PSYCHOACTIVE PROPERTIES OF AMANTADINE

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Amantadine (Symmetrel®) is a unique medication that is used for both the prevention of viral influenza and for the treatment of Parkinson's disease. This agent is also useful in the treatment of the extrapyramidal side effects caused by neuroleptic drugs. The clinical and pharmacological literature contains several references to the side effects of amantadine. There are a number of reports that indicate that this substance has significant psychoactive properties, including both the inducement of hallucinations and mood-altering effects (Flaherty & Bellur 1981; Hausner 1980; Borison 1979; Safta et al. 1976; Postma & Van Tilburg 1975; Harper & Knoth 1973).

PHARMACOLOGY

Amantadine is a synthetic compound of the amine group and its chemical structure is unique among therapeutic agents. It is produced as a crystalline powder that is freely soluble in water and soluble in alcohol and in chloroform. It is completely absorbed in the gastrointestinal tract and is excreted unchanged in the urine. The halflife of amantadine is 20 hours.

This drug was first noted as an antiviral agent in 1964 by Davies, Grunert and Haff. It is effective in preventing Asian (A_2) influenza and appears to be active by inhibiting viral penetration of host cells, but the mode of action is not completely understood. The prophylactic antiviral activity of amantadine is limited to a single virus.

Amantadine is also useful in treating Parkinson's disease (Goodman & Gilman 1975). It is effective in many forms of Parkinsonism, including extrapyramidal symptoms caused by antipsychotic drugs, such as haloperidol and fluphenazine. It appears to be effective in this syndrome by causing the release of dopamine from peripheral neuronal storage sites (Grelak et al. 1970). Amantadine not only appears to facilitate dopamine release directly, but also seems to increase the release of dopamine caused by incoming nerve impulses (Farnebo et al. 1971) in the central nervous system (CNS).

The predominant effect of amantadine on the CNS is cerebral stimulation mediated by increased dopamine release in the striatum. This agent is effective in reducing the rigidity and muscle tightness caused by neuroleptic drugs. Amantadine has a synergistic effect with L-dopa when used together in the treatment of Parkinsonism. The ususal dose of this medication is 100 to 200 mg per day. The side effects of amantadine use include insomnia, lethargy and edema (Goodman & Gilman 1975). Amantadine lowers seizure threshold and can cause convulsions in rare cases (Safta et al. 1976). The occurrence of hallucinations seems to be more common when amantadine is used in conjunction with anticholinergic agents, such as benztropine.

The treatment of acute amantadine intoxication is largely supportive. The use of this agent should be discontinued if any side effects are noted. In many cases the cessation of drug intake will be sufficient to reduce toxic symptoms within a few hours. Medical treatment of the physical side effects should be symptomatic. Psychological symptoms are best managed by quiet reassurance. Neuroleptic medications should be avoided due to their inherent anticholinergic effects and tendency to exacerbate Parkinsonism symptoms.

PSYCHOACTIVE PROPERTIES

Amantadine is known to produce changes in both mood and perception. It has been reported to cause visual and haptic hallucinations as well as confusion and delusional thinking (Borison 1979; Postma & Van Tilburg 1975; Harper & Knoth 1973). This agent has a marked effect on mood, with both dysphoria and euphoria noted in subjects using it. Borison has described an incidence of clearly delusional thinking and vivid hallucinations following the use of amantadine in an elderly woman with renal failure. Harper and Knoth reported several cases of visual hallucinations associated with amantadine use. Remarkably, among these reports there seems to be a tendency for Lilliputian hallucinations, where small colorful people are visualized. The occurrence of vivid, colorful hallucinations has also been noted in 13 other cases by Postma and Van Tilburg. However, the Lilliputian quality of the hallucinations was not always consistent among this group.

In a population of 295 normal individuals taking amantadine for influenza prophylaxis, approximately 14 percent reported psychological changes on modest doses of 100 mg per day (Flaherty & Bellur 1981). Nearly half of the individuals in this group reported elevation of mood.

The incidence of psychoactive response to amantadine ranges from 14 to 38 percent (Flaherty & Bellur 1981; Montanari et al. 1976). The intensity of the reaction appears to be dose related, with predominantly mood-altering effects at doses of 100 mg per day and the occurrence of hallucinations noted at doses larger than 200 mg per day. The severity of response seems to

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increase with age and the frequency of hallucinations seems to increase if anticholinergic drugs are taken concomitantly. Distortion of space perception and body image is relatively rare.

CASE REPORTS

This author has seen several patients who used amantadine for the treatment of Parkinsonism. The response of most individuals has been therapeutic and without complications. The cases presented here reflect Parkinsonism of two varieties: One represents familial Parkinsonism and the other represents extrapyramidal symptoms caused by neuroleptic medications. Both patients experienced psychological changes following the use of amantadine.

