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Amantadine for influenza A

As well as, not instead of, immunisation in high risk groups

The outbreak of influenza A in 1989-90 was the worst to have hit England and Wales since 1976 and may have been responsible, directly or indirectly, for about 26 000 deaths.[1] While substantial influenza epidemics are sporadic and difficult to predict influenza surveillance in the United Kingdom and United States has shown that infections with influenza A or B viruses, or both, recur each winter, so efforts at control must be planned annually. Because of the limited efficacy of influenza vaccines much interest has been shown in other anti-influenzal agents. Amantadine and other adamantanes such as rimantadine were first shown to inhibit influenza A in the 1960s, yet few practitioners seem aware of their clinical potential. Is this ignorance acceptable, or are doctors neglecting potentially lifesaving treatment?

Amantadine and rimantadine inhibit H_0N_1, H_1N_1, H_2N_2, H_3N_2, and Hsw_1N_1 strains of influenza type A,[2,3] including "new" epidemic strains. It is therefore expected that future variants, including pandemic strains, will be similarly inhibited. Neither agent inhibits strains of influenza B, and inhibition of parainfluenza and respiratory syncytial viruses requires higher concentrations than can be safely achieved in humans. Drug resistant strains of influenza A, which have complete cross resistance between amantadine and other adamantanes,[4,5] can be readily produced in the laboratory and are being recovered increasingly from humans (EE Mast *et al*, paper to 29th interscience conference on antimicrobial agents and chemotherapy, Houston, 1989).[6-9] Their rapid selection and apparent transmission have resulted in treatment failures when index cases and family contacts were given rimantadine,[7,8] and the emergence of drug resistance was implicated in occasional treatment failures when amantadine prophylaxis was initiated during a nursing home outbreak of influenza (EE Mast *et al*, paper to 29th interscience conference on antimicrobial agents and chemotherapy, Houston, 1989). Illnesses caused by resistant strains are probably no more severe than those caused by wild strains of the virus, and although the emergence of drug resistance is of concern, no reduction of drug efficacy was observed in the Soviet Union over a 20 year period when 142 227 patients were treated with rimantadine.[9]

Currently only amantadine is licensed for use in the United Kingdom. The drug is almost completely absorbed when taken orally and is excreted unchanged in the urine. Because of reduced clearance in the elderly and patients with impaired renal function[10] care should be taken to ensure that the drug does not accumulate to toxic concentrations. Minor neurological symptoms including insomnia, light headedness, difficulty concentrating, nervousness, dizziness, and headaches develop in 5-20% of patients receiving 200 mg daily.[11] Other adverse effects include anorexia, nausea, vomiting, dry mouth, constipation, and urinary retention. They arise mostly during the first few days of treatment and disappear quickly when amantadine is stopped. Because embryotoxic and teratogenic effects have been described in rats receiving 15 times the usual human dose[12] treatment with amantadine is not justified in women of childbearing age except perhaps in life threatening influenzal pneumonia. Amantadine is contraindicated in epilepsy and gastric ulceration and should be used cautiously in patients with cardiovascular or renal disorders or with cerebral atherosclerosis—that is, patients who are at increased risk from influenza.

Before amantadine is prescribed laboratory and epidemiological evidence of an outbreak of influenza A in the community should exist. This may be assumed when general practitioners' returns to the Birmingham research unit of the Royal College of General Practitioners show sharply escalating consultation rates for influenza and influenza-like illness, and the Public Health Laboratory Service reports isolations of influenza A.

Taken prophylactically, amantadine is about as effective as influenza virus vaccine in preventing influenza A. Controlled trials suggest that prolonged administration of amantadine 200 mg daily during community outbreaks of influenza prevents about half the expected infections but prevents or ameliorates 70-100% of the illness.[13,14] This distinction may be desirable as subclinical infection could confer immunity against reinfection. If amantadine or rimantadine is used for both treatment and postexposure prophylaxis in homes, however, rapid selection and apparent transmission of drug resistant influenza A viruses can occur, and the drug may provide little or no protection (EE Mast *et al*, paper to 29th interscience conference on antimicrobial agents and chemotherapy, Houston, 1989).[7,8,15]

