Intradermal pre-exposure rabies immunisation in New Zealand

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Summary

Background. Rabies is a fatal infection and immunisation is important to consider in those travellers going to rabies endemic areas. In those at high risk, a course of three immunisations may be given by the intramuscular (IM) or intradermal (ID) route, both of which are approved by the World Health Organization (WHO) and the Centers for Disease Control (CDC). Little is known in the New Zealand context regarding the effectiveness of pre-exposure ID rabies immunisation.

Methods. The data was collected prospectively on all travellers requiring the immunisation from July 2001 to September 2003 in Auckland. The standard WHO rabies immunisation protocol was used with three ID injections of 0.1 ml, given on days 0, 7, and 21 or 28 with a booster after 12 months. The vaccine used was the Pasteur Merieux human diploid cell vaccine (HDCV) or the Rabipur Purified chick embryo cell (PCEC) vaccine. Both vaccines are approved by the WHO and the CDC, and are interchangeable. Serology was performed approximately 2 weeks after completion of the primary immunisation course or after a booster, wherever possible. Antibody levels were measured using EIA, and levels of \( >0.5 \) IU/ml were considered protective.

Results. Of the 263 travellers assessed in this study, 125 were males and 138 were females. The mean age of the cohort was 34.8 years (SD = 11.7). There were not found to be any statistically significant correlations between age and antibody levels neither was there any significant association between gender and antibody levels. In addition to the sample group, a further 12 travellers had rabies serology performed but were excluded from the study because they had IM vaccines as part of their primary course. Whilst rabies serology ranged from 0.2 to 27.9 IU/ml in the study cohort, the mean antibody level for the group was 4.7 IU/ml (SD = 4.1 IU/ml). The mean antibody level for males was 4.3 IU/ml (SD = 3.3), and for females, 5.2 IU/ml (SD = 4.6). Of the 263 travellers, all had some level of detectable antibodies. The overall seroconversion rate was 95.1%.

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doi:10.1016/j.tmaid.2004.11.005
Conclusions. ID rabies immunisation appears effective, when given according to the standard WHO protocol, in New Zealand. ID rabies immunisation is also more affordable for travellers, especially those on a restrictive budget. ID rabies immunisation can continue to be recommended, particularly where follow-up serology can be done before travel and where there are staff who are experienced in ID immunisation.

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Introduction

Between 40,000 and 70,000 people die each year from rabies1 and about 90% of these deaths are reported in Asia.2 Rabies is an acute fatal encephalitis caused by neurotropic viruses in the genus *Lyssavirus*, family Rhabdoviridae.3 It can be transmitted to humans by the saliva of infected wild and domestic animals, usually dogs.1,3 An effective vaccine is available and, if administered before the onset of symptoms following a bite or lick of an open wound or mucous membrane from an infected animal, it normally prevents the infection developing.2 Because rabies is invariably a fatal disease once symptoms develop, an estimated 10 million people each year receive post-exposure immunisation after being exposed to rabies suspect animals. Such immunisations have traditionally been administered intramuscularly, which represents a huge cost on the economies of both developing countries and of intending travellers. To minimalise costs in the most efficient and effective manner, by administering vaccine by the intradermal route, would be an advantage to target populations.

Rabies is found in most countries of the world, especially in Africa and Asia, where the disease is endemic and account for more than 50% of the deaths due to rabies each year.2 In the Pacific Rim area, New Zealand, Australia, Papua New Guinea, the Pacific Islands and Japan are rabies free.4 Travellers from these countries may, however, be exposed to rabies when they travel to rabies endemic countries. Both the WHO5 and CDC6 recommend that those who are likely to be exposed to rabies travelling to endemic areas should be offered pre-exposure immunisation. This applies particularly to children who are regarded conservatively as being four times more likely to be bitten than adults in both developed and developing countries,7 and travellers who will be either engaged in remote regions in endemic areas or put themselves through high-risk activities, such as bicycling, caving, or working or living with warm blooded animals.4

Pre-exposure immunisation may be given either by the intra-muscular or intra-dermal route. Normally, the WHO recommends 1.0 ml IM or 0.1 ml ID doses which are administered into the deltoid region on days 0, 7 and 21 or 28.4 Serology is recommended 1-3 weeks following the course of vaccines.4 The ID route is preferable to many travellers as it reduces cost and discomfort, however, in Australia there is a requirement for serology to be undertaken following ID immunisation, which can result in delays and inconvenience.8 Whilst this is not yet so in New Zealand, it is increasingly considered an expected part of any consultation on rabies pre-exposure management.

