Purified equine rabies immune globulin: a safe and affordable alternative to human rabies immune globulin*

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Reported are the results of a retrospective study of 3156 patients who were treated at the Queen Saovabha Memorial Institute, Bangkok, with equine rabies immune globulin (ERIG). Only 51 patients (1.6%) exhibited serum-sickness-like reactions, none of which persisted for more than a week, and only 8 of these patients (15%) were treated with a short course of steroids. One patient, whose skin test was negative, had an immediate anaphylactic reaction to ERIG that responded to parenteral therapy with epinephrine and hydrocortisone sodium succinate.

Serum-sickness-like reactions were more frequent among females and over 21-year-olds but were exceedingly rare (0.086%) among children under 10 years of age.

Introduction

Rabies immune globulin (RIG) is an essential component of rabies postexposure treatment (*1*). Equine antirabies serum (ERS) and equine rabies immune globulin (ERIG) have been available commercially for about 40 years but in developed countries have been replaced by human rabies immune globulin (HRIG) (*1*). It has been claimed that ERS and ERIG cause serum sickness in 15–46% of recipients (*1–4*); in general, however, reports have not differentiated between ERS and the newer, purified ERIG preparations in this respect. In contrast, HRIG is well tolerated, and instances of anaphylaxis or serum sickness caused by it are virtually unknown (*5*); HRIG is, however, expensive and not generally affordable in developing countries, where canine rabies remains a serious public health problem (*6*).

In Thailand (population about 55 million), over 100 000 persons receive postexposure rabies vaccination annually (*7*). A labourer or clerk would, nevertheless, have to work an average of 98 days at the minimum daily wage (US$ 3.00) to pay for postexposure treatment with HRIG. A purified imported ERIG preparation, on the other hand, costs only the equivalent of 9 minimum daily wages. At the Queen Saovabha Memorial Institute (QSMI), which operates the principal rabies clinic for the Bangkok Metropolitan Region, ERIG is used almost exclusively for this purpose. Experience at QSMI indicates that some purified ERIG products are much safer than has been reported (*1–4*) and that their reputation of causing serum sickness in up to 46% of recipients is undeserved. For example, in 1987 a prospective study of adverse effects among 485 recipients of ERIG manufactured by Pasteur Vaccins, France, indicated that only 0.87% of these individuals developed serum-sickness-like symptoms and signs (*6*). We have now reviewed the clinical records of all patients who received ERIG (3812) or HRIG (314) at QSMI in 1987 and report our findings here.

Materials and methods

The majority of patients who attend QSMI are poor and are probably representative of those who attend public health institutions throughout Thailand and other developing countries where canine rabies is prevalent. The monthly family income of 48% of the patients was less than US$ 40.

A total of 16 686 individuals seen at the institute in 1987 were considered to have possible, likely, or proven rabies exposures and were therefore treated with purified Vero-cell tissue culture rabies vaccine.[a]

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However, 656 patients, who did not return for follow-up because they lived outside metropolitan Bangkok, received only their primary evaluation and treatment (wound care, ERIG or HRIG injections, purchase of rabies vaccine, and first vaccination) at QSMI. These patients obtained the remaining injections of rabies vaccine at a clinic near their home. Four patients in this group (0.6%) experienced symptoms consistent with serum sickness, but others could have suffered adverse reactions that were treated at local health centres without coming to our attention. We therefore excluded from the study all these 656 patients who received follow-up care elsewhere. The treatment records of the 3156 recipients of ERIG who were followed up at QSMI were therefore used, and all adverse reactions, their time of onset, duration, as well as the sex and age of each recipient as well as the dose of ERIG that each received were tabulated.

Rabies vaccine was administered using the WHO-recommended intramuscular Essen regimen (*1*) or the intradermal multiple-site schedule approved by the Rabies Advisory Committee of the Thai Red Cross (*8*), both of which have similar rates of antibody generation and low rates of adverse reactions (*8, 9*). Of the patients who had undergone severe exposure, as judged by WHO criteria (*1*), 23% had also received ERIG; an additional 314 vaccinees with severe exposures had been given HRIG, usually because they had a positive skin test to ERIG or were tourists, expatriates, or wealthy Thais who preferred and were able to pay for HRIG. All patients who were considered for ERIG treatment were first questioned about previous exposures to equine sera and then skin tested.

