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## AMANTADINE AS AN ANTIVIRAL AGENT IN INFLUENZA

AMANTADINE became the first antiviral agent available for systemic use in the United States when it was licensed by the Food and Drug Administration in 1966 for prophylaxis of Asian influenza (H<sub>2</sub>N<sub>2</sub>). In the first decade after its approval, the drug was not widely used for several reasons.<sup>1</sup>

The occurrence of side effects was worrisome. Furthermore, influenza does not have a specific clinical characteristic, such as paralysis or rash, and hence the disease required laboratory diagnosis, which was not readily available. Finally, with the major shift in strains that occurred with the appearance of influenza A/Hong Kong/68 (H<sub>3</sub>N<sub>2</sub>), amantadine became a licensed antiviral agent for a disease that no longer existed; infections due to H<sub>2</sub>N<sub>2</sub> strains of influenza A disappeared after 1967.

In 1976, the FDA-approved use of amantadine was changed to include relief of symptoms (i.e., therapy) as well as prophylaxis of all influenza A strains. This recommendation was based on new data that had appeared in the decade since the drug was originally approved. This accumulated work also led to a consensus-development conference at the National Institutes of Health, which recommended more widespread prophylactic and therapeutic use of amantadine.<sup>2</sup>

The study by Dolin and his colleagues in this issue of the *Journal* provides solid data in this chain of evidence, proving the prophylactic efficacy of amantadine.<sup>3</sup> Dolin and his co-workers were more fortunate than many other workers in that, shortly after they initiated their study, a sizable outbreak of influenza occurred with two viruses — one of the H<sub>3</sub>N<sub>2</sub> and one of the H<sub>1</sub>N<sub>2</sub> subtype. Because of the high attack rate — 41 per cent influenza-like illness and 21 per cent laboratory-documented influenza in the placebo group — Dolin et al. were able to provide substantial evidence of the protective efficacy of amantadine, which was 78 per cent for prevention of influenza-like illness and 91 per cent for prevention of laboratory-documented influenza. The importance of this study, therefore, is that it provides very clear-cut data concerning chemoprophylaxis against the influenza viruses circulating in January 1981. In addition, a third group of subjects in the controlled study received rimantadine, a drug very similar to amantadine that is widely used in the Soviet

Union. Comparable figures on the efficacy of rimantadine were 65 per cent and 85 per cent, respectively.

It is clear from the study of Dolin et al. and from the previous literature that amantadine is a highly effective prophylactic agent against several strains of influenza. This has been a consistent finding over 15 years of research with a number of different influenza A viruses belonging to the H<sub>2</sub>N<sub>2</sub>, H<sub>3</sub>N<sub>2</sub>, and H<sub>1</sub>N<sub>1</sub> subtypes.<sup>2,4</sup> Similar data are available on the therapeutic use of amantadine.<sup>2,5</sup> Thus, it is clear that there is no pressing need for further studies to prove the efficacy of this drug in influenza A infections. What we do need, however, are studies to explore dose responses in both prophylactic and therapeutic situations, studies of the pharmacokinetics of amantadine and rimantadine, prophylactic studies in the groups with the highest risks of complications and mortality, and studies of the therapeutic effect in patients with pulmonary complications of influenza infection.

Further work on the comparative efficacies of rimantadine and amantadine must be done. A major unresolved question is whether rimantadine should be used in this country. It is clear that this drug is somewhat more active (fourfold to eightfold) than amantadine in vitro, both in tissue cultures and in human tracheal-organ cultures.<sup>6,7</sup> However, in most clinical trials with equal doses, amantadine has been shown to be marginally, although not significantly, superior. Amantadine is associated with a substantially higher frequency of side effects on the central nervous system when the two drugs are used in the same doses.<sup>8</sup> Fortunately, these symptoms are mild and disappear when the treatment is discontinued. There are very limited data comparing the pharmacokinetics of amantadine and rimantadine, and there is little evidence that current dose regimens are equivalent for the two drugs. The fact that similar clinical effects are observed with equal doses despite the lower in vitro activity of amantadine suggests that amantadine is either better absorbed or less well excreted, so that tissue levels of amantadine at the site of infection are higher than those of rimantadine. Thus, I believe that the conclusion of Dolin et al. that rimantadine is superior to amantadine is premature, and that the question of which drug is superior can be answered only after further clinical trials based on pharmacokinetic data are completed.

