Passive Immunization Against Exposure to Hepatitis B Virus in the Military: Potential and Possibilities

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Received December 15, 1975

The value of standard γ-globulin with a low titer of antibody to hepatitis B surface antigen (anti-HB,) vs hepatitis B immune globulin (HBIG) in prevention of icteric hepatitis B in the military is unclear. Although recent studies have shown a decrease in icteric hepatitis after administration of both types of γ-globulin in populations where acquisition of hepatitis B virus (HBV) is most likely the result of nonparenteral transmission, the data pertaining to parenteral exposure suggest that HBIG delays the incubation period of HBV and decreases the development of passive-active immunity. Since no studies have demonstrated efficacy of standard γ-globulin or HBIG in a drug-using population where multiple HBV exposures are likely, the results observed in most trials are not comparable to hepatitis B associated with drug abuse in the military. Therefore, before a recommendation for use of routine γ-globulin or HBIG can be made for drug-related hepatitis in the military, efficacy of standard γ-globulin and/or HBIG should be demonstrated in this population.

Although there is little doubt concerning the efficacy of γ-globulin in decreasing the incidence of icteric hepatitis A, the usefulness of standard γ-globulin or hepatitis B immune globulin (HBIG) containing a high titer of antibody to hepatitis B surface antigen (anti-HB,) for prophylaxis against hepatitis B virus (HBV) is unclear. Data from a number of studies concerning the use of standard γ-globulin of varying anti-HB, titers, HBIG, or nonimmunized controls have recently become available. These recent γ-globulin studies were concerned with the prevention of acquisition of HBV infection by parenteral or nonparenteral means in populations that have an increased risk of hepatitis B such as institutionalized children, dialysis patients, and medical personnel.

Since type B post-transfusion hepatitis is now readily controlled by elimination of HB,Ag+ blood units, the administration of γ-globulin is probably not needed for prevention of type B post-blood-transfusion hepatitis. The detection of HB,Ag in body secretions or excretions would indicate that in contrast to post-transfusion hepatitis, the dose of HBV transmitted by exposure to this material by parenteral or nonparenteral routes is low (6, 13). This observation as well as the initial results of Krugman et al. with HBIG (in institutionalized children (8)) would suggest that passive immunity might alter disease and/or infection in other high risk populations.

There have been a number of studies of γ-globulin administration in a variety of different populations from which the following conclusions may be drawn (Table 1): Three different trials (7, 9, 12) all suggest that there is little difference in the efficacy of standard vs HBIG when given as a prophylactic measure prior to probable nonparenteral exposure to HBV.

(i) Standard γ-globulin which contains a lower titer of anti-HB, has allowed development of passive-active immunity which most likely leaves the recipient with long-term immunity. In the study of Szmuness (12) in which a group not receiving any γ-globulin was included, persons given standard γ-globulin had a rate of HBV in-
Table 1
Clinical Trials of γ-Globulin in Prevention of Hepatitis B Preexposure Prophylaxis

| Reference, population studied | γ-Globulin | Anti-HB₅ titer | Number of subjects | Icterus or serological HBV infection | HB₅Ag anti-seroconversion |
|-------------------------------|------------|----------------|--------------------|------------------------------------|--------------------------|
| Iwarson et al. *            | Standard   | 1:100          | 58                 | 2                                  | 2                        |
| Medical personnel           | HBIG       | 1:355,000      | 60                 | 1                                  | 2                        |
|                               | None       | —              | 125                | 9                                  | unknown                  |
| Szmuness et al. *           | Standard   | 1:16           | 37                 | —                                  | 2                        |
| Institutionalized children  | HBIG       | 1:262,144      | 44                 | —                                  | 1                        |
|                               | None       | —              | 52                 | —                                  | 13                       |
| Ginsberg et al.             | Standard   | 1:4            | 107,000            |                                    |                          |
| Army troops                  |            |                |                    |                                    |                          |

| Dose of globulin             |            |                |                    |                                    |                          |
| 2 ml                         |            |                |                    |                                    |                          |
| 5 ml                         |            |                |                    |                                    |                          |
| 10 ml                        |            |                |                    |                                    |                          |
| Placebo                      |            |                |                    |                                    |                          |

Prince et al.                  | Standard   | 1:50           | 9                  |                                    |                          |
|                                 | intermediate | 1:5,000        | 296b              | 8                                  |                          |
|                                 | hyperimmune | 1:500,000      |                    |                                    |                          |

*Multiple immunizations.

aDialysis staff only (randomized among three groups).

infection similar to that of the control group, but the standard γ-globulin did decrease the incidence of icteric hepatitis B.

