Hepatitis B vaccination schedules in genitourinary medicine clinics

D Asboe, P Rice, A de Ruiter, J S Bingham

Objectives: To compare two vaccination schedules in delivering hepatitis B vaccine to at-risk genitourinary medicine clinic attenders.

Methods: Two vaccination protocols were compared. Between January 1991 and December 1992, individuals had doses of recombinant hepatitis B vaccine at 0, 1 and 6 months (standard). From January until October 1993 doses of vaccine were administered at 0, 1 and 2 months (accelerated), following which timing of a booster dose was made on the basis of hepatitis B surface antibody (anti-HBs) assessment. Case notes were reviewed with regard to compliance rates and anti-HBs levels.

Results: Two hundred and fourteen individuals were included (standard 104, accelerated 110). Of the standard group 80-8% and 61-5% attended for the 2nd and 3rd doses respectively compared with 80-0% and 75-5% of the accelerated group (attendance for the 3rd dose $\chi^2 = 4.19, p < 0.05$). For both of these groups compliance was significantly better in those who requested vaccination rather than being offered it opportunistically ($\chi^2 = 4.86, p < 0.05$). Seroconversion rates were not significantly different between the two groups (87.5% versus 85.1%). A significantly higher proportion of the standard group, however, achieved anti-HBs levels greater than 100 iu/l.

Conclusions: Completion of hepatitis B vaccination was improved by changing to a 0, 1 and 2 month protocol. Levels of anti-HBs achieved in the accelerated group, however, were lower. If it is confirmed that maintaining anti-HBs levels is not important in retaining protection against hepatitis B then the accelerated schedule has clear advantages. If not, the advantages may be nullified by the need, in some, for an early booster.

(Genitourin Med 1996;72:210-212)

Keywords: hepatitis B; vaccination; genitourinary medicine clinics; compliance

Introduction

The introduction of safe and effective hepatitis B vaccines in the 1980s has presented the medical profession with the opportunity to prevent an infection with serious short and long term sequelae. Because of the relatively low prevalence rates within the United Kingdom, it has been policy to vaccinate specific targeted populations—rather than to identify groups at higher risk of acquiring infection and to vaccinate them—rather than the universal approach being used in an increasing number of countries with higher prevalence.

Genitourinary medicine (GUM) plays an important role in this approach, as some of the higher risk groups identified for targeting, especially gay and bisexual men, access clinical services. With all vaccination programmes, however, one of the obstacles to achieving immunisation is poor individual compliance in completing the required schedule. This is emphasised in GUM because of a young and mobile (in this case inner-city) population and the sporadic nature of clinic attendance. The recommended schedule for vaccination consists of doses of vaccine at 0, 1 and 6 months, with antibody titres checked 2 months following vaccination. However, an audit of hepatitis B vaccination in a GUM clinic setting using this schedule found that only 68% of individuals completed the course. This fact coupled with concern at compliance within our own clinic led us, in late 1992, to alter our programme to a 0, 1 and 2 month vaccination schedule, following which a booster dose was recommended at a time determined by serology performed 1 to 2 months following the 3rd injection. It was considered that this may enhance attendance and so was incorporated into the clinic protocol.

The aim of this study was to compare and contrast the two schedules in delivering hepatitis B vaccine to GUM clinic attenders with regard to compliance and post-vaccination antibody levels.

Material and methods

We performed a retrospective casenote review on individuals attending the GUM clinic of St Thomas’ hospital who commenced hepatitis B vaccination between January 1991 and October 1993. All individuals, were demonstrated to be hepatitis B core antibody (anti-HBc) negative (Abbott EIA), prior to vaccination.

During this time, two different vaccination schedules were used. Between January 1991 and December 1992 a 0, 1, 6 month schedule was used. From January 1993 onwards a change was made to a 0, 1, 2 months schedule. All patients were asked to return 1 to 2 months after the 3rd dose for measurement of serum hepatitis B surface antibody (anti-HBs). Samples where the titre was more than 150 iu/l were not diluted to give a precise titre and so...


