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Edited by

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Progress in Medicinal Chemistry 18

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Preface

This volume contains six reviews, covering a wide range of topics in medicinal chemistry. Chapter 1 describes amantadine and its derivatives, compounds originally introduced in 1966 to combat influenza virus infections but later, through a chance observation, used in the treatment of Parkinson's disease. The basis of Chapter 2 resolves around the fact that both the tetrahydroisoquinoline and the tetrahydronaphthalene series contain members with sympathomimetic potencies of a similar order to those of the most active analogues of the natural catecholamine transmitters. Their most significant sympathomimetic effects have been identified as involving β-adrenergic receptors.

The mechanisms of the cytotoxicity of some nitroimidazoles are described in Chapter 3. These drugs are widely used in the treatment of several protozoal diseases such as trichomoniasis and intestinal infections. Reviews of a particular family of organic compounds are useful to medicinal chemists and a survey of recent work on 1,2-benzisothiazoles in Chapter 4 shows that a wide variety of biological activities are exhibited by these compounds.

The biological properties of tilorone and related bis-basic-substituted polycyclic aromatic and heterocyclic compounds are outlined in Chapter 5. These compounds were introduced as orally active anti-viral agents but, as so often happens in medicinal chemistry, other properties emerged and the compounds are now used as low molecular-weight immuno-modulating agents. Synthetic hypoglycaemic drugs were comparative new-comers on the therapeutic scene when they were reviewed in Volume 1 of this Series, and recent developments in this field are discussed in Chapter 6.

It is now twenty years since the first volume of this Series appeared and we hope that readers will welcome the cumulative indexes of all review titles and authors; these are included at the end of this volume.

Much effort has been involved in the preparation of these reviews and we are indebted to the authors for their diligence. We are also grateful to the owners of copyright material which has been reproduced in this volume. Finally, the staff of our publishers have, as usual, assisted us greatly and we acknowledge their contribution.

January 1981

G.P. Ellis
G.B. West

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1 Aminoadamantane Derivatives

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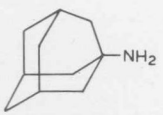
INTRODUCTION

Amantadine hydrochloride (1), 1-aminoadamantane hydrochloride, was introduced for clinical use in the U.S.A. in 1966 under the trade name Symmetrel^{R} (E.I. DuPont de Nemours and Company). Its initial use was restricted to prophylactic treatment for the prevention of respiratory illness due to susceptibe influenza A2-Asian viruses. It was the first orally active antiviral agent to be used in the U.S.A., and, in the intervening fifteen years since its introduction, has been the subject of, or included in, numerous review articles related to its chemistry [1-2] and biological activity [3-12].

Controversy over the clinical efficacy of amantadine against influenza [13-14] and the chance observation of its effect in Parkinson's disease [15] have contributed to a continuing interest in amantadine and the synthesis and evaluation of numerous derivatives. In the present review, recent developments in the clinical applications and mechanism of action of amantadine as well as of the two analogues, rimantadine (2) and memantine (DMAA) (3), which are of current interest as, respectivily, antiviral and anti-Parkinson's agents, will be dicussed. In the last section of the review, data on less extensively investigated compounds incorporating aminoadamantyl or related moieties which show significant biological activity are presented.



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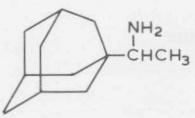

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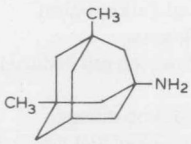

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ANTIVIRAL ACTIVITY OF AMANTADINE HYDROCHLORIDE

The majority of clinical trials with amantadine have been directed at establishing prophylactic or therapeutic efficacy against respiratory disease caused by influenza A group viruses. Other viruses, however, have been reported to be inhibited by amantadine in a variety of test systems such as tissue culture, embryonated eggs, animals and man.

