

Postexposure prophylaxis for prevention of rabies in dogs

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Objective—To evaluate postexposure prophylaxis (PEP) in dogs experimentally infected with rabies.

Animals—29 Beagles.

Procedure—Dogs were sedated and inoculated in the right masseter muscle with a salivary gland homogenate from a naturally infected rabid dog (day 0). Six hours later, 5 dogs were treated by administration of 2 murine anti-rabies glycoprotein monoclonal antibodies (mAb) and commercial vaccine; 5 received mAb alone; 5 received purified, heat-treated, equine rabies immune globulin (PHT-ERIG) and vaccine; 5 received PHT-ERIG alone; 4 received vaccine alone; and 5 control dogs were not treated. The mAb or PHT-ERIG was administered at the site of rabies virus inoculation. Additional vaccine doses for groups mAb plus vaccine, PHT-ERIG plus vaccine, and vaccine alone were administered IM in the right hind limb on days 3, 7, 14, and 35.

Results—All control dogs and dogs that received only vaccine developed rabies. In the PHT-ERIG and vaccine group, 2 of 5 dogs were protected, whereas none were protected with PHT-ERIG alone. Use of mAb alone resulted in protection in 4 of 5 dogs. Administration of mAb in combination with vaccine provided protection in all 5 dogs.

Conclusions and Clinical Relevance—Current national guidelines recommend euthanasia or a 6-month quarantine for unvaccinated animals exposed to rabies. Findings from this study document that vaccine alone following severe exposure was unable to provide protection from rabies. However, vaccine combined with mAb resulted in protection in all treated dogs, revealing the potential use of mAb in PEP against rabies in naïve dogs. (*Am J Vet Res* 2002;63:1096–1100)

Domestic dogs remain the most important reservoir for rabies throughout the world. Strict animal control and mandatory vaccination regulations in the United States have largely eliminated rabies in dogs, except for occasional foci near the Texas-Mexico border.¹ Nonetheless, current vaccination coverage of dogs is incomplete, and management of unvaccinated dogs exposed to wildlife or other sources of rabies is problematic.² Currently, national guidelines concerning unvaccinated dogs that are exposed to rabies recommend that these dogs be euthanatized or confined in strict quarantine for 6 months.³ During quarantine, exposed dogs may succumb to rabies or, in many cases,

remain clinically normal (ie, do not become rabid), which is most likely attributable to the fact that most quarantined dogs are suspected of having been exposed rather than actually having been observed to have been bitten by a known rabid animal.

In the United States, there have not been any documented failures of postexposure prophylaxis (PEP) in humans since cell culture vaccines and human rabies immune globulin (HRIG) became available for use.⁴ Currently, vaccination alone (ie, without concurrent administration of rabies immune globulin) cannot be relied on to prevent rabies in humans, particularly for severe exposures.⁵⁻¹⁴ However, HRIG is prohibitively expensive, and the worldwide supply of HRIG is chronically restricted. As an alternative, equine rabies immune globulin (ERIG) has been widely used,¹⁵ but in many cases, even this biologic may be prohibitively expensive. Moreover, manufacturers of HRIG and ERIG are adding additional steps to ensure the safety of their products, such as heat treatment to reduce the theoretic risk of adventitious agents in sera.¹⁶ The impact of new manufacturing processes on the in vivo prophylactic efficacy of these products is unknown, because their potency evaluation is largely conducted through in vitro tests. Evaluation of heat-treated products suggests a difference in pharmacodynamics, raising concerns about efficacy.¹⁷⁻¹⁹ Because of advancements in molecular biology and production techniques, monoclonal antibodies (mAb) could theoretically provide an efficacious and economic alternative to polyclonal rabies immune globulin.²⁰⁻²³ Such advances could alleviate current shortages and facilitate wider access to affordable, maximally efficacious rabies PEP in humans, particularly in areas where it is critically needed.

In addition to the obvious potential clinical application of rabies PEP in exposed dogs and other domestic animals, the development of a PEP model in dogs allows for a proof-of-principle determination, which may directly benefit humans in need of rabies PEP. The study reported here evaluated the efficacy of rabies PEP that involved the use of a polyclonal purified, heat-treated, equine rabies immune globulin (PHT-ERIG) in comparison to 2 murine anti-rabies glycoprotein mAb. Passive immunotherapy (PHT-ERIG or the 2 mAb) was administered alone and in conjunction with a series of 5 doses of vaccine, compared with administration of vaccine alone and with untreated control dogs.