Table 1  Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Accelerated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>104</td>
<td>110</td>
</tr>
<tr>
<td>Mean patient age, years</td>
<td>30-1 (17-64)</td>
<td>30.0 (18-57)</td>
</tr>
<tr>
<td>Percentage male</td>
<td>97.2%</td>
<td>97.1%</td>
</tr>
<tr>
<td>Risk factor (%)</td>
<td>Gay/bisexual 91.8</td>
<td>91.3</td>
</tr>
<tr>
<td></td>
<td>Het male 4.5</td>
<td>5.7</td>
</tr>
<tr>
<td></td>
<td>Het female 2.7</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>IVDU 1.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

are represented as > 150 iu/l. In those vaccinated at 0, 1, and 2 months the anti-HBs results led to the following recommendations: anti-HBs recommendation: < 10 repeat vaccination course 10–50 booster dose immediately 51–100 booster dose 1 year 101–150 booster dose 2–3 years > 150 booster dose 5 years

Patients with either no response or a good level of anti-HBs after immunisation were advised regarding further booster doses in accordance with the published guidelines from the Department of Health’s Joint Committee on Vaccination and Immunisation.1 Those patients with poor responses of between 10 and 50 and 51–100 iu/l were managed in general agreement with the findings of a study examining persistence of antibody in vaccinees.4

Vaccination was with yeast-derived, recombinant hepatitis B vaccine (20 ug Engerix B, SmithKline Beecham) injected intramuscularly. Neither individuals known to be HIV antibody positive, nor those indicating they would complete vaccination elsewhere were included in this analysis. Importantly, during the time covered by this study, there was no recall system in place for those failing to attend for vaccination.

Results

A total of 224 individuals were identified. Of the 214 sets of notes which were located, 104 individuals were vaccinated via the standard (std) protocol, and 110 via the accelerated (acc) schedule. Demographic and risk factor characteristics of the two groups were comparable (table 1).

Thirty-eight (63-5%) of the standard group and 43 (60-9%) of the accelerated group were either HIV antibody positive at the initiation of vaccination, or have subsequently tested negative. In the remainder HIV status was unknown. In 43 individuals (20-5%) it was clear from the notes that the individual concerned had requested vaccination (std 21.1%, acc 19.1%). It was assumed vaccination was offered opportunistically for the remainder.

The percentage of individuals attending at each stage of the vaccination programme is shown in table 2. Included are attendance figures stratified into those either requesting or being offered vaccination. Inclusion in this analysis was determined by attendance for the 1st dose; therefore attendance at this stage, by definition, was 100%. For the 2nd dose attendance was similar in both groups. For the 3rd dose however, attendance was significantly better in the accelerated group (χ² = 4.19, p < 0.05). These differences were maintained when attendance rates for post-vaccination serology assessment were examined. Also, we found that attendance was better in those who requested vaccination, with little difference between the standard and accelerated groups.

Thirteen patients undergoing accelerated vaccination were deemed to require an immediate booster (as a result of post-vaccination serology) of whom 10 were given this on returning for the serology result. Three did not attend. Nine out of 13 (69-2%) who were recommended a booster in 1 years time complied. Twenty-three had anti-HBs levels of greater than 100 iu/l and so were recommended to have a booster dose in 2 to 5 years’ time. Of the 5 who had anti-HBs levels of between 10 and 100 iu/l following standard vaccination, 4 returned and were given a booster. Those with levels greater than 150 iu/l were advised to have the levels checked in 5 years.

Post-vaccination anti-HBs results are shown in table 3. There was no significant difference in the percentage of responders (with this defined as those achieving an anti-HBs level of greater than 10 iu/l) between the two groups. There was, however, a significantly higher percentage of accelerated vaccinees achieving only a moderate response (anti-HBs between 10 and 100 iu/l). The percentage of individuals whose HIV status was unknown and who returned for serological assessment was not significantly different in the standard and accelerated groups (std 40-0%, acc 47-5%).

