Postexposure Treatment of Rabies Infection: Can It Be Done without Immunoglobulin?

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The last remaining international manufacturer of equine rabies immunoglobulin (ERIG) discontinued production in 2001. However, ERIG remains an essential biological that has no substitute other than human rabies immunoglobulin (HRIG), which is in short supply and virtually unaffordable in developing countries. Physicians in regions where canine rabies is endemic and neither ERIG nor HRIG is available are providing less-than-optimal treatment to patients exposed to rabies. If no immunoglobulin is available, they have only 1 therapy option: use of a vaccine schedule that produces the highest and, hopefully, earliest neutralizing antibody response. However, treatment failures must still be expected. Early, aggressive wound cleansing and more intensive efforts at canine control and are ever more important. Countries that have the resources to manufacture their own rabies immunoglobulins must be encouraged to do so.

More than 5 decades have passed since Habel, Koprowski, Baltazard, and others [1–4] first demonstrated the need for equine rabies antiserum as part of the initial optimal treatment of severely rabies-exposed patients (those with bleeding wounds or mucous-membrane exposure to rabies virus). Their work has been confirmed in numerous additional experimental and field studies. The use of human rabies immunoglobulins (HRIG) and of purified pepsin-digested equine products (equine rabies immunoglobulin, or ERIG) have since saved the lives of countless patients who would have died if treated with vaccine alone [5]. Two problems, however, have continued to plague postexposure rabies treatment (PET). It is very expensive and not readily available where it is needed the most, in poor, countries where canine rabies is endemic [6]. Optimal PET is therefore virtually unaffordable in most of the developing world [6]. ERIG, which replaced the crude and adverse reaction–prone unpurified antiserum samples, sold at ∼20% of the cost of HRIG in Asian countries [6]. Therefore, it was almost affordable. Most of the 8 million PETs administered annually worldwide annually, however, still use dangerous and often poorly immunogenic brain tissue–derived vaccines without rabies immunoglobulin (RIG) [7]. No accurate worldwide statistics of rabies vaccine treatment failures have been compiled, but numbers are thought to be significant. Most failures have been in subjects who have not received RIG [8, 9]. Good wound care and potent vaccines, administered promptly without RIG, have no doubt saved the lives of countless individuals exposed to rabies [7, 10, 11]. We do not know, however, which patient is doomed if not given HRIG or ERIG as well as vaccine [8, 9, 11]. RIG serves to neutralize virus at the inoculation (e.g., bite) sites. It reduces the virus load that can replicate in muscle cells and later invade nerve endings. RIG thus closes the gap until endogenous antibodies elicited by active immunization appear [8, 9, 11]. It is for these reasons that the World Health Organization (WHO) Rabies Expert Committee recommended the use of RIG in all severe rabies exposures such as single or multiple transdermal wounds regardless of body site [7, 12]. RIG must be injected into and around the wounds, ideally at the time of the first vaccine dose [7, 12]. ERIG and HRIG have therefore been placed on the WHO list of essential drugs and biologicals [13].

ERIG and HRIG are in short supply worldwide [14]. Many rabies-control clinics in developing countries have had to wait months for orders to be filled, and some remain unfilled. Thus, countless patients worldwide who should receive HRIG or ERIG are being treated
with vaccine alone [7]. Production of HRIG hinges on the availability of human donors who have been immunized against rabies and requires an expensive screening and production process. Production of ERIG requires a constant supply of serum from horses that have been immunized against rabies. Large multinational manufacturers have been reluctant to maintain such facilities because of pressures from animal rights groups, increasing production costs, and ever more complex directives from national regulatory authorities [14]. ERIG is used only in developing countries, where patients are usually unable to pay a price for it that would generate enough profit for international firms to cover current production costs. Three major European manufacturers (Behring, Sclavo, and Berna) have discontinued production of ERIG during the past 2 decades. The last remaining manufacturer, Aventis Pasteur, announced that it will not be able to fill orders after the end of 2001. A new chromatography-purified and heat-treated ERIG is now in the final development phase, but when it will appear on the market and whether it is as effective in neutralizing virus as the older products are not known [15, 16]. This leaves only a few small producers in developing countries. Most of them are not manufacturing ERIG using current “good manufacturing practices” standards and in sufficient quantity to satisfy home-country requirements. To the best of our knowledge, among Asian nations, only Thailand has been producing a moderate quantity of HRIG, from unpaid volunteer donors at the Thai Red Cross National Blood Center in Bangkok [17].