Materials and Methods

Animals—The study population consisted of 29 purpose-bred adult Beagles (12 females and 17 males) obtained from a commercial breeder. Dogs ranged from 4.9 to 9.8 kg and were randomly assigned to treatment groups. The dogs

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were housed separately and identified by a unique tattoo. Food and water were offered ad libitum. All animal care and experimental procedures were performed in compliance with guidelines established by the Centers for Disease Control Institutional Animal Care and Use Committee.

Experimental protocol—Material from the salivary glands of a naturally infected rabid dog from Texas was homogenized to a 10% suspension (wt:vol), using diluent containing 2% horse serum in sterile distilled water, and the suspension was clarified by use of low-speed centrifugation (500 × g for 10 minutes) to prepare the challenge-virus suspension. The challenge-virus suspension had an original concentration of 10^{7.0} median mouse intracerebral lethal dose/ml,

and it was stored at -70 C. The rabies challenge virus (reference 3374 R) was characteristic of the virus variant in circulation among dogs and coyotes (*Canis latrans*) near the Texas-Mexico border.²⁴

On the day of rabies virus inoculation, the challenge-virus suspension was thawed under cold running water and diluted 1:1,000 in 2% horse serum. All dogs were sedated with an IM injection of a product^a that contained a combination of tiletamine hydrochloride and zolazepam hydrochloride. Dogs were administered the product at a rate of 0.5 to 1.0 mg/kg. Sedated dogs then were inoculated in the right masseter muscle with 0.5 ml of the challenge-virus suspension (day 0).

Six hours after inoculation with the challenge-virus sus-

Table 1—Rabies virus neutralizing antibodies* and survival among dogs inoculated with rabies virus† and administered postexposure prophylaxis beginning 6 hours after inoculation

Group‡	Dog	Days after inoculation of rabies virus											Survival
		0	3	7	9	10	11	12	13	14	22	35	
mAb and vaccine	1	< 5	50	45	—	—	—	—	—	≥ 56	—	≥ 1,200	S
	2	< 5	50	25	—	—	—	—	—	≥ 56	—	320	S
	3	< 5	13	11	—	—	—	—	—	≥ 56	—	280	S
	4	< 5	40	9	—	—	—	—	—	≥ 56	—	≥ 1,100	S
	5	< 5	25	10	—	—	—	—	—	> 56	—	> 1,100	S
	GMT	< 5	32	16	—	—	—	—	—	> 56	—	> 630	
mAb alone	1	< 5	25	16	—	—	—	—	—	13	—	10	S
	2	< 5	25	14	—	—	—	—	—	< 5	—	< 5	S
	3	< 5	40	10	—	—	—	—	—	≥ 56	45	—	D
	4	< 5	50	9	—	—	—	—	—	< 5	—	< 5	S
	5	< 5	17	8	—	—	—	—	—	< 5	—	< 5	S
	GMT	—	29	11	—	—	—	—	—	4	—	4	
PHT-ERIG plus vaccine	1	< 5	< 5	≥ 56	—	—	—	—	—	≥ 56	—	≥ 1,400	S
	2	< 5	19	50	—	—	—	—	—	≥ 56	—	480	S
	3	< 5	17	54	—	—	—	—	—	≥ 56	—	—	D
	4	< 5	< 5	9	—	—	—	—	—	≥ 56	—	—	D
	5	< 5	< 5	54	—	—	—	> 56	—	—	—	—	D
	GMT	—	—	3	37	—	—	—	—	—	≥ 56	—	> 812
PHT-ERIG alone	1	< 5	< 5	6	—	—	—	—	—	50	—	—	D
	2	< 5	< 5	< 5	—	—	—	—	—	50	—	—	D
	3	< 5	< 5	< 5	—	—	—	—	—	≥ 56	—	—	D
	4	< 5	< 5	< 5	—	—	—	—	—	≥ 56	—	—	D
	5	< 5	< 5	< 5	—	—	—	> 56	—	—	—	—	D
	GMT	—	—	1	—	—	—	—	—	≥ 56	50	—	—
Vaccine alone	1	< 5	11	≥ 56	≥ 56	—	—	—	—	—	—	—	D
	2	< 5	6	54	—	≥ 56	—	—	—	—	—	—	D
	3	< 5	< 5	50	—	≥ 56	—	—	—	—	—	—	D
	4	< 5	13	54	> 56	—	—	—	—	—	—	—	D
	GMT	—	5	54	—	≥ 56	—	—	—	—	—	—	
Control dogs	1	< 5	< 5	< 5	—	—	—	—	13	—	—	—	D
	2	< 5	< 5	7	—	—	—	—	≥ 56	—	—	—	D
	3	< 5	< 5	< 5	—	—	—	—	≥ 56	—	—	—	D
	4	< 5	< 5	< 5	—	—	—	54	—	—	—	—	D
	5	< 5	< 5	< 5	—	—	—	42	—	—	—	—	D
GMT	—	—	1	—	—	—	39#	—	—	—	—		