(ii) Prince (9) found no difference in the efficacy of standard vs intermediate-titer anti-HB₅ globulin vs HBIG in preventing HBV infection in the medical staff of dialysis units. However, a statistically significant reduction in the rate of HBV hepatitis was noted among dialysis patients who were recipients of HBIG, although no significant difference was found between the intermediate and standard γ-globulin groups.

(iii) A third series of studies deals with administration of globulin after accidental parenteral exposure to HBV-containing blood. Grady et al. (5) and Seeff et al. (11) have demonstrated a significant decrease in icteric hepatitis B over a 6-month period in recipients of HBIG as compared to recipients of standard globulin (Table 2). In at least one trial (5) the effect was nullified by the lack of development of passive–active immunity in the HBIG-treated group. The impression gained from this study as well as that of Redeker et al. (10) is that hyperimmune γ-globulin decreases the incidence of icteric hepatitis B but that this effect is only temporary. Furthermore, HBIG often suppresses passive–active immunity and may simply increase the incubation period of hepatitis B. Certainly the results of these studies appear to be somewhat paradoxical in that the level of anti-HB₅ in some cases (9, 12) for presumed low dose nonparenteral HBV exposure appears to be as efficacious as hyperimmune γ-globulin. Only Szmuness (12) and Iwarson (7) could show a beneficial effect of γ-globulin over placebo, since appropriate untreated controls were included. However, because of the marginal level of anti-HB₅ in the majority of standard γ-globulin preparations used in these studies and the lack of placebo (5, 9, 11) controls,
IMMUNIZATION AGAINST HEPATITIS B VIRUS

TABLE 2
Clinical Trials of γ-Globulin in Prevention of Hepatitis B Postexposure Prophylaxis

| Reference, population studied | γ-Globulin | Anti-HB, titer | Number subjects | Icterus or serologic HBV infection | HB, anti genemia (%) |
|--------------------------------|------------|---------------|-----------------|-----------------------------------|---------------------|
| Krugman et al. Institutionalized children | Standard | 1:16 | 5 | 3 |
| Redeker et al. Spouses of acute HBV cases | Standard | 1:200,000 | 25 | 1 |
| Grady et al. Medical personnel Intermediate | Standard | 1:50 | 251 | 17 |
| Seeff et al. Medical personnel | Standard | <1:8 | 129 | 8 |

a Approximation data derived from personal communication with Dr. Grady.

b Statistically significant difference at 6 months, but six more cases beyond 6 months in HBIG group developed nullifying statistical significance.

As a result of these recent studies, several recommendations concerning the use of γ-globulin have been formulated. In an editorial comment Alter et al. (2) suggest that HBIG or standard γ-globulin (containing a low anti-HB, titer) be given (see Table 3) until such time as a preparation of high-titered anti-HB, is commercially available. Because of the noncomparability of military populations with those on which these recommendations were based, the control of HBV infection by HBIG in the military cannot be assumed from these studies. From the military viewpoint, the data derived from such trials and the recommendations issued must be examined in light of several unique epidemiological aspects not encountered in the present clinical trials.

Over the last 10 years, a new social phenomenon, illicit drug use, has resulted in significant increases in HBV infection rates in the military. Epidemics of hepatitis B mainly due to HBV/ayw subtype, directly related to illicit drug use, have been observed as bases in the United States (1), as well as in Viet Nam and Germany (3) (Ta-

TABLE 3
Indications for use of Hyperimmune Hepatitis B Globulin or Standard Globulin

| Indications |
|-------------|
| 1. Acute “intense” exposure to HBV |
| a. Parenteral inoculation with HB,Ag in blood or secretions |
| b. Intimate contact with patients who have acute HB,Ag positive hepatitis |
| 2. Repeated HBV exposure (dialysis wards, endemic areas) |
| a. Standard γ-globulin may be more efficacious if passive-active immunity is increased |

| Contraindications |
|-------------------|
| 1. Individuals positive for anti-HB, (relative) |
| 2. Post-transfusion hepatitis; few cases exist at present with sensitive RIA techniques that eliminate HB,Ag + blood units |

