CHAPTER 1

INTRODUCTION

Hyperimmune serum has been used to prevent and treat hepatitis B, botulism, diphtheria, gas gangrene, tetanus, snake bite and rabies, etc.(1,2,). Antisera may be obtained from human or animal sources. Horse antiserum is the most commonly used heterologous antisera in clinical practise (3). It is much cheaper than human antisera because of the relative ease of production. However, heterologous antisera frequently result in complications (4). The complication may arise from a single injection of foreign serum but more commonly occurs in the patients who have previously been injected with protein from the same or related species. Reactions range in severity from local reaction to systemic anaphylaxis whereas anaphylaxis and serum sickness are the 2 major allergic reactions commonly recognized with the administration of heterologous serum (5).

Anaphylaxis or immediate hypersensitivity is IgE-mediated reaction. It may be local (such as urticaria, bronchospasm, etc.) or systemic affecting several organ

systems simultaneously. Systemic anaphylaxis usually occurs rapidly and may result in death through respiratory obstruction or irreversible vascular collapse (6). It is the result of a foreign antigen (horse serum) reacting with IgE antibody bound to mast cell or basophils. The binding of antigen crosslinks adjacent IgE antibodies, causing an explosive degranulation of mast cells and basophils with release of preferined and newly synthesized chemical mediators with vasoactive and inflammatory properties which account for most of the pathophysiologic changes in anaphylaxis (7,8,9,10).

Incidence of anaplhylaxis following heterologous antivenom ranges from 3% to 54% (11). Moynihan et al. and Black et al. reported that incidence of serum sickness following equine tetanus antitoxin and botulinal antitoxin was 2 in 7580 (0.0002%) and 5 in 268 (2%) respectively (12,13).

Serum sickness is a systemic type III immune complex complement dependent reaction to an extrinsic antigen. The classic manifestations include fever, cutaneous eruption, lymphadenopathy and joint symptoms (14,15). It frequently occurs after the administration of heterologous antiserum but may also occur with drugs,

infections and neoplasm. Exposure to large dose of protein antigens will elicit a brisk IgM and IgG antibody response (1). Antigens and antibodies will from complexes. At certain sizes or molar makeups of the antigen-antibody complexes, the complexs may deposit on the vascular linings of various organs and initiate fixation and activation of complement resulting in inflammatory tissue damage (1,3,16).

Von Pirquet and Bela Schick first recognized this delayed allergic response to horse diphtheria antitoxin in 1905. Many reports have followed, confirming the existence of such nonfatal, delayed allergic response to foreign serum (17-29). The incidence of serum sickness following the administration of heterologous serum varies from one report to another depending on the amount and type of serum used (3,13,17,30). If 5 to 10 ml of equine tetanus antitoxin was injected 5% to 10% of the treated patients might develop serum sickness, whereas 80 ml would almost always produce serum sickness (1). Incidence of serum sickness following equine botulinal antitoxin is approximately 4%. Hosty and Hunter (1953), and Karliner and Belaval (1965) reported that the incidence of serum sickness after receiving antirabies horse serum was 15.6% and 16.3% respectively (17,19). Wilde et al (1989) studied the adverse effects of eqine rabies immune

globulin (ERIG) manufactured by Pasteur, Swiss Serum and Vaccine Institute, and Scalvo in Thai patients and found that the incidence of serum sickness was 0.87%, 6.19% and 3.58%, respectively (20,21,22). The difference may be attributed to the purification and the protein content of the ERIG preparations. The processes of gamma globulin purification of ERIG from various manufacturers are different and it was found that pasteur's ERIG contained the least amount of protein per unit of ERIG activity, followed by Scalvo and Swiss Serum respectively (Wilde et al, unpublished observation).

Rabies remains a major public health problem in developing countries. In Thailand, over 100,000 persons are given post-exposure rabies prophylaxis every year, and 250-300 rabies deaths are reported annually (21). The combined administration of rabies vaccine and hyperimmune serum in post-exposure prophylaxis is widely accepted. This regimen provides early passive immunity as a result of the heperimmune serum, subsequently followed by active immunity as a result of the response to the vaccine (4,5).

There are 2 sources of rabies immune globulin, namely equine rabies immune globulin (ERIG) and human rabies immune globulin (HRIG)(4). HRIG is the product of choice but its high cost precludes most of the Thai

patients from receiving it. Therefore, more than 95% of the Thai patients have to receive ERIG for treatment (21).

The Queen Sauvabha Memorial Institute (QSMI) of the Thai Red Cross Society in Bangkok treats 1200-1400 patients every month for post-exposure rabies prophylaxis. Every patient will receive a course of tissue culture rabies vaccination and approximately 30% will also receive rabies immune globulin (RIG). ERIG was used in 95% of cases and HRIG was used in the other 5% of cases (21).

Prior to the administration of ERIG, it is the accepted practice to perform skin test on the patients for any evidence of IgE-mediated reaction to equine globulin (1,10). If skin test is positive, HRIG will be highly recommended to replace the use of ERIG or, ERIG will have to be administered under close observation in places well equipped for emergency resuscitation (10,20,31,32). However, many authors have challenged the value of such allergic skin testing (21).

Therefore it is the purpose of this study to evaluate the correlation of specific IgE antibodies to horse gamma globulin with the skin test results and the clinical outcome of ERIG administration. In addition, IgM and IgG antibodies to horse gamma globulin were also

sequentially followed in 104 patients following ERIG administration. This was aimed to study the usefulness of these antibodies to predict and to diagnose serum sickness following administration of equine immune globulin.