

THE MILWAUKEE PROTOCOL SHOULD NOT BE USED FOR THE TREATMENT OF RABIES

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Until the 1970s human rabies was thought to be a uniformly fatal disease. Since that time several patients have recovered. Most survivors received rabies vaccine before the onset of symptomatic rabies. In 2003 recommendations on management of rabies suggested consideration of antiviral agents, immunotherapies, ketamine, and use of a combination of therapies. A 15-year-old patient with rabies, who had neutralizing rabies antibodies on presentation, survived rabies in 2004. She received therapeutic coma (midazolam and phenobarbital given to maintain a burst-suppression pattern on the electroencephalogram), ketamine, ribavirin, and amantadine (dubbed the "Milwaukee Protocol"). There have been at least 26 subsequent reports of failures of the major components of this therapy, including a Canadian case with complete loss of neurons in the cerebral cortex at autopsy, and no new successes. There is no scientific rationale for the use of therapeutic coma in human rabies. There are serious potential adverse effects. Further studies in primary neurons and a mouse model of rabies have cast serious doubt about the efficacy of ketamine therapy for rabies. New approaches for treatment of human rabies need to be developed rather than repeating ineffective therapies. For example, brain-selective hypothermia might reduce neuronal injury while allowing the development of a systemic immune response and minimizing systemic adverse effects. Finding an effective neuroprotective drug is unlikely with a "trial and error" approach. A better understanding of the mechanisms involved in producing a fatal outcome in rabies may help in the development of novel approaches to therapy of this dreaded disease.