*Rabies virus neutralizing antibodies reported as the reciprocal dilution with 50% reduction of fluorescent foci as determined by use of the rapid fluorescent focus inhibition test. †Rabies virus (Reference 3374 R; 10^{7.0} median mouse intracerebral lethal dose/ml) was from homogenates of the salivary glands of a naturally infected rabid dog. Challenge-virus suspension was diluted 1:1,000 in 2% horse serum and inoculated in the right masseter muscle (day 0). ‡Six hours after inoculation of rabies virus, dogs in the respective groups were treated by administration of 2 murine monoclonal antibodies (mAb; 20 IU/kg, IM) in the right masseter muscle plus 1 ml of a commercial rabies vaccine administered IM in the right hind limb, administration of mAb alone (20 IU/kg, IM), administration of purified, heat-treated, equine rabies immune globulin (PHT-ERIG; 20 IU/kg, IM) in the right masseter muscle plus 1 ml of a commercial rabies vaccine administered IM in the right hind limb, administration of PHT-ERIG alone (20 IU/kg, IM), administration of rabies vaccine alone, and untreated control dogs. Dogs administered rabies vaccine on day 0 received additional doses of vaccine on days 3, 7, 14, and 35. # = Represents GMT on the day of death of the control dogs. S = Dogs remained healthy, survived until day 90, and had negative results for rabies when tested by use of the direct fluorescent antibody test. D = Dogs had clinical signs of rabies, were euthanized, and had positive results for rabies by use of the direct fluorescent antibody test. GMT = Geometric mean titer. — = Not determined.

pension, 5 dogs were treated by administration of a combination of 2 murine anti-rabies glycoprotein mAb (designated 1112 and 523).²⁵ The dosage was 20 IU/kg. Volume of injection varied from 1.3 to 1.7 ml on the basis of body weight, and injections were administered in the right masseter muscle (ie, at the site of inoculation of the rabies challenge-virus suspension). In addition, 1 ml of a commercial rabies vaccine^b was injected IM in the right hind limb. Five dogs received mAb alone (20 IU/kg, IM) in the right masseter muscle; volume of injection varied from 1.2 to 2.0 ml on the basis of body weight. Five dogs received PHT-ERIG^c (20 IU/kg, IM).¹⁹ Volume of injection varied from 0.9 to 1.3 ml, and injections were administered in the right masseter muscle. In addition, 1 ml of a commercial rabies vaccine^c was injected IM in the right hind limb. Five dogs received PHT-ERIG alone (20 IU/kg, IM). Volume of injection varied from 0.9 to 1.5 ml, and injections were administered in the right masseter muscle. Four dogs received a commercial rabies vaccine^b alone, which was injected IM in the right hind limb. Five control dogs were not treated following inoculation with challenge-virus suspension. Dogs that were vaccinated on day 0 received additional 1-ml IM injections of rabies vaccine on days 3, 7, 14, and 35. Following rabies virus inoculation and during PEP, dogs were observed multiple times daily for clinical signs suggestive of rabies, such as lethargy, anorexia, agitation, paresis, paralysis, and cranial nerve deficits, or acute death.

A blood sample (2 to 4 ml) was collected from a cephalic vein of each dog on days 0, 3, 7, 14, and 35. Dogs were manually restrained or sedated for sample collection. When clinical signs of rabies were detected, a blood sample was collected from the sedated dog before the dog was euthanatized. The titer of rabies virus-neutralizing antibodies (VNA) was determined by use of the rapid fluorescent focus inhibition test.²⁶

On detection of clinical signs suggestive of rabies, affected dogs were examined, sedated as needed, and euthanatized by IV or intracardiac administration of a barbiturate solution.⁴ After dogs were euthanatized, necropsies were performed, and brain tissue was collected and examined for rabies antigen by use of the direct fluorescent antibody (FA) test. Dogs that did not have clinical signs of rabies after inoculation with rabies challenge-virus suspension were sedated and euthanatized on day 90. Necropsies were performed, and brain tissue was collected and examined by use of the direct FA test.

