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Significant potentiation of anticoagulation by flu-vaccine during the season 2001-2002

Influenza-vaccination is increasingly used in patients under chronic anticoagulation. Whether it interferes with oral anticoagulants is under debate. We found, in a case-control study in ninety patients in the 2001-2002 season, that flu-vaccine induced a significant increase of INR, particularly in a subgroup of patients. INR should be carefully monitored in anticoagulated patients after flu vaccination.

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Whether flu vaccination causes modifications of the prothrombin time in patients receiving oral anticoagulants is a clinically important controversy. In two small, prospective

studies a prolongation of prothrombin time was demonstrated while in several other reports, mostly of small series, influenza vaccine was not found to interfere with anticoagulation.¹⁻⁴ However, the latest ACCP consensus conference on antithrombotic therapy discussing drug interactions with warfarin classified flu vaccine as an INR-potentiating drug.⁵

Anticoagulated patients are increasingly part of old age range groups and are often affected by ischemic heart disease, heart failure or diabetes, all conditions in which flu-vaccination is strongly indicated.⁶ In the past vaccination season we evaluated, in a case-control study, the effect of flu-vaccination on prothrombin time in patients receiving chronic oral anticoagulant treatment. The INR of these patients had been stably within the therapeutic range over the previous 3 months. Ninety consecutive patients (58 males, 32 females, mean age 74, 69 with INR range 2-3, 21 with INR range 3-4.5, mean INR 2.79 ± 0.83 ; 98% anticoagulated with warfarin, 2% with acenocoumarol) were enrolled in the study. One of the following flu vaccines was administered by a single intramuscular injection: Inflexal V (Berna), Isiflu V (Kedrion), Fluad (Chiron), or Agrippal (Chiron). In all patients INR values were recorded 3 times before (the last of which 5-7 days prior to) vaccination and once 7-10 days after vaccination. Forty-five patients not receiving vaccination and followed during the same period in our Center, well matched for gender, age, type of anticoagulant drug, INR target and stability within range over the past three months, were randomly taken as controls (Table 1). The INR was recorded in the controls at the same four time-points as in the cases. Influenza immunization produced an average increase in INR of 0.56: INR before vaccination (average of three determinations) was 2.79 ± 0.83 in patients and 2.67 ± 0.90 in controls ($p=NS$), while 7-10 days after flu-vaccination it was 3.35 ± 1.04 in patients and 2.59 ± 0.90 in controls ($p<0.00005$). Using a cut-off INR change of ≥ 0.5 , two subpopulations were distinguished: in 49 out of 90 patients vaccination produced a clear increase in INR (mean INR before 2.64 ± 0.98 ; mean INR after 3.85 ± 0.98 , $p<0.00001$). In this subgroup 2 patients had bleeding episodes after the flu vaccination: epistaxis and muscular hematoma. In the remaining 51 patients no INR changes were observed (mean INR before 2.82 ± 0.92 ; mean INR after 2.79 ± 0.82 , $p=NS$) (Figure 1). No patient in this subgroup or in the control group had any bleeding in the same period. There were no differences in age, sex, type of oral anticoagulant, or average anticoagulant dose between the two subgroups. We cannot exclude that administration of different flu vaccines may have accounted for the different response. Indeed, in a previous series, a significant potentiation of anticoagulation by flu-vaccination observed in

Table 1. Characteristics of cases (vaccinated patients) and controls (not vaccinated patients).

	Cases	Controls
Age (mean)	74	69
Sex (M/F)	58/32	30/15
Low range INR 2-3 (N)	69	37
High range INR 3-4.5 (N)	21	8
Warfarin/Acenocoumarol (W/A)	88/2	44/1
Major bleeding complications (N)	0	0
Minor bleeding complications (N)	2	0
Thrombotic complications (N)	0	0

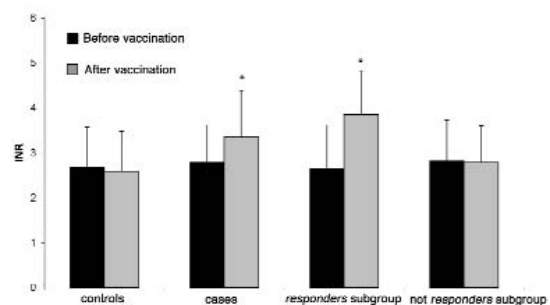


Figure 1. Effect of flu vaccination on INR in patients under long-term oral anticoagulation. INRs were recorded three times before (the last of which 5-7 days prior to) and one time (7-10 days) after vaccination in the cases and at the same time points in the controls. Data are expressed as means \pm SD. * $p<0.00005$; $^{\circ}p<0.00001$.

the 1982-1983 vaccine season was not seen in the following vaccine season, suggesting possible differences depending on vaccine batches.² Unfortunately, in our study the information concerning the type of flu vaccine administered was not available. Our data, from the largest controlled series so far reported, support the existence of a potentially serious interaction between warfarin and flu vaccine, which might be due to inactivation of the cytochrome p450 system.⁷ This implies that INR values should be monitored carefully in anticoagulated patients in the immediate period following flu vaccination.

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