SPECTRUM OF ACTIVITY

The cytotoxicity of amantadine and its activity against different viruses have

been reviewed by Hoffmann [4]. Although differing in sensitivity, all strains of influenza A group viruses were inhibited by amantadine with newer isolates more sensitive, in general, than the older ones [4]. More recently, a virus which was serologically related to the swine virus implicated in the 1918-1919 pandemic was associated with an outbreak of influenza in 1976, and, this virus, influenza A/New Jersey/8/76 (Hsw1N1), was found to be inhibited by the drug in experimental animals and in tissue culture [16-19]. Of particular importance has been the finding that group B influenza viruses and other respiratory pathogens such as rhinoviruses and respiratory syncytial and adenoviruses were resistant to amantadine. However, other viruses inclusing parainfluenza, pseudorabies, rubella, murine, and avian tumor viruses, arena viruses, lymphocytic choriomeningitis and junin virus were reported to be inhibited by amantadine in tissue culture or in experimental animals [4]. Very recently, Koff, Elm and Halstead [20] showed that amantadine decreased the titers of all four types of dengue viruses grown in LLC-MK2 cells by more than 90% at a concentration of 50μg/ml. It was also shown that the growth of dengue virus type 2 was reduced in both human and rhesus peripheral blood leukocytes by the drug. Although amantadine has shown activity against different viruses, its clinical use is currently limited to group A influenza viruses.

MECHANISM OF ACTION

The mode of action of amantadine against susceptible viruses has been the subject of numerous studies, and yet the exact mechanism responsible for its antiviral effect has not been clearly established. It does not inactivate the virus on contact nor is virus adsorption into or release from infected cells inhibited, but it must be present immediately after the absorption period for an antiviral effect to be achieved [4, 21-22]. Initial studies by the DuPont group suggested that amantadine inhibited virus penetration of infected cells [23-24], but a subsequent study with fowl plague virus [25] reported that it interfered with the uncoating of the virus but not with penetration. Later electron microscope studies also indicated that it did not inhibit the penetration of the chick chorioalantoic membrane by influenza A2 viruses [26] or the penetration of chick embryo fibroblasts by fowl plague virus [27].

In a study of the effect of amantadine on early events following influenza virus infection [28], it was suggested that the release of virus RNA into cells may consist of two steps, one of which is inhibited by amantadine: (a) uncoating of the virus envelope, and (b) release of RNA from the nucleocapsid. An analysis of fowl plague virus-specific RNA synthesis in chick embryo fibroblasts [27] indicated that the presence of amantadine from the time of virus

addition prevented expression of the virus genome and the synthesis of even the first detectable transcripts catalyzed by the polymerase of the infecting virus particles was prevented. The earlier report [29] of an inhibitory effect of the drug on the viral RNA-dependent RNA polymerase was not confirmed either *in vitro* or *in vivo* [27]. Addition of amantadine immediately after virus adsorption has been shown [18, 27] to inhibit virus-specific protein synthesis. At present, it is only possible to state that amantadine prevents some unknown post-adsorption stage of the virus replication cycle before virus RNA transcription occurs [11, 27].

The development of resistance to amantadine by influenza A virus has been demonstrated in experimental animals [30]. It has subsequently been shown that the infection of embryonated eggs, cell culture or mice with a mixture of amantadine-resistant and amantadine-sensitive strains of influenza virus resulted in the transfer of amantadine-resistance or sensitivity between strains [31]. It was further shown that the response of a recombinant virus to amantadine was not related to either of its surface antigens (hemagglutinin or neuraminidase) and that resistance to amantadine was transferred as an all-or-none character [31]. Additional studies with influenza virus recombinants have indicated that the gene coding for the M protein influences sensitivity or resistance to amantadine and this suggests a possible association of the M protein with the process inhibited by amantadine [32].

It is of interest to note that, with the exception of amantadine, compounds inhibiting penetration and/or viral uncoating are not clinically useful [33].