Statistical analysis—An ANOVA was used to determine significant overall differences. Post hoc analyses that adjusted for multiple comparisons were used to identify specific differences among groups on days 3 and 7. Statistical analyses were conducted by use of a commercially available software program.^c Values of $P < 0.05$ were considered significant.

Results

None of the dogs had detectable amounts of rabies VNA at the initiation of the study. All 5 control dogs developed signs of rabies and were euthanatized on days 11, 12, or 13 (Table 1). Similarly, all 4 dogs treated with vaccine alone developed signs of rabies and were euthanatized on days 9 or 10. Two of 5 dogs administered PHT-ERIG and vaccine were protected, whereas none of the 5 dogs were protected by administration of PHT-ERIG alone. Use of mAb alone provided protection for 4 of 5 dogs, whereas administration of mAb in combination with vaccination provided protection for all 5 dogs. Rabies was confirmed by use of

the direct FA test on brain material from all dogs that manifested clinical signs of rabies. Rabies virus antigen was not detected by use of the direct FA on the brain of dogs that survived until day 90.

With regard to serologic results, the overall F test indicated significant ($P < 0.001$) differences in geometric mean titer (GMT) among groups. After adjusting for multiple comparisons, the GMT on day 3 for the dogs receiving mAb plus vaccine or mAb alone was significantly higher than the GMT for dogs receiving PHT-ERIG plus vaccine, PHT-ERIG alone, and vaccine alone as well as the untreated control dogs. The GMT for dogs receiving PHT-ERIG plus vaccine or PHT-ERIG alone and the untreated control dogs did not differ significantly. The GMT for dogs receiving vaccine alone was not significantly different from that for dogs receiving PHT-ERIG plus vaccine, but it was significantly higher than the GMT for dogs receiving PHT-ERIG alone and the untreated control dogs. After adjusting for multiple comparisons, the GMT on day 7 for dogs receiving PHT-ERIG alone and the untreated control dogs was significantly lower than GMT for dogs receiving mAb plus vaccine, mAb alone, PHT-ERIG plus vaccine, or vaccine alone. The GMT for dogs receiving mAb plus vaccine, PHT-ERIG plus vaccine, or vaccine alone did not differ significantly. The GMT for dogs receiving mAb plus vaccine was not significantly different from the GMT for dogs receiving mAb alone, but the GMT for dogs receiving mAb alone was significantly lower than the GMT for dogs receiving PHT-ERIG plus vaccine or vaccine alone.

Discussion

Currently, there are no licensed products or nationally established protocols for rabies PEP of naive rabies-exposed animals, including domestic dogs. Nonetheless, the knowledge and biologics for potential PEP of such animals exist. In 2 studies,^{27,28} dogs were protected against rabies when treated in accordance with a protocol that emulated rabies PEP in humans with regard to biologics and schedule of administration. However, HRIG is in critically short supply on a global basis. The limited availability and subsequent high cost of HRIG limits its use for PEP of humans in developing countries.²⁹ Clearly, human fatalities result when modern PEP is needed and not available.¹⁴ In cases in which HRIG is not available or the price is too high, commercially purified ERIG is often substituted with apparent efficacy and minimal adverse effects.¹⁵ Although postcollection manufacturing steps have advanced, the fundamental production of polyclonal HRIG from immunized humans and ERIG from horses has not changed substantially during the past 50 years.^{29,30} A novel alternative to polyclonal rabies immune globulin may be a combination of mAb. In view of advances in hybridoma technology, production of appropriate mAb combinations would be expected to be economical and potentially of sufficient magnitude to meet a global need for rabies PEP in humans as well as for naive exposed domestic animals.

As part of recent trends to minimize theoretic risks of adventitious agents, a prolonged heat-treatment manufacturing step has, in some cases, been imple-