*Editorial (Alter et al. (2)).
TABLE 4
Recent Epidemics of Hepatitis B in the Military

| Location                  | Year | Clinical attack rate |
|----------------------------|------|----------------------|
| Fort Bragg, North Carolina | 1970 | 20/1000*             |
| Fort Hood, Texas           | 1972 | 19/1000              |
| Fort Riley, Kansas         | 1973 | 10/1000*             |
| Germany (USAEUR)           | 1973 | 26/1000              |
| Camp Zama, Japan           | 1974 | 123/1000             |
| Viet Nam                   | 1972 | 9.9/1000             |
| Korea                      | 1971 | 9.2/1000             |

*Approximation.

ble 4). Attack rates for clinical hepatitis B in some specific units in U.S. Army Divisions in Germany have exceeded 100-200/1000/yr, with an overall attack rate of 26/1000. The economic impact, when one considers length of hospitalization, convalescent leave following hospitalization, and the effect of loss of manpower to the military unit, is significant (Table 5). The average length of hospitalization at Fort Hood was 22 days for the acute hepatitis B patient, followed by 30-60 days of convalescent leave. In addition, approximately 9% of the patients with acute hepatitis have been readmitted for recurrence of hepatitis associated with abnormal liver function tests. The cost of HBV disease in Germany alone to the taxpayer is conservatively estimated to be more than $20,000,000/yr.

Unlike many other infectious diseases, HBV infection, because of its prolonged incubation period, causes the epidemics to be prolonged over many months to years. Because of long foreign tours of duty, isolation, frustration, inability to communicate with local populations, and boredom, many low-ranking soldiers turn to occasional drug use as a means of escape. The recycling of troops with and without previous HBV experience (as measured by anti-HB) in and out of such areas leads to a situation where herd immunity, even among those most likely to use drugs, is rarely achieved as long as susceptibles are continually admitted to the endemic area. Several studies (1) have documented that soldiers with an overseas tour have a prevalence of anti-HB of 25% as compared to 10% in soldiers of the same age with no foreign experience. In addition, persistence of HBsAg in a limited study at Fort Hood, Texas, revealed that 5% of patients with acute HBsAg+ hepatitis failed to clear their antigenemia 4 months after their initial illness. Thus, a higher prevalence

TABLE 5
Economic Impact of Hepatitis B Infection in Troops at Fort Hood, Texas

| Economic Impact                        | Value               |
|----------------------------------------|---------------------|
| Average length of hospitalization      | 20 Days (30-60)     |
| Convalescent leave                     | 30 Days             |
| Assuming an attack rate of 10/100 men among 40,000 troops at Fort Hood | 400 Cases/year |
| Work days lost by acute hepatitis B at Fort Hood | 20,000 Days |
| Dollar estimate of loss to U.S. Army in Germany/year (LaVoie, 1974) | $20,000,000 |

*Based on 3,975 hospitalized cases of Hepatitis in 1973.

1Dr. Conrad, personal communication (Chief of Clinical Research Walter Reed Army Institute of Research, Wash., D.C.).
of antigenemia in populations to which anti-HB, -negative susceptibles are continuously added leads to sustained outbreaks of hepatitis B, particularly when illicit drug use is in vogue.

Throughout all the recent military hepatitis B epidemics, it appears that, at least initially, illicit drug use is the major reason for increasing hepatitis rates. Although difficult to prove, it is likely that nonparenteral HBV transmission due to close contact also increases in this setting. Such social phenomena as smoking pot and sharing wine bottles, an almost universal habit among young soldiers, may be a major source of nonparenteral transmission of HBV in the military. Certainly, if low-titered \( \gamma \)-globulin in the military were shown to prevent icteric type B hepatitis and lead to enhancement of passive-active immunity, repeated exposure to HBV, which probably occurs in a drug user, would most likely cause a boost in the individual's anti-HB.

No trial of \( \gamma \)-globulin or hyperimmune \( \gamma \)-globulin to date has been concerned with a drug-using population, and therefore the data derived from the clinical trials can only titillate those who would attempt to prevent hepatitis B in the military. Nevertheless, it is important to recognize that an appropriate trial could be undertaken which might answer the question of \( \gamma \)-globulin prophylaxis in the military. Of necessity, at present certain prerequisites would have to be included: (i) The trial would have to take place in Germany, where overall attack rates for HBV infection have declined from 26/1000 in 1973 to 12–15/1000 in 1975. Specific battalion-sized units with higher attack rates could, however, be selected. (ii) Followup observation of randomized groups would require at least 1 year from the initial immunization and take an additional 6 months for analysis of data. (iii) Because of the possibility of multiple HBV exposures, repeated passive immunizations would have to be given consideration in the experimental design. This factor would expand the size of the test population considerably. (iv) Perhaps, under the present ethical conditions, willingness of soldiers, commanders, and particularly drug users to volunteer for such studies must be clearly recognized as the single most important factor in limiting any trial in the military, let alone one that is linked to the politically volatile issue of hepatitis and drug abuse.

