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REPORT OF INFORMAL DISCUSSIONS
ON INTRA-DERMAL APPLICATION OF MODERN RABIES VACCINES
FOR HUMAN POST-EXPOSURE TREATMENT
Geneva, 22 January 1993

The meeting was called to review the section of the 8th report of the WHO Expert Committee on Rabies¹ (meeting held in September 1991) dealing with the use for postexposure treatment of modern tissue culture and embryonating egg derived vaccines administered by the intradermal route (ID). This report stated that tissue-culture or purified duck embryo vaccines with a minimum potency of 2.5 IU/dose could be applied using 0.1 ml intradermally according to the 2-2-2-0-1-1 schedule (2 sites on days 0, 3 and 7, and 1 site on days 30 and 90). However, a report made early in December 1992 suggested that virus neutralizing antibody titres in volunteers receiving one of these vaccines intradermally according to the 2-2-2-0-1-1 schedule, were not satisfactory. This inaccurate report which was subsequently retracted, indicated low titres following intradermal postexposure prophylaxis with PDEV and equine rabies immune globulin (ERIG).

All members of the group stressed the following:

Licensing

None of the vaccines is licensed in any country for postexposure use by the intradermal route. In Germany, one reason for this is that there is no need to apply more than one postexposure treatment at any given time because there is only very rarely more than one person requiring postexposure treatment at any one time. None of the manufacturers plans to apply for a license for using its vaccine intradermally in a developed country. Nonetheless, these vaccines are accepted for use by the ID route in countries where they have been studied.

Application of Intradermal Doses

There was uniform agreement that intradermal postexposure prophylaxis should be applied only in specialized centres where a number of postexposure treatments are given each day, and not in small clinics where only a few treatments are administered each week. The relatively small number of doses applied at any time with the 2-2-2-0-1-1 regimen does not provide the margin of safety that the 4 and 8 site regimens provided. For example, there have been documented failures in the application of PPD by the ID route and BCG has been given incorrectly in Germany.

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It should, however, be noted that the Expert Committee indicated a number of precautions to be taken when using the ID route:

"Separate syringes and needles must be used for each dose. Intradermal injections should be administered only by staff who have been trained in this technique. Vaccine vials should be stored between 4°C and 8°C after reconstitution and the total contents should be used as soon as possible"

Stability and Sterility Following Reconstitution

None of these vaccines are produced in vials for multiple dose use, and only one, Purified Duck Embryo Vaccine (PDEV) contains a preservative (thiomersal). Although the stability of liquid after reconstitution is good, the warnings in the last WHO Expert Committee report to use the vaccine soon after reconstitution are appropriate since fatal infections have been observed following the contamination of similarly prepared (non-rabies) vaccines.

Immunogenicity and Efficacy of Tissue Culture Vaccines Applied by the Intradermal Route

The group reviewed published and unpublished data on the immunogenicity and efficacy of three tissue-culture and purified duck embryo vaccine, applied ID or intramuscularly (IM) in actual and simulated postexposure settings. Following are summaries of the experience of the three manufacturers represented at the meeting.

According to L. Teulières the extensive experience-acquired in Thailand with the purified vero cell rabies vaccine (PVRV) using the 2-2-2-0-1-1 schedule makes this vaccine the standard against which others should be compared. A number of articles on the immunogenicity and efficacy of PVRV have been published in scientific journals². The following Criteria for evaluating vaccines to be used according to a multisite intradermal schedule were suggested:

- Adequate virus neutralizing antibody (VNA) titres on day 14 after the first inoculation (all vaccinees should have titres > 0.5 IU/ml) ;
- Geometric mean (VNA) titres on day 14 should be compared to those elicited by PVRV;
- Virus neutralizing antibody titres should be maintained between day 30 and day 90;
- Vaccines should demonstrate their efficacy in field studies involving exposed patients (with laboratory confirmed exposure);
- Articles on these studies must be published in peer reviewed journals.

Dr Glück presented an analysis of results of the PDEV study involving altogether 180 volunteers made at the Queen Saovabha Memorial Institute in Thailand. An error in performing the RFFIT test was responsible for the initial report of low titres. In one experiment, three groups of 15 subjects each received ERIG and 0.1 ml ID doses (following the 2-2-2-0-1-1 schedule) of one of the three vaccines (PDEV, PVRV, or PCEC -purified chick embryo cell vaccine). The repeat titration of the sera (coded) revealed that the three groups had approximately equivalent VNA titres on day 30, but that titres in the group that received PDEV were significantly higher on days 7 and 14 (Day 7 $P > 0.001$, Day 14 $P > 0.05$). Similarly early detectable VNA titres were observed in parallel studies using PDEV applied according to the 2-2-2-0-1-1 (0.2 ml per site) ID schedule without ERIG and the conventional Essen IM regimen (1 ml per injection on day 0, 3, 7, 14, 28, 90).

Dr von Hedenström reviewed a number of published and unpublished studies with PCEC. A simulated postexposure study compared the immunogenicity of the 2-2-2-0-1-1 (0.1 ml) ID regimen to the conventional Essen regimen (1 ml dose on days 0,3,7,14,28,90). Titres were approximately equivalent on days 7 and 14 and somewhat higher with the IM regimen on days 30, 90, 180, and 365, no statistical comparison was presented.

