Lysosomotropic Agents in AIDS Treatment

TO THE EDITOR: There is currently considerable interest in the etiology, diagnosis and treatment of the acquired immunodeficiency syndrome (AIDS). While the incidence of AIDS continues to increase exponentially, there is no currently proved treatment or prophylactic agent.[1] Substantial evidence has accumulated to implicate a novel retrovirus—human immunodeficiency virus (HIV)—in the pathogenesis of AIDS. This virus appears to have a tropism for helper T lymphocytes expressing the T4 (CD4) antigen, and the cytopathic effect of the virus on helper T lymphocytes accounts for the major clinical manifestations of AIDS.[1] A recent report[2] suggested that the T4 antigen is in fact the cell surface receptor for the AIDS virus and that the virus subsequently enters the cell via endocytosis. The process of receptor-mediated endocytosis has been well characterized for a number of proteins, hormones, toxins and viruses, including retroviruses.[3-6] Acidification of the endosome is a frequent, if not universal, step in the endocytotic process.[3,4] It has been shown for a number of viruses (including retroviruses and human pathogens such as influenza A) that acidification triggers fusion of the viral membrane with the endosomal membrane, probably by a pH-induced conformational change in the viral membrane glycoprotein.[7] So-called lysosomotropic agents, weak bases which enter endosomes, have been shown to inhibit endosome acidification and thus block viral entry and infection[3,4,8-10] Two of these agents, chloroquine and amantadine, are widely used clinical drugs.

In the case of amantadine, although influenza A entry is blocked at clinically relevant concentrations, retrovirus entry is only inhibited at concentrations approximately two orders of magnitude higher. For chloroquine, clinically relevant plasma concentrations (100 to 300 ng per ml) are only three to ten times below the concentrations needed to cause 75% inhibition of viral entry in vitro.[8,11] Severe toxicity at higher doses precludes the use of substantially higher doses of chloroquine.[12] However, chloroquine is highly concentrated in certain tissues in vivo, notably in the cerebrospinal fluid (10 to 30 times plasma level), the reticuloendothelial system (6,000 times) and leukocytes (100 to 200 times).[13] This suggests that chloroquine could be effective in vivo, even though usual clinical plasma concentrations are somewhat below those needed for in vitro effects.

I suggest that amantadine, chloroquine and other antimalarials related to chloroquine[13-15] may be promising as rational agents for the prevention and early treatment of AIDS. Although their antiviral action of blocking pH-dependent viral entry into lymphocytes would be predicted to be a virustatic rather than virucidal action, they could still be of great potential value in preventing, slowing or arresting the relentless progress of the illness. Furthermore, the high concentrations attainable in cerebrospinal fluid suggest these agents might be especially valuable in treating central nervous system complications of AIDS where other drugs were excluded by the blood-brain barrier. Although evaluation of the anti-HIV effect of these drugs in vitro is a logical first step toward their clinical use, higher drug concentrations may be needed in vitro than in plasma due to the tissue concentrating effects described above. Since the effects of lysosomotropic agents can be additive in raising endosomal pH, the combination of these two drugs should be considered. Chloroquine has also been in wide use as a prophylactic antimalarial agent. Its relative lack of side effects, even during long-term administration, makes it a potentially attractive prophylactic agent for individuals known to be at high risk for AIDS. The low toxicity of these agents render them suitable as potential adjunctive treatments as well, in some form of combination chemotherapy.

I recommend that preclinical and clinical trials be carried out in research centers capable of measuring plasma drug levels, antibody titers and lymphocyte function in addition to clinical status so that a fair evaluation of the potential of these agents can be made.

BRUCE L. KAGAN, MD, PhD
Departments of Psychiatry and Physiology
UCLA School of Medicine and
West Los Angeles Veterans Administration Medical Center
Los Angeles, CA 90024

REFERENCES

1. Gluckman JC, Klatzman D, Montagnier L: Lymphadenopathy-associated-virus infection and acquired immunodeficiency syndrome. Annu Rev Immunol 1986; 4:97-117

2. Research news. Science 1986; 233:160

3. Goldstein JL, Brown MS, Anderson RGW, et al: Receptor mediated endocytosis: Concepts emerging from the LDL receptor system. Annu Rev Cell Biol 1985; 1:1-39

4. Helenius A, Mellman I, Wall D, et al: Endosomes. Trends Biochem Sci 1983; 8:245-250

5. Helenius A, Marsh M, White J: The entry of viruses into animal cells. Trends Biochem Sci 1980; 5:104-106

6. Kagan BL, Finkelstein A, Colombini M: Diphtheria toxin fragment forms large pores in phospholipid layer membranes. Proc Natl Acad Sci USA 1981; 78:4950-4954

7. White J, Kielian M, Helenius A: Membrane fusion proteins of enveloped animal viruses. Q Rev Biophys 1983; 16:151-195

8. Pazmiño NH, Yuhas JM, Tennant RW: Inhibition of murine RNA tumor virus replication and oncogenesis by chloroquine. Int J Cancer 1974; 14:379-385

9. Wallbank AM, Matter RE, Klinikowski NG: 1-Adamantanamine hydrochloride: Inhibition of Rous and Esh Sarcoma viruses in cell culture. Science 1966; 152:1760-1761

10. Ohkuma S, Poole B: Fluorescence probe measurement of the intralysosomal pH in living cells and the perturbation of pH by various agents. Proc Natl Acad Sci USA 1978; 75:3327-3331

11. Alving AS, Eichelberger L, Craige B Jr, et al: Studies on the chronic toxicity of chloroquine. J Clin Invest 1947; 27:60-65

12. Good MI, Shader RI: Lethality and behavioral side effects of chloroquine. J Clin Psychopharmacol 1982; 2:40-47

13. Dubois EL: Antimalarials in the management of discoid and systemic lupus erythematosus. Semin Arthritis Rheum 1978; 8:33-51

14. Isaacson D, Elgart M, Turner ML: Anti-malarials in dermatology. Int J Dermatol 1982; 21:379-395

15. Goodman LS, Gilman A (Eds): Goodman and Gilman's The Pharmacologic Basis of Therapeutics, 7th Ed. New York, MacMillan, 1985, pp 1029-1048, 1232

AIDS Vaccine Trial Volunteers Can Be Found

TO THE EDITOR: New California state legislation supportive of the development of an acquired immunodeficiency syndrome (AIDS) vaccine presumes that a sample of willing volunteers will submit to a vaccine trial. In terms of screening, subjects must be seronegative for the human immunodeficiency virus (HIV)—previously designated HTLV-III—at baseline, in a population where seroprevalence is increasing, and must be engaged in activity between baseline and follow-up likely to lead to viral infection. Injecting individuals with a vaccine, then expecting them to be engaged in behavior capable of exposure to HIV, poses ethical dilemmas. Testing persons for AIDS antibody before and after such a trial would require special assurances of confidentiality and may have psychological impact.[1] The question becomes, Who would volunteer?

Every six months since November 1983, the University of California, San Francisco, AIDS Behavioral Research