Influence of smoking on immunological responses to hepatitis B vaccine

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When 115 health-care workers participated in a study that monitored their serological responses to hepatitis B vaccine at regular intervals, it was found that smoking significantly affected their antibody titre responses adversely. The study group was randomly allocated into two comparable groups that received hepatitis B vaccine either in a rapid schedule (vaccination at 0, 1, 2 and 12 months) or a standard schedule – most commonly used worldwide – (vaccination at 0, 1, and 6 months). A significantly higher proportion of smokers, in both schedules, failed to seroconvert and to achieve higher antibody levels at month 3 ($p=0.01$) *and at month 13* ($p=0.0003$). *At month 7 a similar pattern was noted in smokers following the standard vaccination schedule* ($p \leq 0.05$), *but not in those following the rapid schedule.*

Keywords: Hepatitis B vaccine; smoking; seroconversion

Cigarette smoking is associated with a range of alterations in immune function, the mechanisms of which are not yet fully understood[1]. While these immunological effects have been extensively studied in relation to diseases such as asthma and allergic alveolitis, little attention has been paid to the possible influence of smoking on responses to vaccination. Modern vaccination programmes which include follow-up assessment of antibody responses, provide an opportunity to study this interaction more extensively and we considered this aspect during a study of health-care workers receiving hepatitis B immunization.

METHODS AND RESULTS

One hundred and fifteen healthy adult volunteers participating in an open study comparing two immunization schedules provided information on their smoking history. All subjects had been randomly allocated to receive hepatitis B vaccine (Engerix B) in either a rapid schedule (vaccination at 0, 1, 2 and 12 months) or a standard schedule (0, 1 and 6 months). Each dose (20 $\mu g\ ml^{-1}$) was administered by intramuscular injection to the upper arm. Hepatitis B surface antibody (anti-HBs) titres were measured at months 3, 7 and 13 of the study by radioimmunoassay (Ausab, Abbot Laboratories, Chicago, IL, USA) using standard preparations of known titre to produce a calibration curve. A logistic regression analysis was carried out on all assessable data to investigate simultaneously the effects of age, gender, smoking habit, type of vaccination schedule and their interactions on seroconversion and anti-HBs levels at each of these time points. The characteristics of the study group are shown in *Table 1*.

Younger people from the sample were more likely to seroconvert and achieve higher antibody levels than older subjects at months 3 ($p=0.00001$), 7 ($p=0.002$) and 13 ($p=0.06$). No significant interactions were found with age.

Women from the sample were more likely to seroconvert and achieve higher antibody levels than men at month 3 (odds ratio (OR) 2.18, 95% confidence interval (CI) 0.99–4.81, $p=0.05$) and with a similar (but not statistically significant) trend at month 7 (OR 2.06, CI 0.78–5.55, $p=0.15$) and at month 13 (OR 3.8, CI 1.08–13.42, $p<0.05$) for those subjects in the standard schedule only. (At month 13 a significant interaction between sex and vaccination schedule was noted.)

Smoking was found significantly to affect antibody titre response at months 3, 7 and 13 and the results are summarized in *Table 2*. Compared with non-smokers, a higher proportion of smokers failed to seroconvert and achieve higher antibody levels at month 3 ($p=0.01$) and at month 13 ($p=0.0003$), regardless of vaccination schedule. At month 7, a significant interaction ($p=0.04$) was discovered between vaccination schedule and smoking. Smokers following the standard vaccination schedule at this month had significantly less chance of seroconverting and achieving higher antibody levels than non-smokers ($p \leq 0.05$). In those following the rapid schedule, this did not reach statistical significance ($p>0.05$).