CURRENT USE AND RECOMMENDATIONS

Earlier reviews of amantadine have described the results obtained against experimental and naturally-acquired respiratory disease caused by influenza A virus strains [4, 8, 10-12, 34, 35]. The main conclusion drawn from numerous clinical studies was that amantadine had both prophylactic and therapeutic efficacy and was well tolerated by the vast majority of patients. More recently [36], amantadine was demonstrated to be effective in preventing illness and infection caused by Russian (H1N1) influenza.

Although fifteen years have elapsed since the introduction of amantadine in 1966 for prophylactic use against influenza A2/Asian infection and even though clinical efficacy has been amply demonstrated, the use of amantadine as an antiviral has remained controversial and limited in extent. It was only in 1976 that amantadine was cleared for use in the U.S.A. for the prevention and symptomatic management of infections caused by influenza A virus strains other than A2/Asian [8]. Chang and Butler [37] have analyzed several of the factors

responsible for the limited use of amantadine by physicians. These included (a) an unfavourable evaluation of the early clinical trails with amantadine [13-14], (b) the short duration of prevalence of influenza/Asian viruses and the lack of effect of amantadine against influenza B virus strains, (c) the difficulty of diagnosing sporadic cases of influenza, and (d) the degree of side effects of the drug. In addition, the belief that uncomplicated influenza usually requires no treatment has contributed to the reluctance of many physicians to use the drug. Opposed to this view are data from studies of pulmonary function in patients with uncomplicated influenza which commonly reveal peripheral airway dysfunction as well as gas-exchange abnormalities [38-42]. These abnormalities, suggesting involvement of the lower respiratory tract, may persist for weeks or even months. It has been shown that the use of amantadine in uncomplicated influenza improves the abnormalities in lung function [39-41] and when used as prophylaxis markedly reduces the occurrence of chest complications [42].

A Consensus Development Conference entitled, 'Amantadine: Does it Have a Role in the Prevention and Treatment of Influenza', was held at the National Institute of Health (U.S.A.) in the Fall of 1979. Sponsored by the National Institute of Allergy and Infectious Disease, a panel of experts from the U.S.A., United Kingdom and the Soviet Union met to consider four specific questions: (a) what are the potential benefits of the prophylactic and therapeutic uses of amantadine for influenza A infections, (b) who should take amantadine, and when should it be taken, (c) what are the risks associated with the use of amantadine and (d) is there a role for the use of amantadine in combination with vaccines [43]?

The panel of experts concluded that the use of amantadine, as a prophylactic agent as well as for the treatment of influenza A, had significant potential value in reducing the morbidity associated with this respiratory disease and its complications. Use of amantadine was judged to be of particular value among persons with cardiopulmonary disease – especially the elderly who are suffering from more severe, life-threatening forms of disease where pneumonic complications are more likely. It was felt that, under epidemic conditions, the use of amantadine in institutionalized aged persons would be of benefit to the patient population and the staff that care for them. A similar beneficial effect of amantadine would be expected in the case of vulnerable patients exposed to influenza A in hospitals. An earlier report had produced evidence for the prophylactic use of amantadine for high risk patients who had not been immunized or in whom a vaccine had not had sufficient time to produce a serologic response [44]. The panel suggested that other high-risk groups among whom beneficial results may be expected under epidemic conditions would include public ser-

vants such as firemen, policemen and military personnel, especially those without adequate influenza virus vaccine immunization [43].

When there is both epidemiologic and virologic evidence of an outbreak in the community or region, the panel designated the following groups with highest priorities for receipt of amantadine: (a) unvaccinated children and adults at high risk of serious morbidity and mortality because of underlying diseases (pulmonary, cardiovascular, metabolic, neuromuscular or immunodeficiency), (b) non-vaccinated adults whose activities are required for community function and (c) persons in semiclosed institutional environments – especially older persons who have not been adequately immunized. Since the teratogenic risk of amantadine in pregnant women is not well understood, the panel suggested that amantadine should be administered to pregnant women only after a comparative evaluation of the possible risks to the foetus and the benefits to the patient.

