Preliminary Report

COMPARISON OF TWO DOSES OF GAMMA GLOBULIN IN PREVENTION OF INFECTIOUS HEPATITIS

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THE USE of gamma globulin in the prevention of clinically detectable infectious hepatitis has been studied many times in institutional populations (*1–3*) and in families in the general population (*4–6*). With a few exceptions (*7*), the studies conducted in the general population have dealt with epidemic situations. Repeated investigations have shown that 0.01 ml. gamma globulin per pound body weight is effective in prevention of clinically discernible infectious hepatitis (*5, 8, 9*). We have found only three studies reported that tested the dosage of 0.005 ml. per pound of body weight. Two of these were performed during institutional outbreaks (unpublished data of H. Holzer and associates and *10*) and the other during an epidemic in the general population (*11*).

The supply of gamma globulin continues to fall far short of the need. Furthermore, there is little indication that the supply will be increased appreciably or the demand reduced in the near future. The recent revival of interest in the administration of gamma globulin to persons receiving blood transfusions adds new weight to the problem. Therefore, use of the smallest effective dose in each situation is to the best interest of all concerned. This study was designed to compare the efficacy of 0.01 ml. and 0.005 ml. of gamma globulin per pound of body weight in prevention of infectious hepatitis with jaundice among household contacts of reported cases in the general population over a 2-year period.

Method of Study

The Memphis and Shelby County Health Department, Memphis, Tenn., offers gamma globulin to household contacts of reported cases of infectious hepatitis in families unable to pay for this service. Private physicians in the community have been informed of the service, and, owing to the high cost of the material, a large percentage of private patients and all of the medically indigent receive gamma globulin for prophylaxis against infectious hepatitis from the health department.

Gamma globulin is administered only in the central health department communicable disease clinic. Beginning on July 1, 1962, when persons or families entered the clinic to receive gamma globulin, each name was listed in order of decreasing age. A coin was flipped to determine whether a 0.01-ml. or a 0.005-ml. dose of gamma globulin per pound of body weight was to be given to the first contact listed for each primary case. The doses administered to the remaining contacts were alternated, and this procedure was repeated with each group of contacts. To calculate the dose, each person was weighed fully clothed.

The interval between diagnosis of the index case and administration of gamma globulin to the contacts was not tabulated; however, in each instance an attempt was made to make this time as short as possible. This interval was usually less than a week and rarely over 2 weeks.

The signs of clinical jaundice were described to each treated contact, and he was instructed to notify the health department if any sign of jaundice developed. On notification, a research assistant, a junior medical student who was unaware of the dosage administered, visited the

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Table 1. Results of prophylaxis against infectious hepatitis in household contacts, by sex, race, and dose of gamma globulin

Dose of gamma globulin (per pound body weight)	Sex		Race		Lost cases		Hepatitis with jaundice	Total [1]
	Male	Female	Negro	White	Number	Percent		
0.01 ml	220	238	194	264	44	8.8	1	458
0.005 ml	214	215	188	241	46	9.7	1	429
Total	434	453	382	505	90	9.2	2	887

[1] Excluding patients lost from observation.

patient. He completed a checklist of clinical findings and obtained a specimen of urine, which was tested for the presence of bilirubin by the Ictotest tablet method. The patient's condition was graded as no jaundice, equivocal jaundice, or definite jaundice. Followup contact with recipients of gamma globulin was made by telephone or home visit 60 days and again 6 months following the injection to determine if jaundice had occurred. All contacts who developed jaundice after receiving gamma globulin were considered secondary cases and were included in the results. No effort was made to identify anicteric hepatitis.

Results

From July 1, 1962, to the end of October 1963, a total of 1,387 household contacts were seen in the clinic and all received injections of gamma globulin. Followup has been completed on 977 contacts, and this preliminary report is based on 887, those for whom information is available. A total of 90 contacts, 44 in one group and 46 in the other, were lost from observation.

The two samples were similar in terms of sex, race, and proportion lost from observation (table 1). The age group 1 through 14 years was slightly larger in the sample receiving the 0.01 ml. dose than in the other sample (table 2). The probability is 0.09 that a difference this great would occur on a chance basis with random selection as used in this study.

One case of infectious hepatitis occurred in each study group. LA, a 13-year-old Negro girl, received 0.01 ml. gamma globulin per pound body weight on April 17, 1963, 1 day after her brother was diagnosed as having infectious hepatitis. On September 21, 1963, about 5 months after receiving gamma globulin, LA was admitted to the hospital with a severe case of hepatitis, and she died 16 days after admission. A diagnosis of viral hepatitis was confirmed by autopsy.

DB, a 7-year-old Negro boy received 0.005 ml. gamma globulin per pound body weight on July 19, 1963, when his mother was diagnosed as having infectious hepatitis. At the time of the routine 2-month followup visit, DB was recovering from an illness with jaundice, which had begun approximately 2 weeks previously. He had unequivocal clinical jaundice and a strongly positive test for urine bilirubin.

