The uses of gamma globulin in the prevention of virus diseases

by Dora S. K. Tan

Virus Research Officer,
Institute for Medical Research,
Kuala Lumpur.

ON MANY AN OCCASION, the clinician finds himself faced with a situation in which his client has been exposed to a highly infectious virus disease, where the use of vaccine would be too late to prevent the infection and where, if he does become infected, serious consequences are likely to result.

Chemotherapy of viral diseases is still very much in the experimental stage and even then, is applicable to only a very limited range of virus diseases. The only resort left to the clinician under these circumstances would be to give immune or hyper immune gamma globulin with its high concentration of specific antibodies. Unfortunately, the limited availability and the high cost of human immune globulin precludes its use by the general public.

The virus diseases which have been subjected to treatment with gamma globulin may be dealt with under three categoris:

1. Those which can be modified or prevented by gamma globulin:
   (a) Infectious hepatitis
   (b) Serum hepatitis
   (c) Rubeola (measles)
   (d) Varicella (chickenpox)
   (e) Variola (smallpox) and vaccinia
   (f) Mumps
2. Those which give equivocal results with gamma globulin and require further investigation:
   (a) Rubella (German measles)
   (b) Rabies

3. Those which are generally not affected by gamma globulin:
   (a) Poliomyelitis
   (b) Influenza.

Infectious Hepatitis

Infectious hepatitis, like poliomyelitis, occurs most often in children and may have a latent, mild and anicteric course. In fact, it may be so mild in children and young infants as to escape notice altogether. The disease is detected usually by the presence of icterus while inapparent infections have been detected on the basis of elevated serum transaminase activity. In Asian countries, the prevalence of hepatitis has been estimated to be 1% to 2% in recent studies using liver biopsy as well as the other criteria mentioned above (cited from Editorial, J.A.M.A., 1969).

Over the past 25 years or so, a number of studies have demonstrated the efficacy of gamma globulin in modifying the clinical features of infectious hepatitis without reducing the attack rate when administered during the incubation period (20-40 days). Wart et al. (1960) found that gamma globulin can be effective even when given as late as 6 days before onset of the disease.

Yarrow (1964) reported the efficacy of gamma globulin in bringing to a quick end an outbreak of infectious hepatitis in a rural school. It has also been found that a single dose of gamma globulin given to intending travellers protects them for about 6 months (Pollock & Reid, 1969). Peace Corps volunteers, given semi-annual injections of 0.05 ml. of immune serum globulin per pound of body weight, showed a marked reduction of cases over those unprotected (Woodson & Clinton, 1969).

Groups of children inoculated with gamma globulin and subsequently heavily exposed to hepatitis virus under endemic conditions over a period of several months sustained a more permanent protection (Krugman & Ward, 1961-62) as the partial passive protection is supplemented by active immunity.

Doses of 0.06 to 0.12 ml./lb given intramuscularly are protective. As passive immunity conferred by gamma globulin lasts from 3 to 6 months, the administration of gamma globulin every 4 months to western travellers to the east for prolonged periods would give adequate protection from infectious hepatitis.

Serum Hepatitis

The effect of gamma globulin on serum hepatitis is similar to that on infectious hepatitis in that the course of the illness is modified and the incidence of jaundice reduced without a reduction in the attack rate itself (Mirick et al., 1962). The use of gamma globulin in conjunction with transfusion significantly reduces the severity of post-transfusion hepatitis.

Statistical data concerning morbidity and mortality associated with post-transfusion hepatitis (Allen & Sayman, 1962) suggest that serum hepatitis is a very dangerous disease for patients over forty years of age. However, it is not practicable to give gamma globulin with every tranfusion with the present inadequate supply of gamma globulin. In specific cases, the dosage recommended is 2 doses of immune globulin, 10 ml. each one month apart, with the first dose given within a week after the blood transfusion (Grossman et al., 1945).

Rubeola (Measles)

Measles has been recognised as a clinical entity for at least 1,900 years and has generally been accepted as an inevitable feature of childhood. Although it is usually mild and therefore often treated with contempt, its dangers, especially for malnourished and debilitated children and for young infants, are real.

The past ten years have seen great strides in the development of measles vaccines and countless trials of these vaccines have been conducted. However, they still remain relatively expensive and produce many reactions not experienced with vaccine for other diseases. Moreover, it is still not known how long the effect of the several vaccines lasts and vaccination may merely postpone the attack of measles to another year and not prevent it altogether.