This critical situation was discussed at the WHO “Rabies in Asia” conference at Hanoi, Viet Nam, in March 2001, and again at Geneva, Switzerland, in July 2001. The consensus opinion was that countries where canine rabies is endemic would have to develop their own ERIG and HRIG manufacturing capabilities in order to provide optimal PET in the future. This will require motivation, investment, and technology transfer. Only a few nations will be willing and able to muster the needed efforts. It should, however, be possible to produce ERIG in existing plants that make purified equine or ovine antivenom serum samples. Some larger blood banks, which can process blood components, could also produce HRIG. The Thai Red Cross, in spite of serious economic difficulties facing the nation in the late 20th century, is upgrading and enlarging its snake antivenin plant and horse farm in order to manufacture purified and pepsin-digested ERIG.

How can one approach patients who, under present guidelines, require RIG when none is available? Wound care becomes ever more important and must be carried out rigorously with scrupulous cleansing and deep irrigation, followed by application of a potent antiseptic agent [18]. The question also arises of whether the risk of rabies can be reduced by using an accelerated vaccine schedule, which induces higher antibody titers and perhaps even an earlier cellular response than the “gold standard” 5-dose intramuscular (“Essen”) schedule or the WHO-approved Thai Red Cross intradermal treatment schedule [12]. Could such a regimen reduce the number of vaccine failures that one must expect in severe exposures when no immunoglobulin is administered? Studies elsewhere [19–25] have shown that a higher neutralizing antibody response could be induced by injecting multiple intradermal doses of vaccine at different lymphatic drainage sites. This led to WHO approval of 2 intradermal postexposure schedules [7, 12]. Both have been extensively tested and are in daily use in some Asian and African countries. They have been found effective, but, like the Essen regimen, only when used together with rabies immunoglobulin [19–23]. The Thai Red Cross regimen (TRC-ID) consists of 0.1 mL of any potent tissue culture vaccine injected at 2 different sites intradermally on days 0, 3, and 7.0.1 mL at 1 site on days 28 and 90 [12].

### Table 1. Humoral immune response for human diploid cell vaccine (potency, 3.16 IU/mL) given intramuscularly and intradermally.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. of patients</th>
<th>GMT of antibody (range), IU/mL, by day after vaccination</th>
<th>Seroconversion on day 7, % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramuscular × 5</td>
<td>22</td>
<td>0.17 (0.02–1.3) 10.99 (1.5–71.6) 12.98 (1.4–60.73) 2.8 (0.23–9.2)</td>
<td>7</td>
</tr>
<tr>
<td>Intradermal 4-4-4-0-1-1</td>
<td>19</td>
<td>0.32 (0.2–1.64) 9.88 (4.0–48.45) 9.34 (3.71–30.96) 3.57 (1.04–10.42)</td>
<td>27</td>
</tr>
</tbody>
</table>

**NOTE.** Data are from Ubol et al. [25]. GMT, geometric mean titer.

a The Essen regimen: 1 full dose of vaccine injected intramuscularly on days 0, 3, 7, 14, and 28.

b Double-dose Thai Red Cross regimen: 0.1 mL of vaccine injected intradermally at 4 different lymphatic drainage sites on days 0, 3, and 7, none on day 14, and 0.1 mL of vaccine injected intradermally at 1 site on days 28 and 90.
postexposure rabies treatment. We do not have any prospective studies that show that increasing the dose of antigen or the number of intradermal injections will reduce treatment failures when no RIG is administered. Phanuphak et al.’s work, showing that the cellular immune response is induced earlier with multisite intradermal rabies vaccination, however, may provide some hope and needs to be investigated further [21]. Because we have now reached a crisis situation regarding RIG availability, we suggest that, when absolutely no HRIG or ERIG is available, one should apply one of the regimens that offer the highest neutralizing antibody responses and that may induce earlier cellular immunity. This would either be the “double-dose” TRC-ID schedule (4-site 0.1 mL on days 0, 3, and 7 and at 1 site on days 28 and 90) or the 8-site Oxford regimen.