The skin test was performed by injecting a 1:10-dilution of ERIG intradermally into the flexor surface of the forearm to raise a weal of 3-mm diameter. If within 15 minutes the diameter of the weal increased to >6 mm and became surrounded by a flare, this was interpreted as a positive reaction, provided a subsequent saline test was negative. ERIG from Pasteur Vaccins, France, was given to 84%, and that from the Swiss Serum and Vaccine Institute to 16% of patients. Those who exhibited a positive skin test were usually given HRIG. All adverse reactions were recorded when the patient returned for wound care, injection of vaccine, or other treatment.

The severity of the serum-sickness-like reactions was graded according to the number of symptoms and signs that developed, although the quality of records and description of clinical symptoms and signs varied somewhat. The results were tabulated as follows: delayed local reaction at intramuscular and wound injection sites (swelling or erythema >3-cm diameter), generalized urticaria or any erythematous rash, arthralgia, arthritis, measured fever >37 °C with or without malaise, and generalized lymphadenopathy. Patients with one symptom or sign were classified as grade I, those with two as grade II, and those with three or more as grade III. Details of all treatments given were also tabulated, and the duration of the illness and response to treatment were recorded.

Results

We identified 10 352 patients who received only rabies vaccine in 1987 and who were followed up at QSMI over their entire immunization series. Of these patients, 49 (0.47%) reported serum-sickness-like symptoms or signs (headaches, low fever, erythematous or urticarial rashes, and arthralgia that appeared 6–14 days after the first dose of vaccine and deteriorated or recurred after subsequent doses) that could have been due to the rabies vaccine alone.

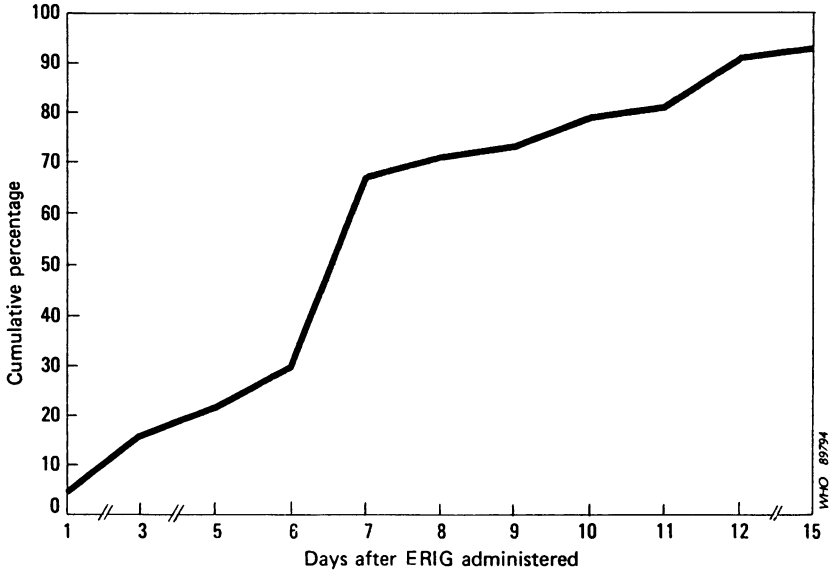
Of the 3156 patients who received ERIG and who were followed up for at least 1 month, 51 (1.6%) developed one (or more) symptom or sign that was characteristic of serum sickness (Table 1). The time of onset of these adverse reactions is shown in Fig. 1. Approximately 30% of patients treated with ERIG had also received antibiotics (usually penicillin) or tetanus toxoid and analgesics. An unknown proportion was also likely to have taken a variety of traditional herbal medicines. Because the study was retrospective, it was impossible to identify which of the adverse reactions may have been caused by antibiotics, analgesics, tetanus toxoid, traditional medicines, intercurrent viral illness, or rabies vaccine. None of the 314 HRIG recipients reported side-effects other than occasional discomfort at injection sites.

The age and sex distributions of the 3156 patients who were treated with ERIG are shown in Fig. 2, while the distributions by age, sex, and severity of symptoms of the 51 recipients who developed reactions that were characteristic of serum sickness are shown in Table 2.

