NOTES

Promising Rabies Vaccine for Postexposure Prophylaxis in Developing Countries, a Purified Vero Cell Vaccine Produced in China

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We evaluated the immunogenicity, safety, and antibody persistence of a Vero cell rabies vaccine manufactured in China, compared with that of Verorab. Adequate titers of antibody were observed for the two vaccines. ChengDa rabies vaccine could be a promising alternative vaccine for many developing countries which cannot afford expensive rabies vaccines.

Although effective rabies vaccines for postexposure treatment are available (3), there are still about 50,000 to 60,000 human deaths annually. China, as the largest developing country in the world, has endeavored tremendously in rabies prevention and vaccine manufacturing. China accounts for almost two-thirds of the total rabies vaccines used in Asia (9), with the locally produced tissue culture vaccine being safe and relatively inexpensive (5). Currently, the most common rabies vaccine used in China is purified Vero cell vaccine, referred to as ChengDa (Liaoning ChengDa Biological Co., Ltd., Shenyang, China). ChengDa rabies vaccine is grown on a Vero cell line utilizing the L. Pasteur 2061 strain of rabies virus. It is inactivated with β-propiolactone (BPL), lyophilized, and reconstituted in 0.5 ml of physiological saline. It is manufactured according to good manufacturing practices (GMP) and strictly fulfills the WHO recommendations for potency (8). ChengDa was licensed by the Health Ministry of China and the State Food and Drug Administration of China (SFDA) in 2002 and has been marketed throughout the country since that time.

This study was designed to compare the immunogenicity, safety, and persistence of the two different Vero cell rabies vaccines (ChengDa and Verorab) available in China. The study was conducted in the Emergency Department, Beijing University People’s Hospital, and the antibody evaluation was performed primarily at the National Institute for the Control of Pharmaceutical and Biological Products. Formal ethical approval was obtained from the ethics committee of Beijing University People’s Hospital. Written informed consent was obtained from each subject and/or his/her legal representative. Intramuscular doses of either 0.5 ml of ChengDa or 0.5 ml of Verorab were given to 500 patients on days 0, 3, 7, 14, and 28.

Blood samples from all vaccinees were taken on days 0, 7, 14, 45, and 365. Antibody testing was performed using the rapid immunofluorescence assay. The adjusted geometric mean titers (GMT) were 24, 40, 81, 217, and 142 for ChengDa and 40, 46, 84, 202, and 130 for Verorab, respectively. The GMTs of both vaccines were comparable, indicating that ChengDa is as effective as Verorab. The antibody persistence was also comparable between the two vaccines, with 80% of the subjects still having detectable antibody titers at 365 days after vaccination.

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FIG. 1. Study flow chart.
fluorescent focus inhibition test (RFFIT) in 96-well microplates according to the technique of Zalan et al. (10).

From February 2006 to September 2008, a total of 500 patients with WHO-designated category I or II rabies exposure were enrolled and randomly assigned to the ChengDa group or the Verorab group. A study flow chart is shown in Fig. 1. The baseline demographic characteristics are demonstrated in Table 1, and subjects were similarly distributed in the two groups. The exclusion criteria included poor compliance, primary or acquired immunodeficiency, corticosteroid intake, and previous rabies immunization. Rabid patients and patients who were simultaneously in other clinical trials were also excluded.

ChengDa rabies vaccine, lot numbers 20060123-20070213 and 20080712-20080810, with a registered potency of 4.5 IU/0.5 ml, and Verorab, lot numbers D0033-1-D0043-1 and Z0096-2, with a registered potency of 3.1 IU/0.5 ml, were used. The Essen intramuscular regimen was adopted in this study (7). SPSS 11.5 was used for statistical analysis, and a $P$ value of <0.05 was considered significant. The chi-square test was used for the comparison of adverse reaction rates.

Overall, only 46 local reactions were reported for 34 subjects (13.6%) in the ChengDa group, and 41 reactions were reported for 32 subjects (12.8%) in the Verorab group. No significant differences were observed in adverse reaction rates between the two groups (chi-square value = 0.348, $P > 0.05$). The details are shown in Table 2. From day 14, all patients in both groups had levels of neutralizing antibody to rabies virus in excess of adequate titers (>0.5 IU/ml) as defined by the WHO, and data on immunogenicity and persistence are shown in Table 3.

ChengDa rabies vaccine offers an alternative with a high degree of efficacy and yet limited side effects, similar to Verorab, and ensures that the exposed patient will be on the safe side of the rabies risk by the 14th day at the latest and probably sooner; however, the price of ChengDa rabies vaccine is almost half of that of Verorab.

### Table 1. Baseline demographic characteristics of subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ChengDa</th>
<th>Verorab</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (no. of males/no. of females)</td>
<td>159/91</td>
<td>163/87</td>
<td>322/178</td>
</tr>
<tr>
<td>Age in yrs (mean/range)</td>
<td>30.8 (9–75)</td>
<td>31.1 (9–73)</td>
<td>31.0 (9–75)</td>
</tr>
<tr>
<td>Exposure (no. of subjects with grade I exposure/no. with grade II exposure)</td>
<td>32/218</td>
<td>25/225</td>
<td>57/443</td>
</tr>
</tbody>
</table>

### Table 2. Adverse reaction summary

<table>
<thead>
<tr>
<th>Side effect</th>
<th>No. of cases</th>
<th>ChengDa</th>
<th>Verorab</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site pain</td>
<td>24</td>
<td>22</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Redness</td>
<td>17</td>
<td>14</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>4</td>
<td>4</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
<td>41</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>No. (%) of affected subjects</td>
<td>34 (13.6)</td>
<td>32 (12.8)</td>
<td>66 (13.2)</td>
<td></td>
</tr>
</tbody>
</table>

* Chi-square test: chi-square value = 0.348, $P > 0.05$.
In most of the developing countries, modern cell culture vaccines are too costly for the poorly developed remote regions, and so dangerous nerve tissue vaccines (NTVs) are still used (1, 2). Therefore, there is an urgent requirement for effective and cheap rabies vaccines worldwide, especially in the developing countries (4, 6). Good efficacy and tolerance, early induction of antibody response, and long-term persistence of protective antibody titer, in addition to more than 5 years of clinical use experience, make ChengDa a promising vaccine for postexposure treatment of rabies worldwide. ChengDa is currently used in China and India, as well as in the regions of Asia, Africa, and the Americas where rabies is endemic.

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REFERENCES