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Case Report

Failure of therapeutic coma and ketamine for therapy of human rabies

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The recent success in treating a human rabies patient in Milwaukee prompted the use of a similar therapeutic approach in a 33-year-old male Thai patient who was admitted in the early stages of furious rabies. He received therapeutic coma with intravenous diazepam and sodium thiopental to maintain an electroencephalographic burst suppression pattern, which was maintained for a period of 46 h, as well as intravenous ketamine (48 mg/kg/day) as a continuous infusion and ribavirin (48 to 128 mg/kg/day) via a nasogastric tube. He never developed rabies virus antibodies and he died on his 8th hospital day. At least three other patients have been treated unsuccessfully with a similar therapeutic approach. Because of the lack of a clear scientific rationale, high associated costs, and potential complications of therapeutic coma, the authors recommend caution in taking this approach for the therapy of rabies outside the setting of a clinical trial. More experimental work is also needed in cell culture systems and in animal models of rabies in order to develop effective therapy for human rabies. *Journal of NeuroVirology* (2006) **12,** 407–409.

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Introduction

In 2004 a young patient survived rabies in Milwaukee (Willoughby *et al,* 2005). It is unknown whether the favorable outcome was related to infection by an attenuated bat rabies virus variant or if her therapy played an important role (Jackson, 2005, 2006; Lafon, 2005). She had rabies virus antibodies at the time of her presentation. We report failure of therapeutic coma and ketamine in the management of a rabies patient in Thailand.

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Case report

A 33-year-old-male patient was admitted to Chulalongkorn University Hospital on March 30, 2006, with a 4-day history of fever, burning sensation of the left hand and arm, and phobic spasms. He was bitten by a dog 2 months earlier, and he had not received post-exposure rabies prophylaxis. Rabies virus RNA was demonstrated in hair follicles on hospital day 1 using nucleic acid sequence–based amplification (NASBA) (Wacharapluesadee and Hemachudha, 2001). He was not given rabies vaccine or human rabies immune globulin on diagnosis of rabies because of a theoretical concern that these therapies might accelerate the disease (Hemachudha *et al,* 2003). He was fully conscious and coherent at the start of an aggressive approach based on the therapy given to the Milwaukee rabies patient (Willoughby *et al,* 2005). He received intravenous ketamine (48 mg/kg/day) and diazepam with a beta activity response on continuous

electroencephalographic monitoring (EEG). Supplemental sodium thiopental was given with dosage adjustments based on his hemodynamic status in order to achieve a burst suppression pattern on his EEG, which was fully achieved within 14 h. Ribavirin (loading dose 66 mg/kg, then 128 mg/kg/day for 2 days, then 48 mg/kg/day for 2 days) was administered via a nasogastric tube at twice the dosage of the intravenous drug given in Milwaukee, because the intravenous formulation was not available. The burst suppression pattern was maintained for 46 h until he developed ventricular tachycardia and cardiac arrest, which responded promptly to resuscitation. His EEG remained in an encephalopathic pattern at 1 to 2 Hz with an amplitude of 150 to 300 μV, and continuous burst-suppression could no longer be maintained even at the highest tolerable dose of barbiturate until the time of his death on hospital day 8. He also had evidence of myocarditis with a left ventricular ejection fraction of 20% and elevated cardiac-specific troponin-T and creatine kinase-MB. His systemic vascular resistance was diminished and his blood pressure was maintained with dobutamine and small doses of norepinephrine, and his urinary output was maintained. Neurogenic pulmonary edema was observed on day 2 and became severe and required positive end-expiratory pressure support of 8 to 10 cm H_2O on day 7. His pulmonary wedge pressure remained normal until day 7, when he developed massive pulmonary edema with cardiac and renal failure. He died on the following day. Rabies virus RNA remained detectable in hair follicles (days 3 and 4) and in saliva from days 2 to 8. He had no detectable rabies virus antibody in sera or cerebrospinal fluid (CSF) by virus neutralization assay during his entire clinical course. Rabies virus was isolated from his brain and spinal cord tissues at necropsy.

Discussion

Six patients have survived rabies, although only the Milwaukee patient did not receive rabies vaccine prior to the onset of her illness (Jackson *et al,* 2003; Willoughby *et al,* 2005). The patient in the present report received therapy with ketamine (48 mg/kg/day) and ribavirin and coma induced with intravenous diazepam with supplemental sodium thiopental in order to produce a burst suppression pattern on the electroencephalogram until this could no longer be achieved. Therapeutic coma is thought to be useful for the management of status epilepticus, although maintenance of a burst suppression pattern on EEG may not be required to control or prevent recurrent seizures (Krishnamurthy and Drislane, 1999; Bassin *et al,* 2002). However, therapeutic coma does not have established neuroprotective value for other neurological conditions. There is no clear scientific rationale for this approach in rabies or any other infectious disease of the nervous system. Publication of the Milwaukee case report in the *New England Journal of Medicine* should not be considered validation of the therapeutic approach, and reservations about this therapy were stated in the accompanying editorial (Jackson, 2005). There is no published experimental evidence supporting a role of excitotoxicity in rabies virus infection (Jackson, 2006), and there is very recent work that argues against this mechanism (Weli *et al,* 2006). Despite abundant evidence of excitotoxicity in animal models of stroke, therapy with a variety of neuroprotective agents with different mechanisms of action has proved disappointing in many human clinical trials (Cheng *et al,* 2004), although a very recent study showed a beneficial effect of a new drug (Lees *et al,* 2006).

This patient failed therapy that included ketamine, ribavirin, and therapeutic coma with diazepam and sodium thiopental. He did not develop rabies virus antibodies during his clinical course, which are necessary but not sufficient for recovery. Neutralizing antibodies may be present earlier in human rabies cases due to bat rabies virus variants than to canine virus like the present case (Hemachudha *et al,* 2002). The adaptive immune response is thought to be an important host mechanism for viral clearance and recovery from rabies (Lafon, 2002; Hemachudha and Wilde, 2005). It is unclear if administration of rabies vaccine would have induced an antibody response prior to death or if this would have had a beneficial or detrimental effect on the disease. We are aware of at least three other patients who have had fatal rabies despite a therapeutic approach that was similar to that taken with the survivor in Milwaukee, including one each in Germany, India, and USA (*Houston Chronicle*, 2006). Because of the lack of a clear scientific rationale, high associated costs, and potential complications of the therapy, we would recommend caution in using therapeutic coma for the therapy of rabies outside the setting of a clinical trial with the usual safeguards. Subjecting numerous patients worldwide to this therapy may actually reduce the chance of a successful outcome in rabies as well as consuming resources that could be much better used elsewhere, especially in developing countries that have a large burden of human rabies. Clearly, more experimental work needs to be done in cell culture systems and in animal models of rabies before an effective therapeutic approach to human patients with rabies can be developed.

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