Table 1: **Distribution of adverse reactions presented by 51 of the 3156 patients who received equine rabies immune globulin (ERIG) and were followed up for at least 1 month**

Adverse reactions	No. of cases
Local reactions	43
Urticaria	33
Rash	23
Arthralgia	10
Arthritis	1
Fever	7
Lymphadenopathy	6

Fig. 1. **Cumulative distribution of the time of onset of symptoms and signs among the 51 patients who received equine rabies immune globulin (ERIG) and were followed up for at least 1 month.**



Only one of the ERIG recipients exhibited an immediate hypersensitivity reaction in 1987. The individual concerned, a 17-year-old male who developed hypotension, a faint erythematous rash, and back pain within a few minutes of being injected with ERIG, responded to treatment with parenteral epinephrine, hydrocortisone sodium succinate, and chlorphenamine. He did not develop serum sickness and gave a negative skin test, although no check on histamine levels was carried out. Also, he did not report any previous exposure to equine sera or ingestion of antihistamines.

Oral antihistamines were administered to 41% of the patients with adverse reactions and 13 patients (26%) also received analgesics, e.g., acetylsalicylic acid, ibuprofen, or paracetamol. Only eight patients (15%) were prescribed a short course of steroids (<7 days); three of these patients had been given the steroids by local physicians, and may well have been treated only with analgesics and antihistamines had they been seen initially at QSMI. Symptoms and signs that were characteristic of serum sickness disappeared in all cases within 7 days of onset, and all patients received their remaining injections of rabies vaccine on schedule. This indicates that the reactions were not due to the rabies vaccine itself. Administration of vaccine was discontinued before completion of the regimen only for those patients who were bitten by an animal that was under observation and continued to be healthy or was found free of rabies at autopsy. Individuals whose serum sickness was believed to have been caused by the vaccine alone were given antihistamines and administered a human diploid cell (HDCV) or purified chick embryo cell (PCEC) rabies vaccine. All of these patients completed their immunization schedules without further incidents.

Discussion

Serum-sickness-like reactions (urticaria, angio-oedema, and arthralgia) among patients who received exclusively tissue-culture rabies vaccine have been reported previously, and in one pre-exposure series where HDCV was used their incidence was up to 2.06% (*10*). In contrast, the incidence of serum-sickness-like reactions among vaccine-only patients in our retrospective study was 0.56%.

The recommendation that RIG be used to treat all patients severely exposed to rabies is based on considerable clinical experience gained over 40 years (*11–14*), while the practice of injecting some of the RIG around bite wounds is based on extensive experimental data in animals (*15–17*). Only one of the 3812 patients who received ERIG exhibited an immediate (anaphylactic) reaction, and he recovered after appropriate treatment.

Females and individuals aged over 21 years had a higher incidence of serum-sickness-like reactions to ERIG ($P > 0.001$, 99.9% confidence limit) (Fig. 2). Such

Fig. 2. **Distribution by age and sex of the 3156 patients who received equine rabies immune globulin (ERIG).**

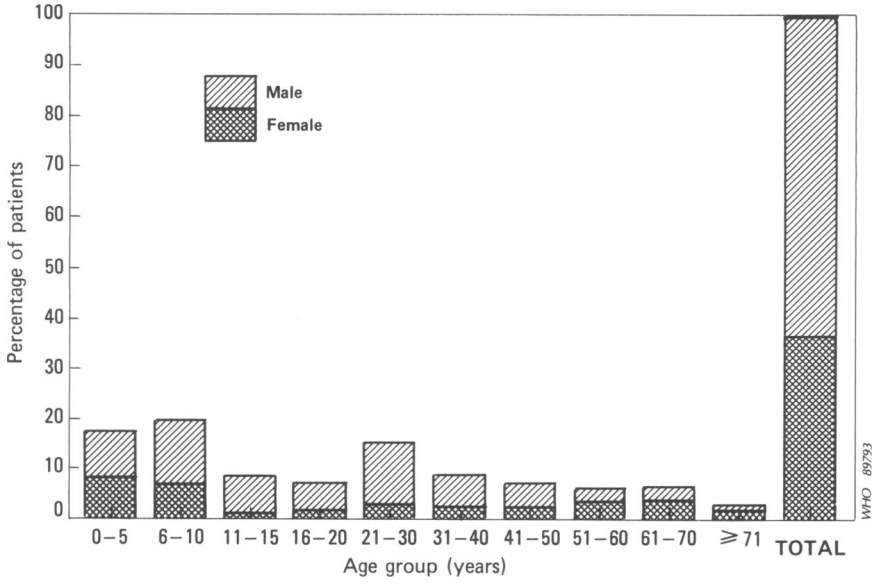


Table 2: **Distribution of the number of adverse reactions, by age, sex, and grade of severity of symptoms, among the 3156 recipients of equine rabies immune globulin (ERIG)**