The results of a published³ immunogenicity study with PCEC comparing two ID multisite (0.1 ml per site) regimens (i.e. 8-0-4-0-1-1 and 4-0-4-0-1-1) with the usual Essen regimen (full dose of 1 ml on days 0, 3, 7, 14, 28, 90) were discussed. Groups of volunteers received different combination of vaccine and immunoglobulin: vaccine alone according to the two above ID schedules, Vaccine "8 sites" plus HRIG or vaccine "4 sites" plus HRIG or ERIG. It is interesting to note that, although there were differences between similar doses according to whether or not IG was administered, there were no differences in antibody titre on day 14 between groups that received 8 doses on day 0 and those which received 4 doses on day 0, controlling for IG.

In a different study, data on PCEC administered ID according to the 2-2-2-0-1-1 with HRIG in 52 health volunteers were compared to PCEC administered ID alone. No suppression of active immunization was noted. All persons had detectable NVA at day 14 and during the year following the first vaccination.

The favourable comparability of PDEV, PCEC and PVRV was discussed at some length. Since PVRV is concentrated more than other vaccines, it would be expected that VNA titres would be higher with equivalent doses of this vaccine. A number of explanations of the similarity in response to these different vaccines were discussed:

1. As PVRV is reconstituted in 0.5 ml and PDEV as well as PCEC in 1 ml, different antigenic contents may be expected in 0.1 ml. Manufacturers of PDEV and PCEC reported that, to be released from the factory, both vaccines must have a minimum potency of 5 IU/dose (1 ml) after reconstitution. Batches of PVRV are released if their potency is ≥ 2.5 IU/dose (in 0.5 ml) after reconstitution. However, the average NIH potency of 30 batches of PVRV at time of release was shown to be 7.4 IU/dose with a minimum of 2.5 IU/dose for one batch. It was reported that the average potency of PDEV and PCEC is about 7 IU/dose. It can therefore be assumed that all three vaccines have very comparable average potency per dose at time of release and that this potency is far above the WHO minimum potency requirement of 2.5 IU/single immunizing dose. Theoretically, the average potency of 0.1 ml of PDEV and PCEC (0.5 to 0.7 IU per 0.1 ml) would be comparable to what would be expected from 0.1 ml of PVRV fulfilling WHO minimum requirements (0.5 IU per 0.1 ml).

2. Results of the NIH test do not correlate with immunogenicity in humans. It was pointed out that, following IM vaccination, minimum serological responses with a low potency lot of PDEV were equal/similar to those with higher potency lots.

3. It seems that there is a maximum in the dose-dependent response when these vaccines are given ID. Similar (maximum) responses can apparently be achieved by injecting less antigen than what is contained in 0.1 ml of PVRV. The immunogenicity of 0.1 ml of these vaccines may actually be similar.

Concluding statements

Dr Glück acknowledged recommendations made by expert committee on ID vaccination. He will try to see that the recommendations are followed. Taken together, the studies of PDEV to date are sufficient to predict that it fulfils minimum immunogenicity requirements when given ID in 0.1 ml doses by the 2-2-2-0-1-1 schedule. He will however continue to recommend the IM route, full dose and if the ID route is chosen higher dose will be recommended (e.g. 0.2 ml per site ID). The amount of experience and data acquired with PDEV given in 0.1 ml doses with ERIG following the 2-2-2-0-1-1 schedule will be increased. There are ongoing studies in China and the Philippines.

Dr Von Hedenström will try to increase the experience and data with PCEC in exposed patients (with proven rabies exposure). Postexposure treatment by the ID route will not be actively promoted, nor be included in the package insert, nor there will an attempt to get official approval for ID postexposure. It would however be useful to be able to provide physicians who choose to use the ID route with convincing data.

Dr Louis Teulières stressed that Pasteur-Mérieux does not recommend the use of PVRV by the intradermal route and has no intention to apply for licensure to use PVRV by the ID route for postexposure prophylaxis in any country. However, PVRV for ID postexposure treatment has been so far used in some 15,000 people in Thailand. More experience with other vaccines should be obtained to prove the acceptability of these vaccines for application by the ID route. Studies of the relation between immunogenicity and potency would also be of interest.

Final Conclusions

Data presented suggest that the immunogenicity of 0.1 ml ID doses of PVRV, PDEV and PCEC are comparable. However this observation is based on a single study with a small number of volunteers receiving each vaccine. The opinion of the group is that the Expert Committee recommendation does not require an erratum or revision at the present time. However, it is suggested that the following studies be conducted to further support existing recommendations:

Experience with the 2-2-2-0-1-1 schedule with vaccines other than PVRV is still very limited. More studies with 0.1 ml ID doses administered following the 2-2-2-0-1-1 schedule plus ERIG should be done on the vaccines for which there is less field experience than with PVRV. Particular attention should be paid to titres on day 14. As much as possible, a second vaccine (HDCV) applied IM, following the conventional Essen IM schedule with ERIG should be included for comparison.

To document that immunogenicity is satisfactory with lots of lower potency (minimum potency fulfilling manufacturers release requirement) investigators should conduct immunogenicity study with at least one lot of vaccine known to have low potency (e.g. 2.5 IU per ml). Ideally, the study should be made in one institute and compare the three vaccines (plus ERIG) with a control group administered HDCV and ERIG according to the Essen IM schedule.

To further explain an apparent discrepancy between antigenic content and immunogenicity, and to clearly define the margins of safety of the 2-2-2-0-1-1 schedule, a simulated dose response study using 0.05, 0.1, and 0.2 ml doses and the 2-2-2-0-1-1 schedule should be conducted, if possible with ERIG.

Given the uncertainties regarding the relation of antigenic value and immunogenicity, the presence of some differences between modern vaccines applied using the same schedule, and clear differences when vaccines are administered with and without immune globulin, future recommendations regarding the use of new vaccines with existing schedules, or new schedules, should be made only after careful review of data with the specific vaccine and schedule under consideration.

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