Discussion

Immunogenicity studies of a recombinant hepatitis B vaccine have shown that both the standard and accelerated schedules generate high concentrations of specific antibody.1 The findings of these studies that antibody levels at 7 months were higher under the 0, 1 and 6 month schedule led to the recommendation

<table>
<thead>
<tr>
<th></th>
<th>Standard (n = 40)</th>
<th>Accelerated (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HBs (iu/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10</td>
<td>5 (12-3)†</td>
<td>10 (16-9)†</td>
</tr>
<tr>
<td>10–100</td>
<td>5 (12-5)†</td>
<td>26 (44-0)†</td>
</tr>
<tr>
<td>&gt; 100</td>
<td>30 (75-0)*</td>
<td>23 (38-9)*</td>
</tr>
</tbody>
</table>

*Standard versus accelerated and level of post-vaccination anti-HBs χ² = 11.58, p < 0.001.
†Increase in the non-responder rate amongst accelerated group 0.044 ± 0.137 (95% confidence interval). χ² = 1.06, p > 0.5.

Table 3  Number of individuals (percentage) versus level of post-vaccination hepatitis B surface antibody

Table 2  Numbers (percentage) of individuals attending each stage of vaccination programme

<table>
<thead>
<tr>
<th></th>
<th>1st inj</th>
<th>2nd inj</th>
<th>3rd inj</th>
<th>Serology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>requested</td>
<td>22 (100)</td>
<td>20 (90-0)</td>
<td>18 (81-8)†</td>
<td>14 (63-6)</td>
</tr>
<tr>
<td>opportunist</td>
<td>82 (100)</td>
<td>64 (78-0)</td>
<td>46 (56-1)†</td>
<td>26 (31-7)</td>
</tr>
<tr>
<td>total</td>
<td>104 (100)</td>
<td>84 (80-0)</td>
<td>64 (61-5)*</td>
<td>40 (38-5)</td>
</tr>
<tr>
<td></td>
<td>Accelerated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>requested</td>
<td>21 (100)</td>
<td>18 (85-7)</td>
<td>18 (85-7)†</td>
<td>12 (57-1)</td>
</tr>
<tr>
<td>opportunist</td>
<td>89 (100)</td>
<td>70 (78-7)</td>
<td>65 (73-0)*</td>
<td>47 (52-8)</td>
</tr>
<tr>
<td>total</td>
<td>110 (100)</td>
<td>88 (80-0)</td>
<td>83 (75-5)*</td>
<td>59 (53-6)</td>
</tr>
</tbody>
</table>

*Attendance rates, standard versus accelerated χ² = 4.19, p < 0.05.
†Attendance rates, accelerated versus opportunistic (standard plus accelerated) χ² = 4.86, p < 0.05.
that routine vaccination should follow this regi-
imen. The studies, however, did not address the
issue of individual compliance. Although Hess found 99% completion rates after 3
doses (standard schedule) this was in a study of
health care workers in a research setting, rather
than a clinical situation. In contrast, we found
completion rates using this schedule to be low.
Upon changing to the 0, 1 and 2 month sched-
ule there was a significant improvement in the
completion of the 3 dose schedule.

The concern that the non-parallel nature of the
two groups may confound the results is valid.
The rate of recruitment of the second
group was faster, raising the possibility that
either more (and perhaps more motivated)
individuals were presenting for vaccination or
that the medical staff were more effective in
identifying at-risk individuals and initiating
vaccination. In the latter scenario any such reli-
dence may have translated directly into better
attendance. In other aspects though the groups
were similar. Firstly, individual characteristics
such as age and identifiable risk factors were
comparable. Secondly, for those parts of the
schedule which were unchanged, completion
rates were virtually identical; significant differ-
ces were observed only where the schedules
diverged. If the acc group were intrinsically
more compliant we might have expected improved
attendance for the second injection.

The percentage of individuals who gener-
ated protective levels of antibody (anti-HBs
> 10 iu/l) was not significantly different in the
two groups. Although the percentage of poor
responders (15%) was high compared with studies in healthy volunteers it is comparable
to the 18% found by Hadler when vaccinating
gay men with plasma derived vaccine.