mented during the production of rabies immune globulins.^{4,16} Both HRIG preparations currently available in the United States are subjected to heat-treatment without apparent reduction in potency as measured by in vitro methods (ie, titration in cell culture against infective virus). However, there is not a required or recognized test for in vivo efficacy prior to marketing. Experimental PHT-ERIG was expected to provide protection equivalent to that of ERIG currently used in humans. The findings from the study reported here suggest that neutralizing capacity of PHT-ERIG as measured in vitro appears comparable to that of commercially available purified ERIG but without apparent efficacy. Evaluations of PHT-ERIG in a rabies PEP model that used hamsters resulted in comparable findings.¹⁸ In that study, commercial HRIG, ERIG, purified ERIG, and PHT-ERIG, each of which was administered in combination with vaccine after inoculation with rabies virus, resulted in 100% of the animals surviving for HRIG and ERIG, 67% surviving for purified ERIG, and 22% surviving for PHT-ERIG, compared with 0% of the control animals surviving. The effect of heat-treatment on a F(Ab)2 product like PHT-ERIG may be greater than its effect upon intact immune globulin such as either of the HRIG products. Clearly, in vitro analyses may not correlate with in vivo efficacy. Future evaluations should consider various animals and models. Implementation of in vivo evaluations of the effect of procedures intended to reduce adverse events and theoretic risks of adventitious agents associated with preparation of immune globulins would be highly desirable prior to commercial release.

In addition to raising the issue of rabies PEP in domestic animals and the relevance of various experimental approaches, our study also provided insight into the mechanism of protection against lethal infection. Dogs that received only PHT-ERIG did not have measurable amounts of rabies VNA on day 3, and rabies VNA were detectable in only 1 of 5 dogs in that group on day 7. Furthermore, none of those dogs survived. In contrast, rabies VNA were detectable on days 3 and 7 in all 5 dogs that received mAb alone, and 4 of 5 dogs in that group survived. In addition, of the 4 dogs that received vaccine alone, 3 had detectable rabies VNA on day 3, and all 4 dogs in that group had detectable rabies VNA on day 7; however, none of the dogs in that group survived. Whereas a general correlation between detectable VNA titers and survival of rabies may exist, it is not absolute, particularly at low concentrations of rabies VNA. We are not aware of a titer against rabies that can ensure protection for humans or domestic animals. Rather, rabies PEP is a complex process in which VNA are but a single effector.

A combined method of immediate passive protection with mAb and active immunization with vaccine, which elicited endogenous rabies VNA, provided substantial efficacy against a lethal rabies virus infection. Although mAb alone provided impressive protection, the dogs were not actively immunized against rabies following treatment and, thus, would presumably still have been susceptible to subsequent infection. Thus, passive protection alone from any source is not recommended, because there was little or no evidence of

VNA at the end of our study, suggesting viral clearance without the apparent induction of active immunity.

Rabies PEP with vaccine-only treatment does not appear to be completely effective against a severe exposure to rabies virus. Recommendations of the World Health Organization may encompass vaccine-only protocols for humans, but these are usually applied to patients only after careful triage for potential severity of exposure and for whom rabies immune globulin is not available. Vaccine-only regimens are not approved for use in the United States because of their lack of efficacy against severe exposure. Despite these observations, a vaccine-only protocol for rabies PEP of naïve dogs has been proposed.³¹ This regimen of 3 doses of rabies vaccine during weeks 1, 3, and 8 after exposure has not been subjected to objective experimental evaluation and, as such, cannot be recommended.³² The potential ramifications of allowing a domestic dog to remain in an owner's home during the potential incubation period of a rabies virus infection and to be part of an experimental regimen in an effort to protect against rabies without first documenting efficacy are troubling and must be carefully considered by veterinary professionals involved in public health.

The study reported here revealed the potential of mAb as a replacement for polyclonal rabies immune globulins in rabies PEP. If they can be developed further and eventually approved, it may be prudent to apply an observation period to dogs that receive rabies PEP. A conservative period of restriction and observation for the potential development of rabies could be 90 days. If rabies PEP were to fail, intervening attempts at protection should enhance the probability of early death phenomenon,³³ thus shortening, rather than prolonging, the incubation period.

The data reported here are promising and merit further consideration with regard to use of mAb as a replacement for rabies immune globulins for rabies PEP in humans and other animals. We believe these results warrant the development of licensed biologics for rabies PEP for use in unvaccinated rabies-naïve dogs or dogs with outdated vaccination histories.

^aTelazol, Fort Dodge Animal Health, Fort Dodge, Iowa.

^bImrab 3, Merial, Athens, Ga.

^cA lot of purified, heat-treated equine rabies immune globulin (a human biologic that is not licensed for use in the United States) was provided by Dr. Charles E. Lutsch, Aventis Pasteur, Marcy L'Etoile, France.

^dBeuthanasia, Schering-Plough Animal Health Corp, Kenilworth, NJ.

^eSPSS for Windows, version 10.0.7, SPSS Inc, Chicago, Ill.

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