

Obesity as a Predictor of Poor Antibody Response to Hepatitis B Plasma Vaccine

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• **Factors associated with lack of antibody response to the hepatitis B virus plasma vaccine were retrospectively evaluated by means of a logistic regression in 194 previously seronegative staff members of a community hospital. All subjects had received three doses of vaccine by intramuscular buttock injection using a 1-in, 23-gauge needle. Overall, only 55.7% of subjects developed detectable antibody to hepatitis B surface antigen in serum after immunization. The weight-height index served as a surrogate measure of obesity. Predictors of poor immunogenic response to hepatitis B vaccine included higher weight-height index, older age, and vaccine batch. Sex, race, timing of vaccine doses, and timing of postimmunization determination of antibody to hepatitis B surface antigen were not predictors of vaccine efficacy.**

(*JAMA* 1985;254:3187-3189)

EARLY field trials of the hepatitis B plasma vaccine (HB vaccine) reported a measurable response in serum of antibody to hepatitis B surface antigen (anti-HBs) to the vaccine in over 85% of recipients.¹⁻⁶ Males undergoing dialysis were reported to respond less well than females,⁶ but among hospital personnel responders and nonresponders did not appear to differ with regard to sex, age, race, or occupational category.¹ On the basis of field trials indicating that the vaccine was both safe and efficacious, the Public Health Service and the American

College of Physicians recommended widespread prophylactic use in medical personnel at high risk of acquiring hepatitis B infection.^{7,8} However, recent communications from community hospitals have reported that response rates to the HB vaccine may be as low as 50% to 75%.⁹⁻¹³ Advancing age^{11,12} and female sex^{12,13} have been reported to be correlated with poor anti-HBs response. In addition, the site of injection has been suggested as a predictor of poor immunogenic response to the HB vaccine, with injections into the buttock less likely to confer immunity than injections into the deltoid.⁹

We report herein the results of a retrospective univariate and multivariate analysis of the risk factors associated with a poor immunogenic response to the HB vaccine among the personnel of a community hospital. The weight-height index, a surrogate measure of obesity, was the best predictor of poor immunogenic re-

sponse and may be directly related to the observation that persons receiving vaccine by buttock injection show a poorer response rate than those receiving vaccine by arm injection.

METHODS

Vaccine Administration

All subjects of this report were full- or part-time employees of a 240-bed multi-specialty North Carolina community hospital. Each high-risk hospital employee was screened for antibody to hepatitis B core antigen and anti-HBs and, if neither was present, was offered the HB vaccine. Vaccine was stored and administered according to the manufacturer's recommendations. Vaccine was administered by a single employee health nurse in the buttock by means of a 23-gauge, 1-in needle at time 0, one month, and six months. Efficacy of the vaccine was determined by rechecking anti-HBs status following completion of all three vaccine doses.

Data Collection

For all hospital employees receiving three doses of the HB vaccine, the following information was obtained by the employee health nurse: age, sex, race, duties, underlying medical diseases, pre-vaccination and postvaccination anti-HBs status and dates the tests were performed, height, weight, dates of vaccination, vaccine batch, and site of vaccine administration. Information was obtained on 219 employees. Twenty-five employees were dropped from further analysis for the following reasons: 11 had received at least one vaccine dose by arm injection, incomplete information was obtained on nine employees, and five employees had underlying medical disorders (pregnancy, chronic phlebitis, angina, diabetes melli-

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Read before the 25th Interscience Conference on Antimicrobial Agents and Chemotherapy, Minneapolis, Sept 30, 1985.

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Risk Factors for Inadequate Response to Hepatitis B Vaccine: Univariate Analysis

Predictor	Antibody Status After Hepatitis B Plasma Vaccine		P
	Positive for Anti-HBs*	Negative for Anti-HBs	
Sex, No. of subjects			
M	15	9	...
F	93	77	NS†
Race, No. of subjects			
White	90	75	...
Black	15	10	...
Other	3	1	NS
Vaccine batch, No. of subjects			
0599K	3	2	NS
1737H	14	6	NS
2131H	23	23	NS
2325H	58	47	NS
2327H	5	10	.07
2444H	29	18	NS
2445H	41	33	NS
2446H	58	50	NS
2448H	8	3	NS
Age, mean years ± SE	34.38 ± 0.81	38.15 ± 1.07	.005
Weight-height index, mean ± SE	29.71 ± 0.54	32.88 ± 0.83	.002
Timing of vaccine doses, mean days ± SE			
1st to 2nd dose	31.5 ± 0.41	31.57 ± 0.58	NS
2nd to 3rd dose	183.58 ± 0.81	181.5 ± 1.20	NS
3rd dose to anti-HBs titer	322.38 ± 8.91	328.84 ± 9.33	NS