Discussion

Since our clinic is a service institution, it was not considered advisable to include a group of controls treated with placebo in the study. Had there been a marked difference in the frequency

Table 2. Age distribution of household contacts of persons with infectious hepatitis, by dose of gamma globulin received

Age groups (years)	Dose of gamma globulin (per pound body weight)		Total
	0.01 ml.	0.005 ml.	
Under 1	18	4	22
1–4	73	48	121
5–9	105	95	200
10–14	45	52	97
15–19	42	31	73
Over 20	175	199	374
Total	458	429	887

of hepatitis between the two samples subjected to different doses of gamma globulin, the lack of untreated controls would be less significant. However, the appearance of only one case of hepatitis in each group makes the need for untreated controls more acute.

This kind of situation forces dependence on the notably unreliable historical control. Among many published reports giving secondary attack rates of infectious hepatitis among family members who received no gamma globulin are those of Clark and associates, by age groups 0.7–7 percent and by size of household 2.3–6.5 percent (*7*); Aach and associates, 4 percent (*11*); Ford, 7.4 percent (*12*); Hsia and associates, children 27 percent and adults 4 percent (*9*); Ashley, by age groups 6–29 percent (*5*); Lilienfeld and associates, 8.8 percent (*6*); Knight and associates, by size of household 13–32 percent (*4*); and Brooks and associates, children 35 percent (*8*). The lowest rate occurred in a group of infants under 1 year of age, a group which seldom acquires detectable infectious hepatitis. The lowest reported secondary attack rate among persons over 1 year of age was 2.3 percent.

The great variability in these reported rates is due in part to the use of different definitions of a secondary case. For example, some authors exclude all family contact cases that occur within 30 days of the diagnosis of the primary case, others use an interval of 14 days. Still others include all cases discovered in the family subsequent to diagnosis of the primary patient. Furthermore, many of the reported groups of family contacts receiving no gamma globulin were not randomly selected control samples but were accumulated by accident, that is, those contacts who failed to secure gamma globulin for whatever reason. Another cause of wide variation is the large difference in the attack rates between children and adults. Some authors separated these groups and others did not.

The literature on this subject, therefore, does not provide a basis for accurately predicting what would happen in a group of untreated familial contacts of patients with infectious hepatitis. However, a comparison of the results observed among our combined sample of 887 contacts, of whom 2 (0.2 percent) developed infectious hepatitis, with the lowest reported secondary attack rate (2.3 percent) for persons over 1 year of age indicates that the gamma globulin used was effective in preventing infectious hepatitis with jaundice.

Four different lots of a commercially prepared gamma globulin, all from the same company, were used in this investigation. Because of the method of assigning contacts to each of the two dosage schedules, each lot number was used to an equal extent at each dose level. Had any of these lots been of low potency a larger number of cases should have been observed and these would have been grouped within the interval when that lot was being used or a few weeks subsequently. Since the commercially prepared gamma globulin of unknown potency used in this study appeared to be effective at both dosage levels used, it is suggested that the availability of gamma globulin with standardized potency would justify the testing of even smaller doses.

Summary

During a 16-month period, household contacts of persons with infectious hepatitis were given prophylactic treatment, and followup was successfully completed for 887. These contacts were randomly allocated to two groups, one of which received 0.01 ml. gamma globulin per pound of body weight and the other 0.005 ml.

The results observed were the same for the two groups, with one case of clinical jaundice occurring in each. No untreated control group was followed. However, when these results are compared with attack rates for untreated household contacts reported by other investigators, it appears that both dosage levels tested were effective.

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Studies on Blood Platelet Replacement

The Public Health Service has awarded four contracts totaling $300,000 for coordinated pilot studies of blood platelet replacement therapy to prevent and control hemorrhage in acute leukemia.

The American Red Cross in Washington, D.C., the Children's Cancer Research Foundation in Boston, the Children's Hospital of Philadelphia, and the Children's Hospital of Los Angeles will conduct the research.

An estimated 17,000 new cases of leukemia will be diagnosed in the United States this year. Hemorrhage, one of the most serious problems in its management, is caused by a deficiency of blood platelets which enable blood to clot. Although it has been known for more than 50 years that transfusions of fresh platelets are effective in preventing and controlling hemorrhage, lack of methods of preserving them necessitates their use within 4 to 6 hours after they are taken from a donor. It has also been difficult to obtain enough to prevent hemorrhage.

Now, however, techniques and simple apparatus have been developed that permit return of red cells to donors after removal of the platelets, allowing donors to give platelets far more often than they could donate whole blood. In addition, pooled platelets from numerous donors have produced desired results without provoking side reactions.

The immediate objectives of the contracted studies are to define conditions under which platelets ought to be given patients, along with results to be expected, and to work out ways of collecting and supplying large amounts on a regular basis.