A drawback of the accelerated schedule lies
in the lower levels of anti-HBs that are pro-
duced. After the 3 doses only half as many
recipients of the accelerated schedule achieved
an antibody level of greater than 100 iu/l. As
the persistence of antibody is related to the
peak level achieved, the consequence of lower
levels of antibody is the shorter duration for
which antibody remains above 10 iu/l. It was
for this reason that the recommendation was
made when using an accelerated protocol that
a 1 year booster be routinely given. However,
rather than using this arbitrary 1 year booster,
we utilised a more flexible approach. The pre-
dictability of decline in anti-HBs enables one
to identify those individuals who require an
earlier booster, whilst allowing those with higher
levels a broader window during which to
return. We took advantage of this by recom-
mending a range of times for a booster dose
from immediate to 5 years.

There are problems with the accelerated
approach. Firstly, because there is a need to
identify those requiring an early booster, attend-
ance for post-vaccination antibody testing is
important. We found, however, that only 71%
of those completing the 3 dose accelerated vac-
cination attended at this stage. Secondly as
more doses of vaccine are being used, this
approach is more costly. Thirdly, for those
requiring an early booster attendance for this
injection is important to ensure antibody levels
are maintained.

There is opinion that concern about declin-
"ing levels of antibody and the subsequent risk
of infection is misplaced. Studies have shown
that although decaying vaccine-induced anti-
body levels render individuals susceptible to
infection, (as evidenced by antico-agulant
conversion) this is rarely accompanied by acute
hepatitis or by the development of carrier sta-
tus. Prevention of these sequela is the
primary goal of vaccination. Should it be
considered that individuals in whom antibody
levels declined to below 10 iu/l were still pro-
tected from these outcomes, the predominant
concern of vaccination would be to ensure that
individuals are immunised and assessed for
evidence of anti-HBs conversion rather than
their declining antibody levels over time. In the
United States of America guidelines do not
include recommendations to monitor antibody
levels and boost when low. Instead reliance is
made on immunological memory to maintain
protection against infection when antibody lev-
dles decline below 10 iu/l. As individuals com-
ply eg, old and unwell, there is no detrimental
effect on seroconversion rate,14 the argument for
this programme under these conditions would be
undeniable.

If the decline of anti-HBs to below 10 iu/l is
deemed important, however, then the advan-
tages of the accelerated over the standard
schedule are debatable. It is evident that more
individuals complete the accelerated vaccina-
tion schedule but potentially at the cost of pro-
tective immunity which is not as long-lasting.
Although we need to be wary about the retro-
spective classification of the requested and
opportunistic groups it would appear there was
little advantage for the group who request vac-
cination as their completion rates were scarcely
different. For the remainder who are vacci-
nated opportunistically, neither the standard or
accelerated protocol give highly satisfactory
results. A prospective study utilising parallel
vaccination groups and ideally some type of
recall system would allow these findings to be
confirmed or refuted.

1 Department of Health, Welsh Office, Scottish Office Home
and Health Department, DHSS (Northern Ireland). Immunisation
2 Kane M. Global programme for the control of hepatitis B
3 Bharti N, Gibson RJC, Brecham M, et al. Failure to deliver
hepatitis B vaccine: confessions from a genitorinary medicine clinic.
Persistence of vaccine-induced antibodies to hepatitis B surface
antigen and the need for booster vaccination in adult subjects.
5 Andre FE. Summary of safety and efficacy data on a yeast-
6 Hess G, Hingst V, Cokele J, Bock HL, Clemens R. Influence
of vaccination schedules and host factors on antibody
response following Hepatitis B vaccination. Eur J Clin
immunogenicity and efficacy of Hepatitis B vaccine in
8 Tilley AJ, Palmer SJ, Banavar JI, Vines SK, Wills PR, Mason WR.
Hepatitis B vaccine boosting among young healthy adults.
9 Hall AJ. Hepatitis B vaccination: protection for how long
10 Tilley AJ. Hepatitis B vaccine boosting: the debate continues.
Hepatitis B vaccination schedules in genitourinary medicine clinics.

D Asboe, P Rice, A de Ruiter and J S Bingham

Genitourin Med 1996 72: 210-212
doi: 10.1136/sti.72.3.210

Updated information and services can be found at:
http://sti.bmj.com/content/72/3/210

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/