Despite the limitations mentioned above, there are substantial data on amantadine, and the drug has been approved. How should we use it? Everyone agrees that influenza vaccine is the mainstay of prevention of influenza. However, the efficacy of the vaccine is incomplete. In addition, only a limited number of persons at high risk — that is, those over 65 years of age and those with underlying disease — receive vaccine annually. Thus, in an epidemic of influenza, amantadine would be indicated for many persons. In addition, patients with renal disease accompanied by azotemia, those with cancer, and those receiving immunosuppressive therapy might not respond to vac-

cine and might be better protected by amantadine. In such cases, the doses of amantadine should be modified to account for altered renal function.<sup>9</sup> Since the protective effect of amantadine is additive to that of vaccination, persons who required maximal protection might be given both vaccine and amantadine. Amantadine may also be indicated for patients and employees in hospitals during an outbreak of nosocomial influenza.<sup>10</sup> Perhaps the drug should also be used more widely for the treatment of influenza.<sup>11</sup> Certainly, it is effective for the relief of symptoms and allows a more rapid return to school or employment. A specific diagnosis of influenza is not required for every patient before administering amantadine; epidemiologic diagnosis will suffice. Thus, in the winter months when the Centers for Disease Control or state or local health departments report influenza A activity in or near the region, a patient with acute onset of fever, chills, headache, and cough can be presumed to have influenza and treated accordingly.

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## SOUNDING BOARD

### PSYCHIATRIC CONSULTATION MASKING MORAL DILEMMAS IN MEDICINE

PSYCHIATRIC consultations are a legitimate and necessary clinical activity in any general medical hospital or clinic. At times, however, psychiatrists are consulted when their fellow physicians face moral dilemmas related to patient care. In this article, we attempt to

show that such moral issues may be masked as requests for help for a "depressed patient" or a "management problem."

The practice of medicine abounds with value-laden decisions. Although this has generally been recognized, it has recently received increased attention in the press and the medical literature. Discussion has focused on the care of the dying, transplantation, abortion, genetic manipulation, behavior control, and other such visible morally debatable and troublesome problems. In addition, as Cassell<sup>1</sup> and Goldworth<sup>2</sup> have pointed out, even the day-to-day practice of medicine can be viewed as a predominantly moral activity supported by technical procedures. Most authors agree with Kass's opinion that medicine is more than merely "a technical service that is delivered, like auto repair or plumbing."<sup>3</sup> It is an enterprise encompassing human agents and wills; at times it touches the most dramatic and difficult situations and choices that people ever face. Medical schools, residency training programs, and continuing-education programs have increasingly recognized the importance of the teaching and discussion of ethics,<sup>4-8</sup> although there is controversy about how to approach the topic.<sup>4,9-11</sup>

Ethical dilemmas in medical care arise when a particular course of action involves a conflict between competing moral values. The patient and the physician may disagree about what is right, proper, or good, or the physician alone may face a choice between two or more difficult options. The opinions or demands of other interests — the patient's family, the law, and society at large — may further complicate the situation.

Sometimes nonpsychiatric physicians turn to their psychiatric colleagues for help and guidance with morally troublesome cases. In these contexts, psychiatrists are not necessarily seen as moral arbiters; rather, we believe they are regarded as experts in mediating and resolving conflict, both intrapsychic and interpersonal. The primary physician is often acutely aware of the patient's psychic distress and of the interpersonal tensions that accompany the medical-moral problems. The psychiatrist is expected to fill a mediating role, often with a mandate to resolve the situation in a particular direction, to persuade the patient or family to act in a certain way. In the process, unfortunately, a moral consideration of the proposed or expected actions and a consideration of the ethical dimensions of the case are often overlooked or ignored by both the primary physician and the psychiatrist.

We have examined three instances of such a series of events as they occurred in a large general hospital. We have no incidence or prevalence figures to quote, but we believe that the problem is regrettably common. In the following discussion, we will highlight the ethical aspects of each case, without undertaking a complete analysis. We will focus on the limitations of the psychiatrist's role and on the constructive part that he or she might properly play in the management of difficult cases that present moral dilemmas.