Case 1

Patient A was a 69-year-old married, White male with a history of familial Parkinson's disease. He had no remarkable psychiatric history. Therapy was begun with amantadine after several years of gradual decompensation in the motor function. This individual took 200 mg of amantadine per day for approximately one week before any psychological changes occurred. After one week the patient developed a pronounced dysphoria. Within hours, this dysphoria was accompanied by morbid delusions. The amantadine was discontinued and both delusions and dysphoria disappeared within 24 hours. Therapy with L-dopa controlled the symptoms of muscle rigidity and the psychological manifestations did not recur.

Case 2

Patient B was a 48-year-old married, White male with a history of chronic paranoid schizophrenia. He had been treated with fluphenazine and experienced a marked reduction in his paranoia. As a side effect of this drug he developed a muscular rigidity of the Parkinsonian type. This condition was treated with amantadine (200 mg per day). After three days on this regimen, the patient presented at the emergency room complaining that he felt insects crawling on and beneath his skin. He reported that he could not see the insects, but that he knew they were there because he could feel them. His amantadine was discontinued and the haptic hallucinations disappeared in 24 hours. Subsequent treatment of muscle rigidity responded to small doses of benztropine without recurrence of hallucinations or disordered thought.

DISCUSSION

The precise psychopharmacological mechanism for the psychoactive properties of amantadine is unclear. It is possible that the euphoria, mood lability and hallucinations may be due to the dopaminergic properties of this drug. The increased release of brain dopamine in subjects treated with this substance is documented (Farnebo et al. 1971; Von Voightlander & Moore 1971; Grelak et al. 1970). The fact that amantadine eases the symptoms of Parkinsonism, a disease of suboptimal dopamine activity, further suggests that it causes increased dopamine availability in humans. The symptoms of amantadine toxicity are similar to the intoxication of known adrenergic and catecholamine agonists, such as amphetamine or cocaine.

The mental status changes noted in the aforementioned cases seem most likely to be due to amantadine use. Neither of these individuals had a history of psychological disturbances like those noted under the influence of this drug and both experienced clearing of symptoms following its discontinuance. Isolated psychological changes have also been reported in a large number of individuals who were free of Parkinson's disease (Flaherty & Bellur 1981). This makes it unlikely that this medical condition interacts with amantadine in such a way as to cause mental status alteration.

Amantidine appears to have psychoactive properties that are characterized by mood changes and hallucinosis. This effect seems to be independent of the condition of the subject taking this substance. The psychoactive properties of this substance appear to be due to its dopaminergic effect. However, further research must be done to clarify this point.

REFERENCES

Borison, R. 1979. Amantadine-induced psychosis in a geriatric patient with renal disease. *American Journal of Psychiatry* Vol. 131(1): 111-112.

Davies, W.; Grunert, R. & Haff, R. 1964. Antiviral activity of 1-adamantanamine (amantadine). *Science* Vol. 144: 862-863.

Farnebo, L.; Fuxe, K.; Goldstein, M.; Hamberger, B. & Ungerstedt, V. 1971. Dopamine and noripramine releasing action of amantadine in the central and peripheral nervous system: A possible mode of action in Parkinson's disease. *European Journal of Pharmacology* Vol. 16: 27-38.

Flaherty, J. & Bellur, S. 1981. Mental side effects of amantadine therapy: Its spectrum and characteristics in a normal population. *Journal of Clinical Psychiatry* Vol. 42(9): 344-345.

Goodman, L. & Gilman, A. (Eds.). 1975. *The Pharmacological Basis of Therapeutics*. 5th ed. New York: Macmillan.

Grelak, R.; Clark, R.; Stump, J. & Vemier, V. 1970. Amantadine-dopamine interaction: Possible mode of action in Parkinsonism. *Science* Vol. 169: 203-204.

Harper, R. & Knoth, B. 1973. Coloured Lilliputian hallucinations with amantadine. *Medical Journal of Australia*. Vol. 1: 444-445.

Hausner, R. 1980. Amantadine-associated recurrence of psychosis. *American Journal of Psychiatry* Vol. 137(2): 240-241.

Montanari, C.; Vellacorsi, G.; Bavazzano, A.; D'Ayalavalva, G. & Sanesi, P. 1976. Clinical trial with amantadine and pemoline in elderly patients. *Age and Aging* Vol. 5: 6-10.

Postma, J. & Van Tilburg, W. 1975. Visual hallucinations and delirium during treatment with amantadine. *Journal of the American Geriatrics Society* Vol. 23(6): 212-215.

Safta, L.; Cuparencu, B.; Danau, M. & Comes, L. 1976. Some behavioral changes induced by amantadine. *Acta Biologica et Medica Germanica* Vol. 35(2): 229-233.

Von Voightlander, P. & Moore, K. 1971. Dopamine release from the brain in vivo by amantadine. *Science* Vol. 174: 408-410.