*Anti-HBs indicates antibody to hepatitis B surface antigen.
†P > .15.

tus, and a recent positive intradermal tuberculosis skin test result). Anti-HBs status was determined by an enzyme immunoassay. Anti-HBs levels were considered normal if they fell below a designated cutoff value based on results of simultaneously run control values as specified by the manufacturer. Results of the enzyme immunoassay were confirmed by testing 54 randomly chosen postimmunization serum samples for anti-HBs by radioimmunoassay. The two test methods yielded a similar anti-HBs status (Spearman's rank correlation, $r = .918$).

Statistical Analysis

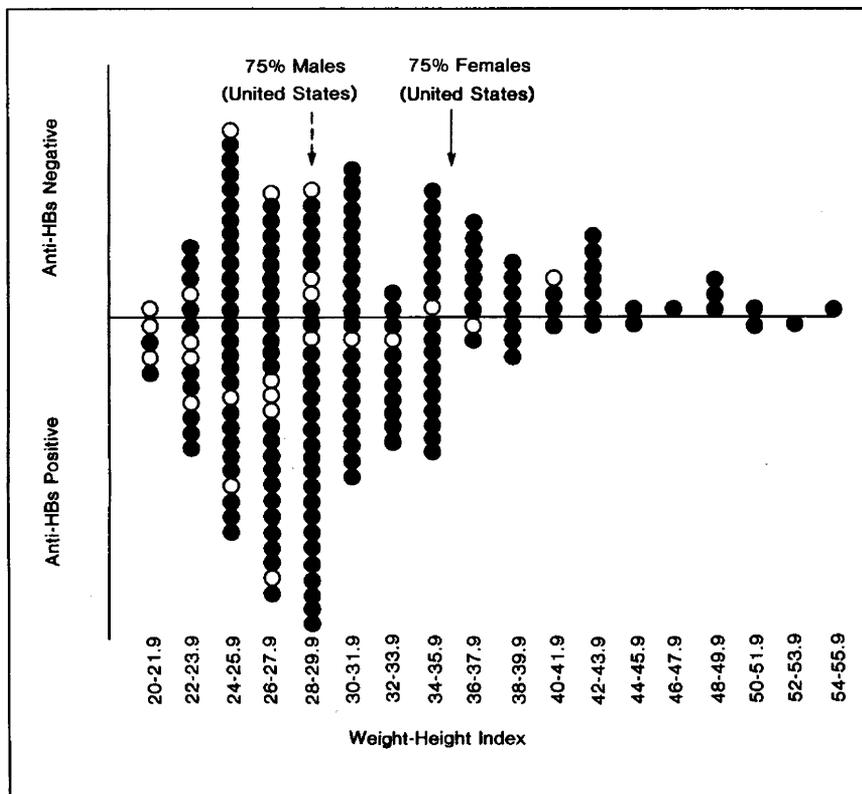
Data were coded and analyzed on a mainframe computer using the Statistical Analysis System package. For the univariate analysis, dichotomous variables were evaluated by χ^2 or Fisher's exact test (two tailed) if expected cell counts contained less than five subjects. Continuous variables were analyzed by the Student *t* test of independent means (two tailed). All variables were further analyzed using hierarchical (nested) logistic regression models according to established techniques.¹⁴ Odds ratios were calculated according to the following formula: $\exp[\beta^* + (Z_{1-\alpha/2}) (SE \text{ of } \beta^*)]$, where $\alpha = 0.05$ and β^* equals the estimated logistic regression parameter β times the number of units used as a standard of comparison between "high-risk" and "low-risk" employees.

Weight-Height Index

The weight-height index¹⁵ was computed as follows: $\text{weight}(\text{kg}) / [\text{height}(\text{m})]^2$, where *p* equals 2 for males and 1.5 for females. The weight-height index was chosen as a surrogate measure of obesity. The sum of triceps plus subscapular skin-fold measurements has been reported to have the following correlation with the weight-height index: $r = .723$ to $.827$ for males depending on age and $r = .770$ to $.857$ for females depending on age.¹⁵ Patients were weighed with clothes on and without shoes; height was measured with shoes off.