Who should receive prophylaxis with amantadine and how might a programme be implemented? Because of amantadine's minor central nervous system side effects prophylaxis is most appropriate for people in high risk groups for whom vaccination is indicated[16,17]; indeed, the World Health Organisation recommends prophylaxis with amantadine or rimantadine for elderly people and those at high risk in institutional settings to augment protection afforded by vaccination.[17] If vaccination has been overlooked high risk patients can still be

vaccinated after an outbreak appears locally, but developing an immune response usually takes several weeks and this vulnerable period (and beyond) can be covered by chemoprophylaxis. When vaccine is unavailable or the influenza A strain causing an epidemic differs greatly from the vaccine strain, amantadine should be given for the entire duration of the outbreak, a period of about four to eight weeks. Chemoprophylaxis should be considered for all unvaccinated household members and medical and paramedical workers in frequent contact with people at high risk in the home, hospital, or institutional setting. It is also advocated to control established outbreaks in facilities that care for people at high risk, regardless of their vaccination state, but in this setting the rapid emergence of resistance may be a problem.

For doctors the main components of a programme of prophylaxis with amantadine are the timely identification of those at high risk, informing them of the risks and benefits of amantadine, and having adequate supplies of the drug available. Identifying people at high risk should occur early in the year when influenza vaccine is ordered. This should pose few problems for computerised practices that can use the computer to generate prescriptions and personalised information sheets for posting as soon as an epidemic is notified. Alternatively, general practitioners could issue prescriptions throughout the year and instruct patients to take the drug only when an outbreak is identified by the local or national press. This should at least ensure that the drug is available when most required.

Treating established influenza A with amantadine, when the drug is started within 48 hours of symptoms, cuts the duration of fever and other effects by one to two days and accelerates the resolution of the peripheral airways abnormalities that usually accompany influenza.[10 18-20] The reduction in symptoms far outweighs the drug's toxic effects.[18 19] Early treatment—that is, before laboratory confirmation of the diagnosis is generally available—seems essential. Treatment for several days is usually effective, and short courses may lessen the selection of resistant strains of virus.[21] During a known outbreak of influenza A most people with acute onset of nasal symptoms, feverishness, shivering, cough, headache, myalgia, or anorexia, without vomiting or diarrhoea, will have influenza[19 22] and can be considered for treatment, particularly those in high risk groups, in whom complications can be expected.

The recommended prophylactic and therapeutic dose of amantadine is 200 mg daily, reduced to 100 mg in those aged 10-15 or over 65; the suggested dose in children aged 1-9 years is 2 to 4 mg/kg. The possibility that drug resistance will increase with the extensive use of amantadine, its minor adverse effects on the central nervous system, and the logistic difficulties in organising timely prophylaxis and treatment underscore the importance of immunisation. On balance the adamantanes are still clinically useful and deserve wider distribution as an adjunct to (not a substitute for) vaccination, but doctors should continue to monitor efficacy and the emergence of resistant strains in formal clinical trials.

KARL G NICHOLSON
Senior Lecturer in Infectious Diseases
MARTIN J WISELKA
Wellcome Fellow

Groby Road Hospital,
Leicester LE3 9QE

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Domiciliary visits

We need to identify the ones worth doing

In most health systems the problem with services paid for by a fee per item of service is to contain them. Surprisingly, this is not the case with domiciliary consultations within the NHS—visits paid for separately and made by consultants at the request of general practitioners to patients who cannot attend hospital. Although domiciliary visits are generally regarded as time consuming and clinically inefficient, most consultants agree to provide them, but their number has been falling since 1978-9.

Although the average number of visits made per consultant and per general practitioner has fallen,[1] large variations in their use remain. The review body, no longer as interested in the sums earned through domiciliary visits as it had been in the early 1980s,[2] nevertheless commented in 1986 on the wide variation between specialties.[3] Ever since O'Brien and Jessops hinted that these variations might be a suitable subject for clinical audit[4] the Northern region has pursued a policy of analysing the data on domiciliary visits and feeding it back to consultants. Donaldson and Hill (p 449) describe the savings the region has made and also provide interesting, though tantalisingly incomplete, data on patterns of use from a prospective survey of nearly a year's data in all the non-teaching districts in the region.[5]

Overall 86% of general practitioners requested fewer than