17 Chandrasekaran S. Review on human leptospirosis. *Indian J Med Sci* 1999;**53:** 291–8.
18 Sharma S, Vijayachari P, Sugunan AP, Natarajaseenivasan K, Sehgal SC. Seroprevalence of leptospirosis among high-risk population of Andaman Islands, India. *Am J Trop Med Hyg* 2006;**74:**278–83.
19 Manocha H, Ghoshal U, Singh SK, Kishore J, Ayyagari A. Frequency of leptospirosis in patients of acute febrile illness in Uttar Pradesh. *J Assoc Physicians India* 2004;**52:**623–5.
20 Jauréguiberry S, Roussel M, Brinchault-Rabin G, Gacouin A, Le Meur A, Arvieux C, *et al.* Clinical presentation of leptospirosis: A retrospective study of 34 patients admitted to a single institution in metropolitan France. *Clin Microbiol Infect* 2005;**11:**391–4.

Is the skin sensitivity test required for administering equine rabies immunoglobulin?

M. K. SUDARSHAN, D. H. ASHWATH NARAYANA, H. S. RAVISH

ABSTRACT

Background. Rabies immunoglobulins are life-saving in patients with severe exposure to rabies. Despite the high degree of purification of equine rabies immunoglobulin (ERIG), the product inserts still recommend a skin sensitivity test before administration of this heterologous serum. A recent WHO recommendation states that there are no scientific grounds for performing a skin test before administering ERIG because testing does not predict reactions and it should be given irrespective of the result of the test. In this conflicting situation, we assessed the use of the skin sensitivity test in predicting adverse events to ERIG.

Methods. The data analysed were from the Antirabies Clinic of the Kempegowda Institute of Medical Sciences Hospital, Bengaluru, India. The period of study was 26 months (June 2008–July 2010). The skin sensitivity test was validated by evaluating its sensitivity, specificity, predictability, false-positive and false-negative results.

Results. A total of 51 (2.6%) adverse events were reported in 31 (1.5%) subjects. Most of these were mild to moderate in nature and subsided without medication. There was no serious adverse event. The sensitivity and specificity of the skin sensitivity test to predict an adverse event was 41.9% and 73.9%, respectively.

Conclusion. Our experience with the skin sensitivity test suggests that it may not be required before administering ERIGs, as recommended by WHO.

Natl Med J India 2011;24:80–2

Kempegowda Institute of Medical Sciences Hospital and Research Centre, V.V. Puram, Bengaluru 560004, Karnataka, India

M. K. SUDARSHAN, D. H. ASHWATH NARAYANA, H. S. RAVISH
Anti Rabies Clinic, Department of Community Medicine

Correspondence to M. K. SUDARSHAN; *mksudarshan@gmail.com*

INTRODUCTION

Human rabies is endemic in India. According to a recent WHO estimate, 55 000 deaths occur annually due to human rabies globally, 20 000 (36%) of which occur in India.[1] Rabies immunoglobulins (RIGs) are life-saving in patients with severe exposure to rabies. Human RIGs are imported, expensive and scarce. However, equine rabies immunoglobulins (ERIGs) are indigenously produced, less expensive and more widely available. Despite the high degree of purification of ERIGs, the product inserts still recommend a skin sensitivity test (SST) before administration of this heterologous serum.[2–4] This has brought disrepute to the product and, as a result, healthcare professionals are reluctant to use it. A recent WHO recommendation states that there are no scientific grounds for performing a skin test before administering ERIG, because testing does not predict reactions and it should be given irrespective of the result of the test.[5] It also suggests that the treating physician should be prepared to manage anaphylaxis which, although rare, could occur during any stage of administration.

Because of this recommendation, we studied the utility of SST in predicting adverse events to ERIG.

METHODS

The data analysed were from the records of the Antirabies Clinic of the Kempegowda Institute of Medical Sciences Hospital, Bengaluru, India. The period of study was 26 months (June 2008–July 2010). A total of 2008 patients had received purified, pepsin-digested ERIGs. The brands used were Equirab (Bharat Serums & Vaccines Limited, Mumbai) in 1560 (77.7%) patients; Abhayrig (Human Biological Institute, Hyderabad) in 404 (20.1%); Zyrig (Zydus Cadila, Ahmedabad) in 40 (2%) and Vinrig (Vins Bioproducts, Andhra Pradesh) in 4 patients (0.2%).

For the SST, 0.1 ml of sterile normal saline was injected intradermally using an insulin syringe (26G needle) into the flexor aspect of the right forearm. This raised a 5–6 mm orange skin-like induration (control injection). Similarly, 0.1 ml of ERIG was

taken in another insulin syringe and mixed with 0.9 ml of sterile normal saline in the same syringe; 0.1 ml of this 1:10 dilution of ERIG was injected intradermally into the flexor aspect of the left forearm, which raised another 5–6 mm size orange skin-like induration (ERIG test dose). A constant watch was kept on the pulse, blood pressure and respiratory rate of the patient for the next 20 minutes. The test was considered positive if there was erythema or a wheal of >10 mm in the left forearm only (test dose of ERIG) or any systemic reaction and the control arm showed no such local dermal reaction. A test was considered negative when there was no reaction in any of the forearms. A list was made of the brand of ERIG, result of SST and type of adverse event. 'Immediate reactions' were those that occurred within 30 minutes after administration of the full dose of ERIG, and included giddiness, vomiting and drowsiness. 'Delayed reactions' were defined as those that occurred within 28 days of ERIG administration. We calculated the sensitivity, specificity, positive and negative predictive value and false-positive and false-negative values of the SST.