DISCUSSION

Smoking has not been generally recognized as a factor which affects responses to vaccination, although a

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Table 1 Characteristics of study group subjects by age, gender, smoking habit and vaccine schedule

	Study group ($n=115$) (group 1 ($n=56$) + group 2 ($n=59$))							
	Smokers ($n=37$)				Non-smokers ($n=78$)			
	Men ($n=11$)		Women ($n=26$)		Men ($n=24$)		Women ($n=54$)	
Age (years)	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
⩽25	–	2	1	3	2	2	13	8
26–40	4	1	5	5	3	9	10	13
⩾41	1	3	6	6	7	1	4	6
Total	5	6	12	14	12	12	27	27

Table 2 Percentage (number) of subjects recording hepatitis B antibody levels (IU l^{-1})

Month	Smoking habit	Schedule	Non-seroconvertors		1–<10 IU l^{-1}		10–100 IU l^{-1}		>100 IU l^{-1}		Missing/ invalid anti-HBS data	Odds ratio[a] (95% confidence interval; p value)
			%	(n)	%	(n)	%	(n)	%	(n)	n	
3	Non-smoker	Standard	10.3	(4)	10.3	(4)	48.7	(19)	30.8	(12)	–	0.35
		Rapid	5.7	(2)	0.0	(0)	34.3	(12)	60.0	(21)	4	(95% CI: 0.15–0.79; $p=0.01$)
	Smoker	Standard	41.2	(7)	11.8	(2)	29.4	(5)	17.7	(3)	–	
		Rapid	15.8	(3)	10.5	(2)	31.6	(6)	42.1	(8)	1	
7	Non-smoker	Standard	0.0	(0)	0.0	(0)	5.3	(2)	94.7	(36)	1	Standard schedule[b]
		Rapid	2.9	(1)	2.9	(1)	26.5	(9)	67.7	(23)	5	0.04
	Smoker	Standard	17.7	(3)	0.0	(0)	35.3	(6)	47.1	(8)	–	(95% CI: 0.01–0.25; $p \leqslant 0.05$)
		Rapid	5.3	(1)	15.8	(3)	36.8	(7)	42.1	(8)	1	Rapid schedule 0.33 (95% CI: 0.01–14.31; $p>0.05$)
13	Non-smoker	Standard	5.6	(2)	0.0	(0)	19.4	(7)	75.0	(27)	3	0.13
		Rapid	2.8	(1)	0.0	(0)	0.0	(0)	97.2	(35)	3	(95% CI: 0.04–0.41; $p=0.0003$)
	Smoker	Standard	28.6	(4)	14.3	(2)	28.6	(4)	28.6	(4)	3	
		Rapid	5.6	(1)	0.0	(0)	11.1	(2)	83.3	(15)	2	

[a]Odds ratio of smokers seroconverting and achieving higher antibody levels. Estimates adjusted for sex, age and vaccination schedule effects
[b]Schedules split due to significant interaction

number of studies have suggested a possible association. In hepatitis B immunization programmes, poorer responses in smokers have been reported immediately following primary immunization[2,3] and at 3-year follow-up[4]. Following immunization with influenza vaccine, more rapid decline in antibody has also been observed in smokers[5]. This study adds weight to these observations, demonstrating that smokers are less likely to seroconvert following hepatitis B immunization, and that those that do achieve lower levels of antibody than non-smokers. At month 7, (the month after completing the standard schedule used most commonly worldwide), the likelihood of achieving an antibody level exceeding either 10 or 100 IU l^{-1} was significantly higher for a non-smoker than for a smoker for those subjects following the standard schedule. The same significant trend was demonstrated at month 13 (the month after completion of the rapid schedule), regardless of which schedule was followed.

While the mechanisms of these effects are beyond the scope of this study, the practical health implications for smokers are substantial, if they show impaired response to immunization. The higher proportion of non-seroconvertors among smokers at the completion of the standard schedule course (17.7%) compared with that encountered in the rapid schedule group (5.6%) may point to the added benefit of the four-dose course in smokers. It is acknowledged, however, that there are limitations in comparing antibody responses to different schedules at specific time intervals. In view of these responses we would advocate the use of postvaccination antibody testing in smokers with consideration of an additional booster dose for poor responders. It is not yet known if these findings apply to a wider range of vaccines, but it would seem prudent to include the impact of smoking in the assessment of new vaccine products.

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