Although immune human globulin has no therapeutic value, it is usally effective in preventing or modifying measles when given soon after a known exposure. Its administration is indicated for the following groups of people exposed to the risk of catching measles;

(a) young children, especially those below 1 year of age,
(b) malnourished and debilitated children, and
(c) children with chronic medical conditions undergoing steroid therapy.

The choice of dose and time of injection of globulin is usually based on whether prevention or attenuation is desired. It is frequently believed that the resulting immunity is only transient if no sign of the disease appears and that a modified form of measles, rather than total prevention, should be aimed at. However, as the available data

supporting this view have not been convincing because most of the investigations of immunity were short-term studies, this presumption remains controversial.

To prevent overt disease, it is recommended that a dose of 0.1 ml/lb be given within 5 to 6 days after exposure to the infection. If a modified form of measles is desired, 0.02 ml/lb may be given, also within 5 to 6 days after exposure.

Varicella (Chickenpox)

Although chickenpox is usually a relatively mild disease, it sometimes tends to be more serious with generalised systemic involvement in the young adult and infant 6 months old or younger. Prevention or modification of the disease is therefore highly desirable in such cases.

Several reports of the use of gamma globulin in individual cases have been made since 1948 but none of these were controlled observations. Ross (1962) conducted a significant study and established that human immune serum globulin given to exposed contacts will modify but not prevent varicella. He suggested that gamma globulin should not be administered to exposed normal susceptible children or routine household contacts but should be reserved for contacts in which varicella has a high risk. These are neonates and infants less than 6 months old and individuals with a blood dyscrasia or those on alkylating, antimetabolite or high-level steroid therapy. He pointed out that although administration of gamma globulin to aduts with no prior history of chickenpox might be valuable if he should contract chickenpox, an enormous amount of gamma globulin would also be wasted in this way, owing to extreme unreliability of histories of adults.

Recommended dosages range from 0.1 to 0.6 ml/lb depending on the degree of risk involved. The material is available only from very limited resources even at the present time.

Variola (Smallpox) and Vaccinia

The chief indications for the administration of hyperimmune gamma globulin in the prevention of smallpox are in post-exposure cases where vaccination would be too late to prevent the disease and in children with chronic dermatitis where vaccination may cause serious complications. It is also of great value in the treatment and prevention of generalised vaccinia, vaccinia gangrenosa and eczema vaccinatum; and in the prophylaxis of post-vaccinal encephalitis.

Serious complications of vaccination tend to occur at or just after the height of primary vaccination. In uncomplicated vaccination, this period coincides with the presence of antibodies which help to prevent the development of viraemia likely to cause complications. However, in some children, this antibody response is absent or inadequate, and vaccination tends to result in viraemia with the subsequent appearance of peripheral lesions. It is presumed that the administration of passive antibody in the form of hyperimmune vaccinal gamma globulin provides sufficient antibodies to terminate viraemia promptly and prevent development of further lesions until the patient develop his own antibodies, if he can. There is, however, no clinical evidence that hyperimmune vaccinal gamma globulin influences the course of vaccinal encephalitis for the better.

Hyperimmune vaccinal gamma globulin may also be given prophylactically to children suffering from eczema and requiring vaccination for overseas travel, after exposure to vaccinated siblings or in the event of a smallpox epidemic in the community. It has been shown that 2 ml. of hyperimmune gamma globulin one or two days before vaccination does not interfere with active immunisation (Grispen et al., 1956).

As the severity of smallpox relates directly to the quantity of the virus liberated in the blood, the object of administrating the gamma globulin in the prevention of smallpox in closed contacts is to reduce or prevent viraemia at the end of the 12-day incubation period of smallpox. Trials using immune gamma globulin prepared from serum of recently vaccinated adults and conducted on close contacts of smallpox cases in Madras showed that the incidence of smallpox in those given the gamma globulin was about a quarter of that in the control contacts — a statistically significant difference (Kempe et al., 1961). However, Downie et al., (1961) found that the antibody levels in gamma globulin, prepared from convalescent serum, were 20 to 100 times higher than those prepared from serum of recently vaccinated subjects and therefore recommend the use of the former in preference to the latter. Ordinary gamma globulin contains less neutralising antibodies than hyperimmune vaccinal gamma globulin.

The usual recommended dosages for hyperimmune vaccinal gamma globulin is 0.2 ml/lb in adults, 0.05 ml/lb in children and from 0.1 to 0.2 ml/lb in infants under 1 year of age.