RESULTS

Of the 2008 patients who received ERIGs, 31 (1.5%) reported a total of 51 adverse events (2.6%). All of these were mild to moderate in severity and most subsided without any medication (73%; Table I). The most common events were itching, fever, pain, rashes, headache, giddiness, vomiting, etc. No serious adverse event was reported. Adverse events were more frequent (58%) in those who had a negative SST. The SST had a sensitivity of 41.9% and specificity of 73.9% for predicting an adverse event. The predictive value for a positive test was 2.4% and that of a negative test was 98.7%. Of these, 26% were false positive and 58% false negative (Table II).

DISCUSSION

ERIGs appear to be reasonably safe. We encountered an adverse event rate of 1.5%, among which none was serious. Most of the adverse events were mild to moderate in nature and subsided without any medication. However, as ERIGs are of heterologous origin, they do carry a small risk of anaphylactic reaction (1/45 000 cases).[5–7]

The procedure for SST is cumbersome and time-consuming, especially in a busy healthcare facility. This may compel the hesitant and reluctant healthcare practitioner to give only the vaccine and skip the ERIG. This would leave the patient rabies prone as the vaccine alone cannot guarantee adequate protection in those with severe (WHO category III) exposures to rabies.

The immediate reactions that occur with the use of heterologous sera may be mediated by IgE and can be detected by SST (anaphylactic reactions), or are triggered by complement activation, non-immunological activation of mast cells or of modulators of arachidonic acid, and do not depend on previous exposure to antigens (anaphylactoid reactions). These are not detected by SST.

Generally, users of ERIGs in Brazil,[8] India,[9–11] Thailand,[12,13] the Philippines[14] and Sri Lanka[15] have found them to be quite safe. SST has been abolished in Brazil and WHO too does not advocate SST any more.[5] In this background of adequate evidence and appropriate recommendations, it is time that we also stop using SST for ERIGs. The producers of ERIGs, after approval of the regulatory authority, i.e. Drugs Controller General of India (DCGI) should modify the product insert by deleting the portion on SST. Consequently, ERIGs should be promoted as an 'institutional product' and given by trained persons in all first referral unit (FRU) hospitals, i.e. community health centres/*taluka*/*tehsil* hospitals and higher-level institutions in the government sector, as has been done with anti-snake venom serum. Healthcare personnel working in these facilities should be prepared to manage anaphylaxis which, although rare, could occur during any stage of administration of ERIG. Similarly, in the private sector, nursing homes, private hospitals, etc. which have similar facilities may provide ERIGs. This would promote the use of ERIGs and go a long way in reducing the burden of mortality due to human rabies in India.

TABLE I. Results of skin sensitivity test and adverse events in each patient who received equine rabies immunoglobulins

Patient	Skin sensitivity test	Adverse events
Immediate		
1	Positive	Giddiness, vomiting, drowsiness
2	Positive	Giddiness
3	Negative	Vomiting
Delayed		
4	Negative	Pain, rashes, itching
5	Positive	Rashes, itching
6	Negative	Pain, rashes, itching
7	Negative	Fever
8	Positive	Headache
9	Negative	Rashes, itching
10	Positive	Pain, fever, headache, giddiness
11	Positive	Rashes, itching
12	Positive	Rashes, itching
13	Positive	Itching, body ache
14	Positive	Pain, itching
15	Negative	Pain, itching
16	Negative	Fever
17	Negative	Fever
18	Negative	Pain
19	Positive	Pain
20	Negative	Fever
21	Negative	Fever
22	Positive	Headache
23	Negative	Swelling
24	Negative	Pain
25	Negative	Vomiting
26	Negative	Redness
27	Positive	Fever
28	Negative	Itching
29	Negative	Rashes, fever, chills, pain abdomen
30	Positive	Nausea, itching
31	Negative	Cough

Of the 51 adverse events, 35 occurred in 21 of 1560 patients who received Equirab and 16 occurred in 10 of 404 patients who received Abhayrig; p=ns (chi-square test)

TABLE II. Relation of adverse events to the results of skin sensitivity test

Skin sensitivity test	Adverse events		Total
	Present (%)	Absent (%)	
Positive	13 (2.5)	515 (97.5)	528
Negative	18 (1.3)	1462 (98.7)	1480
Total	31 (1.5)	1977 (98.5)	2008

Sensitivity 41.9%; specificity 73.9%; positive predictive value 2.4%; negative predictive value 98.7%; false positive 26%; false negative 58%