In considering the therapeutic effect of amantadine, the panel concluded that treatment should be administered as soon as possible and not later than 48 hours after onset of symptoms. Therapy with amantadine was suggested for the following groups: (a) high-risk patients as previously defined, (b) patients with life-threatening primary influenza pneumonia or influenza-associated croup and (c) persons whose functions are vital to the community.

In making an assessment of the risks of the use of amantadine for the prophylaxis and treatment of disease caused by influenza A viruses, the panel drew on the data from numerous clinical trials involving over 11,000 subjects. Approximately 7% of persons receiving amantadine (200 mg daily) had experienced transient nervous system symptoms (insomnia, light-headedness, nervousness, difficulty in concentration, or drowsiness). The experience gained with the use of amantadine in elderly patients with Parkinson's disease did not appear to present special toxicity problems. The panel concluded that the physician must determine when the possible mild impairment of intellectual acuteness and decreased motor function associated with the use of amantadine would present a special hazard to a patient in a particular job situation if prophylaxis with amantadine was to be given.

Because of the effect of amantadine on the nervous system, the panel also evaluated the potential for drug abuse. The use of amantadine for the specific purpose of altering the state of consciousness has not been reported, and it appears to have a low potential for abuse since it does not provide prominent analgesia or euphoria.

The panel also considered the possible selection of amantadine-resistant strains of influenza A virus as a consequence of extensive clinical use of the drug. *In vitro* studies have demonstrated the spontaneous development of amantadine

resistance among influenza A viruses, but such resistant variants have not been isolated from patients who have received the drug. The panel, however, cautioned that the overuse of amantadine may result in an increase in drug-resistant strains of influenza A virus in the population.

In evaluating the role for the combined use of amantadine and influenza immunization, the panel recommended that immunization be used as the primary method for prophylaxis against influenza. Amantadine should be given as adjunctive therapy and discontinued once a seriologic response to the immunization was to be expected. In a subject with a normal immune system who had previously been immunized with antigen related to the current epidemic strain, antibody response of protective quality is achieved about 10 days after administration of the vaccine. Treatment with amantadine is given for four to six weeks after immunization when the subject had not received an antigenically-similar vaccine in the past and when influenza persists in the community [43].

ANTIVIRAL ACTIVITY OF RIMANTADINE HYDROCHLORIDE

Rimantadine hydrochloride or 1-(1-aminoethyl)adamantane (2) is a congener of amantadine that was also developed by the DuPont Company. It has been reported to be active against influenza A, rubella, rubeola, respiratory syncytial and parainfluenza types 2 and 3 viruses [45]. Interest has generally been directed to its effect against influenza A viruses where activity has been shown *in vitro* [45, 46] and *in vivo* [47, 48]. The mechanism of the antiviral effect of rimantadine as well as its antiviral spectrum are similar to those of amantadine [46]. Koff and Knight [49, 50] have recently reported that rimantadine, as is the case with amantadine, acts at an early stage in the influenza A virus replicative cycle. Drug added late in the replicative cycle had no inhibitory effect and addition of rimantadine during the viral adsorption period and removal thereafter did not result in an antiviral effect [49]. It was further shown that rimantadine did not alter the structural integrity of influenza virus. When added after the viral adsorption period, rimantadine inhibited the stimulation of cellular DNA-dependent RNA polymerase II from virus-infected cells but had no effect on RNA polymerase II from uninfected cell nuclei. Rimantadine, present from 0–8 hours postinfection, was shown to inhibit the formation of viral RNA-dependent RNA polymerase activity in infected cells, but inhibition of enzyme activity was not observed *in vitro*. Rimantadine was also shown to inhibit viral and cellular protein synthesis but the inhibition was not considered to be great enough to be responsible for the antiviral effect found with rimantadine against influenza A virus [49]. In a separate study,