What happens if intradermal injections of rabies vaccine are partially or entirely injected subcutaneously?*

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Reported are the results of a study with the Thai Red Cross two-site intradermal purified Vero-cell rabies vaccine (PVRV) schedule that was deliberately injected into subcutaneous tissue. The 44 healthy nonimmune Thai adults who were enrolled in the study were randomly assigned to the following groups and given PVRV as shown: group A (two intradermal injections on days 0, 3, and 7); group B (one intradermal and one subcutaneous injection on days 0, 3, and 7); and group C (two subcutaneous injections on days 0, 3, and 7). Neutralizing antirabies antibody titres were determined on day 14 using the rapid fluorescent focus inhibition test. High rabies antibody titres were obtained for all three groups. These results suggest that the economical and safe Thai Red Cross intradermal PVRV regimen could be used in selected general health care facilities.

Introduction

Intradermal (ID) postexposure immunization with currently available rabies vaccines obtained by potent tissue culture methods is an affordable way in developing countries to eliminate the use of rabies vaccines derived from nerve tissue. Previous studies have shown that ID injection of rabies vaccines obtained by potent tissue culture methods results in antibody levels equivalent to those attained using the conventional intramuscular schedule (1,2). We have previously reported that ID injection of 0.1 ml of purified Vero-cell rabies vaccine (PVRV) (0.5 ml PVRV per ampoule; antigen content >2.5 IU) at two sites on days 0, 3, 7 and at one site on days 30 and 90 (the Thai Red Cross 2–2–2–0–1–1 intradermal (TRC–ID) regimen) produces a similar immunogenic response to the full five-dose intramuscular schedule (3). Also, the ID route is more effective in inducing a specific cell-mediated immune response (3,4). The protective efficacy of the TRC–ID regimen has recently been established in a 1-year prospective study of 100 Thai patients who had been severely exposed to proven rabid animals (5).

The TRC–ID regimen is now routinely used at the Queen Saovabha Memorial Institute, where skilled nurses administer all injections and confirm the correct intradermal placement of the vaccine by the appearance of an intradermal bleed. Concern has, however, been expressed about the effect of introducing the TRC–ID regimen in peripheral health centres for general use by less experienced staff. We therefore conducted a study to evaluate the immunogenicity of PVRV when one or both of the intradermal injections are misinjected into subcutaneous tissue. The results obtained are described below.

Materials and methods

Subjects

The study subjects consisted of 44 healthy nonimmune Thai adults who presented to the outpatient clinic of the Queen Saovabha Memorial Institute with a low risk of rabies exposure, having either petted or been licked by a rabid animal on unbroken skin. All patients were told that they did not need rabies vaccination, but that they might consider pre-exposure immunization since they lived in an area that was endemic for canine rabies. The purpose and nature of the study was then explained to them and their participation was invited. Subjects were randomly assigned to one of the treatment groups described below.

1. Group A (2–ID): 15 individuals (7 males and 8 females), aged 14–54 years (mean, 35.0±14.0 years), who received two intradermal injections of 0.1 ml of PVRV on days 0, 3, and 7 in the deltoid area.

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Reprint No. 5049

Table 1: Comparison of the immunogenicity of purified Vero-cell rabies vaccine (PVRV) when injected using various intradermal (ID) and subcutaneous (SC) schedules

<table>
<thead>
<tr>
<th>Group</th>
<th>Schedule*</th>
<th>n</th>
<th>Age ± s.d. (years)</th>
<th>GMT of rabies antibody on day 14 (IU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2-ID</td>
<td>15</td>
<td>35.0 ± 14.0</td>
<td>15.5 (3.9–41.9)*</td>
</tr>
<tr>
<td>B</td>
<td>ID + SC</td>
<td>14</td>
<td>30.3 ± 8.5</td>
<td>26.4 (5.3–50.9)</td>
</tr>
<tr>
<td>C</td>
<td>2–SC</td>
<td>15</td>
<td>32.8 ± 11.6</td>
<td>18.5 (3.3–41.2)</td>
</tr>
</tbody>
</table>

* 2-ID = 2 ID injections of 0.1 ml each of PVRV on days 0, 3 and 7; ID + SC = 1 ID plus 1 SC injection of 0.1 ml each of PVRV on days 0, 3 and 7; 2–SC = 2 SC injections of 0.1 ml each of PVRV on days 0, 3 and 7

* GMT = geometric mean titre.

