CHAPTER I

Introduction

1.1 General introduction

Serum sickness was originally described as a clinical self-limited syndrome that occurred after the injection of heterologous or foreign protein or serum into human beings.

It is the human equivalent of experimental immune complex diseases (1). Equine antisera are still in clinical use in many parts of the world to treat conditions ranging from allograft rejection to snake bite and rabies. In Thailand, although human rabies immune globulin (HRIG) has been commercially available for over 10 years but the majority of Thai patients still need to receive equine rabies immune globulin (ERIG) for post-exposure treatment due to their financial constraint. Approximately 360-420 patients receive ERIG at the rabies clinic of the Queen Saovabha Memorial Institute (QSMI) monthly (2).

Anaphylaxis and serum sickness are the 2 major serious side-effects associated with the administration of equine or any other heterologous serum proteins. Rate of occurrence of serum sickness reported in many studies were as high as 46% (3). in Thailand, the incidence of serum sickness was found to be only 0.87% and 1.6% in a prospective and retrospective study respectively (3,4).

1.2 Serum sickness

Serum sickness was first deseribed in man by Clemens Von Pirquet and Bela Schick in 1905 (5). Later, large restrospective clinical studies such as those of Kojis (8) and other (6,7) confirmed the observations of Von Pirquet and Schick that there was such clinical syndrome as complication of the administration of foreign serum.

True serum sickness is a relatively rare occurrence today. This is due to the less frequent use of foreign serum,the effective antibiotic therapy, the better immunization coverages and the development of specific antiserum of human origin (9,10). The incidence and severity of serum sickness are definitely related to the type of serum employed and the volume administered (10-14). Pretreatment with antihistamines may diminish the expression of serum sickness (15).

Serum sickness like reactions most commonly occur secondary to the administration of non-protein drugs. It is clinically similar, if not identical, to classic serum sickness (9,10). The most common drugs responsible for serum sickness are penicillin, sulfa, thiouracils, cholecystographic dyes, hydantoins, aminosalicylic acid, dextran, hydralazine, cephalosporins, propanolol, matronidazole and phenylbutazone (10,16).

The relationship of immune complex formation and the development of clinical manifestations in serum sickness is well documented. The individuals will generate antibodies to the antigens,usually to the IgG or IgM class, after a latent period of four to ten days (10,11). The antibody will form complexes with the antigen. The rise in the immune complex levels is accompanied by a decrease in the serum level of C3 and C4 and increase in C3a/C3a des-arginine, a split product of C3 suggestive of complement activation by the immune complexes. These observations are quite similar to those described in animal models of serum sickness(17). Immune complexes are usually rendered harmless by the mononuclear phagocytic system, formerly referred to as the reticuloendothelial system, and only when they deposit in the vessel walls with subsequent inflammatory response is responsible for the widespread vasculitic lesions seen in serum sickness (17,19,20). Immune complexes are deposited in areas of increased vascular permeability. The deposition of immune complexes may be blocked by antihistamines such as hydroxyzine (16,18).

Clinically, serum sickness is manifested by fever, cutaneous eruptions , lymphadenopathy and arthralgia / arthritis. Some feel that at least two or three of these manifestations should be present before the diagnosis can be made (10). It is often associated with proteinurea but

without other evidences of glomerulo nephritis. In human, clinically significant renal disease is relatively rare (34). The diagnosis of serum sickness is based primarily on clinical ground (16). When an individual has received foreign proteins or non-protein drugs and, within the appropriate time interval,the classic symtom complexes of serum sickness are manifested, the diagnosis of serum sickness should be readily apparent. Since there is no abnormality that will be universally present, nor there is any single laboratory test that will be definitely diagnostic (16),it is important to realize that the signs and symtoms of serum sickness may be similar to those of a wide variety of inflammatory or infectious diseases (34). Should symtoms persist for longer than month, the diagnosis of serum sickness should be reconsidered (9). Serum sickness is a classic example of immune complex mediated disease. Immediate hypersensitivity may also play a role 2 by enhancing the immune complex deposition (16). Urticaria in serum sickness reactions may be mediated either by IgE or by complement activation (15,16). Pretreatment with antihistamines diminishes the expression of serum sickness, which suggest most cell or basophil mediator release as a mechanism(15).

Anaphylaxis is another serious side-effect occuring after administration of heterologous proteins. Therefore, skin test has to be done before giving foreign serum. The

incidence of positive skin test to equine serum globulin by intradermal test varies from 5% to 23% (2,3,21,22,23). Some patients with positive skin test did not have anaphylaxis after administration of foreign sera whereas some had anaphylaxis in face of negative skin test (21,22,23,25).

The objectives of this study are to study the incidence of serum sickness following the administration of equine rabies immune globulin and the associated with the administration of ERIG, namely C3, CIC and heterophile antibody in order to find out whether these changes will be the diagnostic for serum sickness. The study will also look at the value of immediate skin test in predicting anaphylactic reaction from ERIG administration.