Thus, in the modern Army such studies of \( \gamma \)-globulin and/or vaccine may be extremely difficult to bring to fruition. Given the above factors, the trial would have to include a placebo control as well as a standard \( \gamma \)-globulin group. The major reason for this control is apparent from the recent studies in which low-titered \( \gamma \)-globulin appeared to be as efficacious as hyperimmune preparations in some studies (9, 12), whereas HBIG prevented passive-active immunity (5). If it is assumed that the data derived from the two recent needle-stick studies of Grady (5) and Seeff (11) represent a one-time parenteral drug-related HBV exposure, there is a suggestion that \( \gamma \)-globulin may be of benefit in eradicating hepatitis B disease in the occasional drug user. It is the low-ranking enlisted man (1) who occasionally uses drugs parenterally who is most likely to develop acute hepatitis B.

The overall objective of such a trial would be to ascertain the efficacy of \( \gamma \)-globulin for drug-associated hepatitis B disease and/or infection in the military. The goal would not be to immunize all troops in the military repeatedly, but, by working in conjunction with local preventive medicine personnel, to identify high risk military units with evolving hepatitis B problems. Such units would then be required to submit to the administration of \( \gamma \)-globulin with the aim of preventing disease but perhaps permitting infection and the resulting synthesis of antibody in all drug abusers. Pro-
vided these conditions were met, standard γ-globulin or HBIG would serve as an immediate preventive measure until a safe vaccine is available.

Only one recent major study of γ-globulin in military troops has been conducted. The work of Ginsberg et al. (4) showed a decrease in endemic hepatitis B in troops receiving γ-globulin in Korea. The anti-HB, titer of this preparation was 1:4 by passive hemagglutination, or 1:1024 by radioimmune assay. The hepatitis B cases in this study were identified early in the evolution of radioimmune assay tests for HB,Ag, before problems of HB,Ag specificity were recognized. Further, the investigators used extremely sensitive and possibly less specific criteria for stating a test to be positive (i.e., 3 SD above the negative control mean, as opposed to criteria evaluated by Abbott Labs and the FDA of 2.1 × negative mean (SD range 5–13)). Second, the troop population studied was not known to have an illicit drug-use problem, which suggests that the recognized hepatitis B cases most likely acquired their HBV by the nonparenteral route. Thus, this study, although potentially offering a solution to nonparenteral type B exposure in the military, again does not address the problem of prophylaxis against the repeated low dose parenteral exposure experienced by illicit drug users.

In conclusion, it should be noted that, even with all the currently available data, the relevance of this information concerning the efficacy of standard vs hyperimmune γ-globulin to the HBV experience in the military today is unknown. No substantial data exist to provide immediate solutions or recommendations without further investigations within the military. Thus, it may be appropriate to test the efficacy of γ-globulin of varying anti-HB, titers as against placebo and to use varying frequencies of administration, as a means of controlling HBV infection in high risk military units.

γ-Globulin obviously is the only temporary measure available until vaccine development is completed. However, the problem at present is whether to initiate γ-globulin trials based on available data or to await the development of a safe HBV vaccine which is probably 2–5 years in the future. Because of the confusion created by the recent γ-globulin studies as described, a trial in the military of γ-globulin would be more complex than a two-group trial of HBV vaccine vs placebo. In the long run the vaccine, if effective, will be more economical, easier to administer, and more likely to produce long-lasting immunity than a γ-globulin program. The military may be the only large population left where efficacy can be defined, but, because of recent stress on informed consent of volunteers, such testing may not be feasible. Thus, the decision that must be made is whether to initiate γ-globulin trials now as a means of developing a rational policy in view of the nature of the recent hepatitis B experience in the military or whether to await a safe immunogenic vaccine. Either event will certainly be a test of the ability of modern medicine to relate to the modern military in a setting staged by politicians and lawyers.

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