uncomplicated influenza and that persist for several weeks after acute influenza (*22*). Peripheral airway abnormalities, as well as abnormalities of gas exchange, diffusing capacity, and pulmonary mechanics have been reported. Accelerated improvement in amantadine-treated subjects, compared with subjects who received placebo, has been demonstrated. Rimantadine has a very similar therapeutic effect to amantadine (*44*, *47*).

In summary, both amantadine and rimantadine have small but demonstrable therapeutic effects in uncomplicated influenza A infections. Treatment shortens the duration of fever and other symptoms by about 50% and reduced the frequency of pulmonary abnormalities. The frequency and duration of virus shedding are also decreased. The two compounds are approximately equal in efficacy at a dose of 200 mg/day but lower doses of both drugs (100 mg/day) may be equally effective. Controlled studies of treatment of pulmonary complications of influenza with either amantadine or rimantadine, which are lacking, should now be carried out.

CONCLUSIONS

1. *Use of antiviral drugs*

Although immunization remains the major preventive measure against influenza A virus, the vaccines are only partially effective and other approaches for prevention, including the use of anitviral drugs, have a potentially important role. Controlled clinical studies have now been carried out in persons of various age groups (from 1-year-old children to the elderly) which conclusively demonstrate the efficacy of both amantadine and rimantadine for the prophylaxis and therapy of influenza A infections. Side-effects are less frequent with rimantadine (compared with amantadine), at a dosage of 200 mg/day, and are similar to those observed in the placebo group.

2. *Prophylaxis of influenza A virus infections*

The proper use of rimantadine or amantadine requires laboratory and epidemiological evidence of an outbreak of influenza A in the community, since these drugs are not effective against influenza B viruses. Prophylactic use of the drugs in at-risk persons for a period of up to 6 weeks after the onset of an outbreak can be considered. The following are potential target groups for the prophylactic use of the drugs, once influenza A virus activity has been detected in the community:

(*a*) elderly and high-risk individuals residing in nursing homes and similar institutional settings (where the attack rates can be very high), whether or not they have received influenza vaccine;

(*b*) elderly and high-risk individuals living in the general community who have not been vaccinated;

(*c*) hospitalized patients, both adult and paediatric, and staff directly involved in patient care during a nosocomial outbreak of influenza A;

(*d*) healthy individuals who require or desire protection. Particular consideration should be given to adults who perform functions critically important to the community welfare, e.g., public safety and hospital personnel, and persons in critical positions in the transport and communication services.

3. *Therapy of influenza A virus infections*

Both amantadine and rimantadine are partially effective for the prevention and treatment of uncomplicated influenza A. These compounds shorten the duration of fever, headaches, cough, sore throat, general malaise and also reduce virus shedding. A dose of 200 mg of amantadine or rimantadine per day for 3–5 days is effective. It is of particular importance to start treatment on the first day of symptoms.

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