At present, ID immunisation is largely restricted to dedicated travel clinics in New Zealand and Australia, even though current guidelines give ID immunisation as an option in the presence of post-immunisation serology. The restriction largely comes about partly because the immunisation is not presently licensed for ID use in these countries and dedicated travel health clinics have staff trained in giving ID immunisations, and partly because it needs to be administered according to the strict criteria that the WHO outline.5

Although some concerns exist concerning the effectiveness of ID rabies immunisation, a recent Australian study suggested that ID rabies immunisation is effective in the travel clinic setting, when given by trained nurses.9 Little is known in the New Zealand context regarding the effectiveness of pre-exposure ID rabies immunisation. This study was designed to investigate serological response to the standard course of three intradermal rabies vaccinations for pre-exposure immunisation for travellers from New Zealand.

Methods

The data was collected prospectively from July 2001 to September 2003 at a dedicated travel medicine clinic in Auckland, New Zealand. People presenting at the clinic included package tourists, backpackers, expeditioners, those going to work abroad, volunteer aid workers and humanitarian groups. Those going into risk areas, as previously noted, were offered rabies an ID immunisation.
Two hundred and seventy five consultations involved consultation and pre-travel management of rabies pre-exposure immunisation. Included in the cost of immunisation was the cost of having a rabies serological test to confirm WHO acceptable levels for immune status. All medical and nursing staff at the clinic are experienced in the ID rabies immunisation technique.

The standard clinic protocol for ID rabies immunisation is a course of three injections given on days 0, 7, and either on day 21 or 28. A booster is given after 12 months, with a recommended follow up serology 2 weeks later to confirm accepted serological protection. Future boosting is then dependant on monitoring further serology before travel abroad. The vaccines used for the immunisations were either the Pasteur Merieux human diploid cell vaccine (HDCV) or the Chiron Rabipur Purified chick embryo cell vaccine (PCECV).

Serology was offered to all travellers who had any ID vaccines as part of their primary course. It was also offered pre-booster at 12 months. Serology was normally recommended about 2 weeks after the primary course or after a booster to confirm immunity, which we have included as part of this study.

The blood samples were sent via courier on the day of collection to Lab Plus, the Auckland Hospital Laboratory doing the centralised testing. Antibody levels were measured using Enzyme Immuno-Assay (EIA) and levels of 0.5 IU/ml are considered protective. Results were generally available within 1 week, and all travellers were informed, by either phone or email, of their immune status at the earliest availability of serological results. For some, however, this meant part way through their travel. Whenever this occurred, travellers were advised to have a booster dose of cell-derived vaccine. Non-immune travellers, who had results to hand before they travelled, were asked to return for a further dose of ID vaccine, and any non-immune traveller overseas was advised that a full post-exposure series would be required for any adverse event. Those that were initially non-immune, and who had a further dose, were offered repeat serology 2 weeks later. Variations in the standard protocol for immunisation and time lag to serology were due to patient non-compliance or difficulty in returning to the clinic (e.g. patients living in remote areas or overseas). Travellers were excluded from the study if they had any IM injections as part of their primary course or as the booster.

Data was entered using the Statistical Package for the Social Sciences. Missing data has been excluded from analysis.

Results

A total of 263 travellers were included in this study. A further 12 had rabies serology performed but were excluded because they had IM vaccines as part of their primary course. The demographic characteristics of the travellers are given in Fig. 1. The mean age was 34.8 years (SD = 11.7). There were 125 males and 138 females.