We anticipate that physicians in the developing world will continue to be faced with having to provide less-than-optimal postexposure rabies treatment. Some Asian countries (notably China, Myanmar, Nepal, some Indian states, and former Soviet Central Asian republics) have made the calculated decision to accept treatment failures, because of other priorities and the unavailability of RIG. En ergetic and innovative dog control measures are now ever more important. They have not been implemented in many parts of Asia. There were suggestions at the 2 WHO “Rabies in Asia” conferences (March 2001 and July 2001) that preexposure rabies vaccination of selected high-risk children, in regions with a large canine rabies problem, should be considered if it becomes economically feasible. Approximately 40% of exposures and human rabies deaths in developing countries are of children <15 years of age [7, 9]. Preexposure vaccination would be particularly appropriate for countries that have been unable to manage their large stray dog populations because of religious and cultural barriers (Thailand, Laos, Myanmar, Cambodia, India, and Nepal). Such public sector preexposure vaccination can be carried out, however, only if present tissue culture vaccine costs could be dramatically reduced. The introduction of such vaccines in liquid form and as multiple dose vials might be one approach that could reduce the cost. There is fear, however, that such efforts might detract from more intensive dog population control programs and vaccination programs, which must remain the primary objectives in worldwide rabies eradication.

C. E. Rupprecht and others have studied monoclonal antibodies (MABs) and have shown that they can be very effective in neutralizing a wide range of Lyssavirus strains in experimental animals [15, 26]. Further research and industrial application of this promising work might eventually offer an alternative to HRIG and ERIG, but antirabies MABs are not likely to appear on the market in time to solve the present crisis.

Acknowledgments

Rabies research and production of biologicals at the Queen Saovabha Memorial Institute, a WHO collaborating

Table 2. Humoral immune response for purified chick embryo vaccine (potency, 7.5 IU/mL) given intramuscularly and intradermally.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. of patients</th>
<th>GMT of antibody (range), IU/mL, by day after vaccination</th>
<th>Seroconversion % of patients on day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramuscular × 5(^a)</td>
<td>15</td>
<td>0.02 (&lt;0.1–0.2) 3.1 (0.3–16.7) 10.3 (2.1–35.9) 4.9 (1.4–9.6)</td>
<td>7</td>
</tr>
<tr>
<td>Intradermal 8-0-4-0-1-1(^b)</td>
<td>15</td>
<td>0.04 (&lt;0.1–0.3) 5.4 (1.8–16.7) 5.8 (2.4–13.4) 2.7 (0.8–10.2)</td>
<td>7</td>
</tr>
<tr>
<td>Intradermal 4-0-4-0-1-1(^c)</td>
<td>15</td>
<td>0.02 (&lt;0.1–0.3) 7.2 (1.8–26.0) 7.2 (1.5–23.2) 2.7 (0.9–5.9)</td>
<td>20</td>
</tr>
</tbody>
</table>

NOTE. Data from Suntharasamai et al. [24].
\(^a\) The Essen regimen: 1 full dose of vaccine injected intramuscularly on days 0, 3, 7, 14, and 28.
\(^b\) The Oxford regimen: 0.1 mL of vaccine injected intradermally at 8 sites on day 0, none on day 3, at 4 sites on day 7, and at 1 site on days 28 and 90.
\(^c\) 0.1 mL of vaccine injected intradermally at 4 sites on day 0, none on day 3, at 4 sites on day 7, and at 1 site on days 28 and 90.
References