REFERENCES

1 Sudarshan MK, Madhusudana SN, Mahendra BJ, Rao NS, Ashwath Narayana DH, Abdul Rahman S, *et al.* Assessing the burden of human rabies in India: Results of a national multi-center epidemiological survey. *Int J Infect Dis* 2007;**11:**29–35.
2 Equirab Product Insert, Bharat Serums and Vaccines Limited, Mumbai, Maharashtra, India. Available at *http://www.bharatserums.com/pdf/equirab.pdf* (accessed on 15 March 2011).
3 Abhayrig Product Insert, Human Biologicals Institute, Hyderabad, Andhra Pradesh, India. Available at *http://www.indimmune.com/abhayrig.html* (accessed on 19 Apr 2011).
4 Vinrig Product Insert, VINS Bioproducts Ltd., Mahaboobnagar District, Andhra Pradesh, India. Available at *http://www.vinsbio.in/rabies2.html* (accessed on 15 March 2011).
5 Rabies vaccines: WHO position paper. *Wkly Epidemiol Record* 2010;**85:**309–20.
6 Wilde H, Chomchey P, Punyaratabandhu P, Phanupak P, Chutivongse S. Purified equine rabies immune globulin: A safe and affordable alternative to human rabies immune globulin. *Bull World Health Organ* 1989;**67:**731–6.
7 Suwansrinon K, Jaijareonsup W, Wilde H, Benjavongkulchai M, Sriaroon C, Sitprija V. Sex- and age-related differences in rabies immunoglobulin hypersensitivity. *Trans R Soc Trop Med Hyg* 2007;**101:**206–8.
8 Cupo P, de Azevedo-Marques MM, Sarti W, Hering SE. Proposal of abolition of the skin sensitivity test before equine rabies immune globulin application. *Rev Inst Med Trop Sao Paulo* 2001;**43:**51–3.
9 Sudarshan MK, Mahendra BJ, Ashwath Narayana DH, Sanjay TV, Anand Giri MS, Venkatesh GM. Evaluation of safety and efficacy of a new indigenous equine rabies immunoglobulin. *J Assoc Prev Control Rabies India* 2006;**8:**13–16.
10 Sudarshan MK, Kodandaram NS, Venkatesh GM, Mahendra BJ, Ashwath Narayana DH, Parasuramalu BG. Evaluation of a new premedication protocol for administration of equine rabies immunoglobulin in patients with hypersensitivity. *Indian J Public Health* 2007;**51:**91–6.
11 Mahendra BJ, Sanjay TV, Ashwath Narayan DH, Sudarshan MK. Rabies immunoglobulins in post-exposure prophylaxis: Study of 236 subjects. *J Assoc Prev Control Rabies India* 2003;**5:**26–33.
12 Tantawichien T, Benjavongkulchai M, Wilde H, Jaijaroensup W, Siakasem A, Chareonwai S, *et al.* Value of skin testing for predicting reactions to equine rabies immune globulin. *Clin Infect Dis* 1995;**21:**660–2.
13 Wilde H, Chomchey P, Prakongsri S, Punyaratabandhu P. Safety of equine rabies immune globulin. *Lancet* 1987;**28:**1275.
14 Quiambao BP, Dy-Tioco HZ, Dizon RM, Crisostomo ME, Teuwen DE. Rabies post-exposure prophylaxis with purified equine rabies immunoglobulin: One-year follow-up of patients with laboratory-confirmed category III rabies exposure in the Philippines. *Vaccine* 2009;**27:**7162–6.
15 Kularatne SA, Gihan MC, Jameel AM, Wimalaratne O. Outcome of skin sensitivity testing for predicting reactions to rabies equine immunoglobulin. *Ceylon Med J* 2007;**52:**149.

KIDNEY TRAY

Some years back, Bengaluru achieved the dubious distinction of being the capital of clandestine kidney transplants. New and stricter regulations have made the procedure more transparent now. Those days, kidneys were procured for a price from poor donors. Slumlords were known to even coerce people to donate their kidneys for a commission. There was much hue and cry in the press and surgeons, too, came in for a fair bit of justified criticism. There were widespread rumours that kidneys were being removed from ignorant poor people who got admitted for some other reason. It was against this background that the following incident occurred in one of the hospitals. A patient was admitted for a minor procedure, i.e. to have an abscess drained. This was being done under local anaesthesia. After giving the local anaesthetic, the surgeon proceeded to incise the abscess. No sooner had he inserted the knife than a stream of pus welled out of the cut. To prevent spillage, he told the nurse with some urgency, 'Quick, get me the kidney tray.' The horrified patient jumped and ran out of the room. It took the combined might of 3 attendants and the surgeon to convince the patient that 'kidney tray' refers to a receptacle and it is not a tray to hold the kidney.

News of this incident spread to all the hospitals in Bengaluru and it sounded a warning not to mention the dreaded word in front of conscious patients undergoing procedures!

B. C. RAO, *Bengaluru, Karnataka*
A modified version was first published in Dr B. C. Rao's blog