- Group B (ID + SC): 14 individuals (7 males and 7 females), aged 18–43 years (mean, 30.3 ± 8.5 years), who received one intradermal and one subcutaneous (SC) injection of 0.1 ml of PVRV on days 0, 3, and 7 in the deltoid area.
- Group C (2–SC): 15 individuals (8 males and 7 females), aged 15–55 years (mean, 32.8 ± 11.6 years), who received 0.1 ml of PVRV subcutaneously at two sites on days 0, 3, and 7 in the deltoid area.

Purified Vero-cell rabies vaccine (potency, by NIH test: 10.35 IU per ampoule at 4 °C)* was given to all study subjects. The vaccine was lyophilized and reconstituted with 0.5 ml of the diluent provided.

Serum collection and antibody determination

Blood was collected on days 0 and 14 and stored at −70 °C until assayed. Neutralizing antirabies antibodies were determined using the rapid fluorescent focus inhibition test (RFFIT) (6,7). Titres were expressed in IU per ml using the international equine rabies immune globulin reference standard (Tollwut Standard Serum, WS5, 275 IU/ml). Geometric mean titres (GMTs) were calculated and compared using Student’s t-test.

The study was reviewed and approved by the Ethics Committee of the Science Division of the Thai Red Cross Society.

Results

None of the subjects had detectable rabies antibodies prior to vaccination. On day 14, a week after the last dose of vaccine had been given, all vaccinees in the three groups had developed antirabies antibodies in titres that ranged from 3.3 to 50.9 IU/ml. The GMT for group B (ID + SC) was significantly higher than that for group A (2–ID) or group C (2–SC), but the GMTs for group A (2–ID) or group C (2–SC) were not significantly different (Table 1).

Discussion

The results of the study confirm that the intradermal two-site PVRV vaccine schedule is highly immunogenic (3). Furthermore, intentional administration of one or both injections at a subcutaneous rather than an intradermal site of the deltoid region did not diminish the antibody response on day 14. These results were unexpected and contrast with the findings reported by Bernard et al. (8) that subcutaneous injection of reduced doses of human diploid cell rabies vaccine for pre-exposure immunization, although sufficiently immunogenic, is significantly less than that produced by intradermal schedules. This may have arisen because of the high potency of the PVRV vaccine or the immunization schedule, i.e., closely separated in time and two-site injections. The study should therefore be repeated using other tissue-culture rabies vaccines and other schedules.

The results indicate that the Thai Red Cross two-site ID regimen with PVRV should be field tested in selected peripheral health centres. Tissue culture rabies vaccines are still very expensive in developing countries and constitute a major drain on public health budgets in poor regions where canine rabies is prevalent. Use of the Thai Red Cross two-site ID regimen reduces by 68% the amount of vaccine used compared with the conventional five-dose intramuscular schedule. It therefore offers an alternative and economical approach to attempts to eliminate globally the routine use of rabies vaccines derived from nerve tissue.

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WHO Bulletin OMS Vol 68:1990
Résumé

Qu'arrive-t-il si les injections intradermiques de vaccin antirabique sont administrées en partie ou en totalité par voie sous-cutanée?

Cet article rapporte les résultats d'une étude dans laquelle le vaccin antirabique purifié obtenu en cellules Vero pour injection intradermique en deux sites a été administré selon le schéma de la Croix-Rouge thaïlandaise mais en injectant délibérément le vaccin dans le tissu sous-cutané. Les 44 sujets adultes non immuns, en bonne santé, qui ont été recrutés pour l'étude, ont été répartis au hasard dans l'un des groupes suivants: groupe A (deux injections intradermiques les jours 0, 3 et 7), groupe B (une injection intradermique et une injection sous-cutanée les jours 0, 3 et 7); groupe C (deux injections sous-cutanées les jours 0, 3 et 7). Les titres d'anticorps antirabiques neutralisants ont été déterminés le jour 14 par épreuve rapide d'inhibition des foyers de fluorescence. Des taux élevés ont été obtenus dans les trois groupes. Les injections sous-cutanées suscitent une excellente réponse immunitaire, probablement en raison de l'activité élevée du vaccin employé.

D'après ces résultats, le schéma économique de la Croix-Rouge thaïlandaise avec administration intradermique du vaccin antirabique pourrait être utilisé dans certains centres de soins généraux. Il serait ainsi possible de réaliser une économie notable et d'envisager le remplacement complet, à l'échelle mondiale, des vaccins obtenus en culture tissulaire, plus sûrs.

References