An effective chemoprophylactic agent in variola and vaccinia is methisazone (Marboran) the dosage of which is 2-4 gm daily orally for 2 days beginning 1-2 days after exposure.

Mumps

Prevention of mumps in children is not considered of great importance because, as a rule, the disease is mild in childhood and leaves a lasting immunity. The main indications for passive or active immunisation are in adults in whom orchitis and other "complications", e.g. encephalitis and meningitis, are more frequent and troublesome.

About 40% of all mumps infection are inapparent and many adults with no history of past experience may, nevertheless, be immune. In susceptible adults, even transitory protection is desirable after exposure to mumps. This may be achieved by passive immunity in the form of concentrated gamma globulin prepared from convalescent serum which has been shown to be of some value in preventing the development of orchitis if given after the onset of parotitis. (Gellis et al., 1945). Concentrated normal gamma globulin has proved to be of no value under these circumstances.

Treatment of established orchitis and meningitis has been attempted but with equivocal results. It is thought that once the virus has caused cellular injury, a procedure of this sort would not prove to be efficacious.

Durable immunity for 3 years, following vaccination of children with Jeryl Lynn strain live mumps virus vaccine, has been shown by Weibel et al., (1969) who observed that the pattern for mumps antibody persistence after vaccination paralleled that following natural mumps infection. Moreover, the vaccinated children developed CF antibodies against both the soluble (S) and the viral (V) antigens indicating that the resulting immunity equates with that of natural mumps infection.

Rubella

The problem of rubella prophylaxis, from the practical viewpoint, concerns primarily the management of the woman who is exposed to rubella during the first trimester of pregnancy. Although "normal" and "rubella convalescent" pools of gamma globulin have been found to contain significant levels of rubella antibody (Krugman, 1963; Schiff et al., 1963) the use of gamma globulin has been attended with equivocal results.

While earlier studies (Krugman & Ward, 1958; Lundstom et al., 1961), performed before the development of more reliable laboratory methods for assaying the rubella antibody, indicated some efficacy in the prevention of rubella in administrating large doses of gamma globulin to pregnant women exposed to the disease, more recent studies have shown otherwise. Krugman (1963) found that the administration of immune globulin known to contain rubella antibody to children within 24 hours of exposure showed no protective effect. Moreover, as the rubella virus may be recovered from pharyngeal secretions as early as 7 days before the appearance of the rash, gamma globulin, even if effective when given prior to the development of the rash, may have limited value for a pregnant woman who is in continuous daily contact with a child incubating rubella. A recent study by the Public Health Laboratory Service Working Party on Rubella (1970) revealed that immune globulin of known antibody content given to 5,449 pregnant women after exposure to rubella, did not appear to affect the incidence of rubella when compared with an uninoculated group of 652 adult women exposed to the same risk.

There is, therefore, no definite recommended course of action to take in the management of the pregnant woman who contracts rubella during the first trimester. The alternate long-term prophylactic measure is vaccination with the attenuated live vaccine virus. Even then, caution in the use of this vaccine must be exercised. Because it contains a live virus likely to affect foetal formation, care must be taken not to give it when the woman is in the first 4 months of pregnancy and the vaccinated woman must practise birth control for at least 3 months after inoculation. As it is difficult for a married woman to know whether or not she is pregnant during the first month of her pregnancy, the vaccine should be given only to women after medical consultation to ensure that they are not pregnant and to girls on reaching puberty. The male population and children may be left unvaccinated to allow the virus to circulate among them, as natural infection is a much better barrier to reinfection than vaccination.

Rabies

Possibilities for obtaining convalescent-phase serum from persons who have had active immunisation after bites from suspected rabid animals exist. Hosty et al. (1959) prepared human gamma globulin from serum of volunteers inoculated with duck-egg inactivated vaccine followed by attenuated chick-embryo vaccine and found that on administrating the human immune globulin, the decline in circulating antibody was more gradual than with horse anti-rabies serum although the passive antibody levels were much higher with the more potent horse serum than the weaker human anti-rabies gamma globulin. Further work is required to achieve the preparation of a more potent human immune globulin.

Poliomyelitis

The course of poliomyelitis is not altered by convalescent serum or gamma globulin. The present availability and effectiveness of the vaccines, killed or live, precludes the use of any other material for the prophylaxis of this disease.

Influenza

Extensive studies by the Commission on Influenza (1943) with large inhalation of sprayed human convalescent serum followed by induced infection showed no evidence of protection from or therapeutic effect on influenza.

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