An antibody levels in this study ranged from 0.2 to 27.9 IU/ml with a mean of 4.7 IU/ml (SD = 4.1). Some results were reported by the laboratory as ‘> 9’ or ‘> 8.8’ rather than as a specific titre. These were recorded as 9 or 8.8, respectively, rather than the true values. The mean antibody level for males was 4.3 IU/ml (SD = 3.3), and for females, 5.2 IU/ml (SD = 4.6) (Fig. 2). The overall mean antibody level after a primary course was 7.28 IU/ml and after a booster, 15.30 IU/ml. Of the 263 travellers, all had some level of detectable antibodies. The overall seroconversion rate (i.e. those that showed a level of 0.5 IU/ml or over, as per WHO criteria) was 95.1%. There were no statistically significant correlations shown to exist between age and antibody levels, neither was there any significant association found between gender and antibody levels (Fig. 2).
Discussion

This is the first New Zealand data to report on seroconversion rates after ID rabies immunisation. It has shown that ID rabies vaccine with either of the interchangeable WHO approved vaccines was very effective and had a seroconversion rate of 95.1%. This is consistent with other studies in Australia\(^8\) and the USA.\(^{12,13}\)

Whilst the mean rabies serology level is acceptable, it may in fact have been underestimated for two principle reasons:

- A significant delay in obtaining serological confirmation in a subset of the sample cohort, and
- The laboratory reporting of mean antibody levels as \(> 9\) or \(> 8.8\), rather than the true values.

As expected, in confirmation of other studies, there was neither an association between gender and serological titre nor was there any between age and serology.

It is well established that IM immunisation will give higher antibody titres than ID immunisation, using a similar schedule of 0, 7, 28 days.\(^6,14\) Nevertheless, this study has used the recommended WHO/CDC ID schedule\(^5,6\) on an intending travelling population from New Zealand.

Reported effectiveness of ID rabies immunisation is variable.\(^7,8\) Vaccinator’s skill in ID administration is a major factor in this. Another is the interval between the completion of the immunisation series and serological testing. A Thai study showed that the response to standard post-exposure treatment in previously vaccinated individuals was insufficient during the first 5 days, but that all had adequate levels by day 14.\(^{15}\) The same study also suggested that patients with high risk and severe exposure to rabies, and who have had prior pre-exposure ID immunisations, be treated for exposure to the disease as if they had not previously been

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**Table 1** Advantages and disadvantages of pre-exposure rabies immunisation.

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages of pre-exposure rabies immunisation</th>
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<tbody>
<tr>
<td>Provides psychological security for travel to endemic regions(^{16})</td>
<td>Cost a factor in compliance, especially with IM immunisation, although reduced with ID immunisation(^6,8)</td>
</tr>
<tr>
<td>Delays in post-exposure treatment are less crucial(^8)</td>
<td>Multiple doses are required, which travellers may not have time to complete prior to travel</td>
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<tr>
<td>Avoids the need for human or equine immunoglobulin(^6,8,16)</td>
<td>No licensed “rapid series” available for early departing travellers</td>
</tr>
<tr>
<td>Protects against anticipated exposure(^6)</td>
<td>Disadvantages specifically for ID rabies immunisation</td>
</tr>
<tr>
<td>Enables medical facilities to be reached before infection(^16)</td>
<td>Serology requires an extra visit to the clinic at 2 weeks and a further delay of a week for the results to be available</td>
</tr>
<tr>
<td>Simplifies post-exposure treatment(^16)</td>
<td>Limited availability of rabies serology</td>
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**Disadvantages**

- Further immunisation may be needed if antibody levels are low\(^8\)
- Local reactions may be higher with ID compared with IM immunisation\(^6,17\)
- Antibody level is reduced if ID rabies immunisation is given concurrently with antimalarials such as chloroquine\(^7,18\)
- Immunosuppression with concurrent steroids will effect immunity of ID rabies immunisation\(^6\)
immunised. It would be useful in future studies to examine any differences in serology between primary vaccinations and with that after boosting.

The advantages and disadvantages of pre-exposure rabies immunisation have been summarised in the Table 1

Conclusions

ID rabies immunisation appears very effective when given according to the standard WHO protocol in a cohort of intending New Zealand travellers. As ID rabies immunisation is more affordable for the majority of travellers, especially those on a tight budget, this result is very acceptable in considering rabies as a highly vaccine preventable disease. ID rabies immunisation is highly recommended for those at risk of exposure, particularly where follow-up serology can be done before travel and where there are staff who are experienced in ID immunisation.

References