RESULTS

Vaccine recipients were overwhelmingly female (88%) and relatively young (Table). Serum anti-HBs was detected by enzyme-linked immunosorbent assay in 108 (55.7%) of 194 subjects who received three doses of the HB vaccine. Univariate analysis (Table) revealed no significant differences between vaccine responders and nonresponders with regard to sex, race, and timing of postimmunization anti-HBs determination. Timing of the second and third vaccine doses



Relation of weight-height index to postimmunization antibody to hepatitis B surface antigen. Solid circles indicate females; open circles, males.

was very close to the recommended one- and six-month intervals and was similar between responders and non-responders. Vaccine batch 2327H was somewhat more likely to have been administered at least once to nonresponders ($P=.07$), but other vaccine batches were not associated with a poor immunogenic response. However, the weight-height index and age were both found to be significantly elevated in the nonresponders.

To evaluate the simultaneous effects of potential predictors, logistic regression analyses were performed using the following variables: weight-height index, age, sex, race, vaccine batch, duration between vaccine doses, timing of postimmunization anti-HBs determination, and interaction terms among sex, weight-height index, and vaccine batch. This analysis revealed that the weight-height index was an important predictor for lack of antibody response to the hepatitis B vaccine (Wald, $P=.004$). Age (Wald, $P=.05$) and vaccine batch (Wald, $P=.02$) each independently improved the model. However, race, sex, duration between vaccine doses, timing of postimmunization anti-HBs determination, and interaction terms were not significant predictors of a poor immunogenic response ($P>.15$). The odds ratio for age was 1.72 (95% confidence interval, 1.01 to 2.91) assuming a 15-year difference between compared individuals. The odds ratio for the weight-height index was 2.01 (95% confidence interval, 1.23 to 3.91) assuming a ten-unit difference between compared individuals.

Only 29.5% of employees with a weight-height index greater than the

sex-adjusted 75th percentile for all US persons¹⁵ developed significant postimmunization anti-HBs levels, compared with 63.3% of those employees under the 75th percentile (Figure) ($P<.01$).

COMMENT

In early trials of the HB vaccine, more than 85% of subjects developed anti-HBs. Recently, several community hospitals have reported that anti-HBs responses have occurred in only 50% to 75% of vaccine recipients.⁹⁻¹³ Preliminary reports have suggested that age, sex, and the site of injection may be related to poor antibody responses, with subjects receiving intramuscular buttock injections being less likely than subjects receiving deltoid injections to mount a detectable anti-HBs response. It has been suggested¹⁰ that inadvertent deposition of vaccine into fat may be responsible for the lower response rate following buttock injection. A recent study using computed tomography to assess gluteal fat thickness has estimated that buttock injection using a 3.5-cm needle results in deposition into fat in 85% of men and 95% of women.¹⁶

In our study, we found that an elevated weight-height index was a significant predictor of lack of detectable antibody response following administration of HB vaccine. The weight-height index is highly correlated with obesity as determined by skin-fold measurements and has been found to be the most satisfactory relative weight index.^{17,18} Our study therefore lends support to the hypothesis that vaccine deposition into

fat is an important factor in the poor immunogenic response rates to HB vaccine being reported. However, other factors may also be important, as some very thin subjects failed to respond to the HB vaccine (Figure). Our logistic model also suggests that advancing age and vaccine batch are independent predictors of inadequate vaccine response. Age has also been found to be associated with vaccine response in some previous vaccine immunogenicity studies and may be an important factor regardless of the site of administration.

We were unable to evaluate the effects of site of immunization and needle size on immunogenic response to the hepatitis B vaccine, but we would expect shorter needles to be associated with a lower likelihood of seroconversion. The exact mechanism whereby vaccine deposition into subcutaneous tissue results in reduced immunogenicity is unknown.

We suggest that HB vaccine should be administered in the deltoid using a needle sufficiently long to allow intramuscular injection. It also appears prudent to perform anti-HBs testing on all individuals who received HB vaccine by intramuscular buttock injection, or at least on such employees after percutaneous or mucosal exposure to HBsAg-positive blood or secretions. Further analyses of vaccine response should take into account both the degree of obesity and age of individual subjects.

This project was supported in part by the Epidemiology Section, Division of Health Service, Department of Human Resources, Raleigh, NC.

We wish to acknowledge the aid of John Parsons, MD, in the planning of this study.

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