Age group (years)	No. of recipients		Grade I		Grade II		Grade III		No. of reactions	
	F/M[a]	Total	F/M[a]	Total	F/M[a]	Total	F/M[a]	Total	F/M[a]	Total
0–5	255/286	541	0/0	0	0/0	0	0/0	0	0/0	0
6–10	212/401	613	0/0	0	1/0	1	0/0	0	1/0	1
11–15	38/238	276	1/0	1	0/0	0	0/1	1	1/1	2
16–20	62/169	231	1/1	2	2/0	2	0/0	0	3/1	4
21–30	92/383	475	3/0	3	8/4	12	2/1	3	13/5	18
31–40	88/193	281	1/3	4	2/3	5	0/0	0	3/6	9
41–50	90/138	228	2/1	3	3/0	3	2/2	4	7/3	10
51–60	118/87	205	1/1	2	1/0	1	1/0	1	3/1	4
61–70	132/80	212	0/0	0	0/0	0	0/1	1	0/1	1
⩾71	66/28	94	1/0	1	1/0	1	0/0	0	2/0	2
Total	1153/2003	3156	10/6	16	18/7	25	5/5	10	33/18	51

[a] F = female; M = male.

reactions, however, were exceedingly rare among children aged under 10 years, even though such children represented 37% of the ERIG recipients. Only one out of 1154 such children (0.086%) exhibited a serum-sickness-like reaction. This contrasts with the 2.9-% incidence of adverse reactions among those aged over 21 years (4.8% for females and 1.8% for males); for those aged 21–30 years the incidence was 2.7% for females and 1.05% for males. Reactions were of grade I severity for 31%, grade II for 49%, and grade III for 20% of patients, and all recovered within 7 days of the onset of symptoms and signs. Only eight patients received short-term steroid therapy and three of them were hospitalized for 2–3 days. One patient developed anaphylaxis but was the only such case encountered in 3 years among over 12 000 recipients of ERIG at QSMI. He recovered after appropriate treatment and completed his rabies vaccine series.

The difference in the incidences of adverse reactions to ERIG in our study (1.6%) compared with those reported by other workers (up to 46%) (*2–4*,

Table 3: **The cost of various rabies treatments in Thailand**

Vaccine[a]	Regimen[b]	Cost: (in US$)	Cost: Expressed as the number of minimum daily wages (US$ 3.00)
HDCV	"Essen"	124	41
PVRV, PCEC, PDEV	"Essen"	48	16
PVRV	"Thai Red Cross"	19	6
PVRV	"Zagreb"	38	13
HRIG	For 60-kg patient	296	98
ERIG	For 60-kg patient	28	9

[a] HDCV = human diploid cell rabies vaccine (Merieux; 1-ml ampoule containing >2.5 IU antigen); PVRV = purified Vero-cell rabies vaccine (Merieux; 0.5-ml ampoule containing >2.5 IU antigen); PCEC = purified chick embryo cell rabies vaccine (Behring; 1-ml ampoule containing >2.5 IU antigen); PDEV = purified duck embryo vaccine (Berna; 1-ml ampoule containing >2.5 IU antigen); ERIG = equine rabies immune globulin (Berna, Pasteur; 5-ml vial, 200 IU antigen/ml); HRIG = human rabies immune globulin (Berna, Pasteur; 5-ml vial, 300 IU antigen/ml).

[b] "Essen" = 1 ampoule injected intramuscularly on days 0, 3, 7, 14, and 30; "Thai Red Cross" = intradermal injection of 0.1 ml of PVRV (>0.5 IU antigen) at two sites on days 0, 3, and 7 and at one site on days 30 and 90; "Zagreb" = intramuscular injection of two ampoules of PVRV (>2.5 IU antigen each) at two sites on day 0 and at one site on days 7 and 21 (*22*).

18–20) is interesting. Methods of purifying equine serum products have improved, and the protein content of the ERIG produced by Pasteur Vaccins used in the study was 0.6–2.8%, while that obtained from the Swiss Serum and Vaccine Institute was 7.03–10.2% (B. Fritzell, Pasteur Vaccins, and P. Paroz, Swiss Serum and Vaccine Institute, personal communications). In the past, antirabies sera typically had protein contents of not less than 15% (D. Fishbein, Centers for Disease Control, Atlanta, GA, USA, personal communication). Two recent prospective studies of recipients of ERIG from Pasteur Vaccins and the Swiss Serum and Vaccine Institute revealed differences in the incidences of adverse reactions (*6, 21*). For example, the incidence of adverse reactions among 485 recipients of ERIG from Pasteur Vaccins (lot 5212; reported protein content 0.87%) was 0.82%, while that among 323 consecutive patients who received ERIG from the Swiss Serum and Vaccine Institute (lots 40429 and 37864; reported protein content 7.03% and 10.2%, respectively) was 6.19% (*21*).

ERIG products are currently being produced in several developing countries,[b] but their use may well be associated with adverse reactions whose incidences differ from those we have reported in the present study. Producers of ERIG should be encouraged to standardize and publish their purification procedures and potency criteria, aiming for consistent antibody levels and the lowest possible incidences of adverse reactions among users.

Postexposure rabies treatment represents a drain on scarce budgets in developing countries, where the majority of rabies exposures occur. Worldwide, most patients still receive rabies vaccines derived from brain tissue, which carry a high risk of serious adverse reactions; few receive any immune globulin. Table 3 shows the comparative costs of postexposure rabies treatment in Thailand. It is clear from the data that a dog bite can mean a major financial disaster for many average families and that ways have to be found to control canine rabies and to make adequate postexposure treatment available to all. The introduction of the economical and effective intradermal (*8*) and abbreviated intramuscular (*22*) tissue culture vaccine schedules is a step in this direction. The worldwide shortage of HRIG and its high cost put it out of reach of most patients in developing countries; however, the newer purified ERIG products, when administered with a potent rabies vaccine, provide an acceptable and safe alternative where HRIG is not available or affordable.

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[b] *World survey of rabies XXII (for 1984/85)* Unpublished document WHO/RABIES/87.198, p. 7.

Résumé

Immunoglubiline équine antirabique purifiée: un substitut de l'immunoglobuline humaine antirabique sûr et relativement peu coûteux

Beaucoup de pays en développement n'ant pas les moyens de se prouver de l'immunoglobuline humaine antirabique et la majorité des individus exposés à la rage dans ces pays ne reçoivent pas d'immunoglobine antirabique. En Thaïlande, l'immunoglobuline humaine coûte actuellement dix fois plus cher que l'immunoglobuline équine. On trouvera ici les résultat d'une étude rétrospective portant sur 3156 patients qui ont été traités avec une immunoglobuline équine antirabique fabriquée par Pasteur Vaccins (France) ou par l'Institut suisse des Sérums et Vaccins. Seulement 51 patients (1,6%) ont présenté des symptomes de la nulcidie du serum qui n'ont toute fois jamais persisté plus d'une semaine, et huit d'entre eux seulement (15%) ont dû être traités pendant quelques jours avec des corticostéroïdes. Un patient dont le test cutané avait été négatif a été victime d'une réaction anaphylactique immédiate qui a cédé à des injections d'épinéphrine et de succinate d'hydrocortisone sodique.

Les manifestations de la maladie du sérum ont été plus fréquentes chez les sujets de sexe féminin ou âgés de plus de 21 ans, mais elles ont été extrêmement rares (0,086%) chez les enfants de moins de 10 ans. Ces résultats vont à l'encontre de l'opinion générale selon laquelle l'utilisation d'immunoglobuline antirabique d'origine équine s'accompagne d'un nombre élevé de cas de maladies du sérum. Les immunoglobulines équines antirabiques fabriquées par l'Institut Pasteur et par l'Institut suisse des Sérum et Vaccins sont donc des substituts acceptables de l'immunoglobuline humaine antirabique.

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