Decreased elimination of theophylline after influenza vaccination

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The elimination of theophylline is decreased after vaccination against influenza. In three patients receiving 200 mg of oxtriphylline (equivalent to 128 mg of theophylline) every 6 hours by mouth the serum theophylline levels rose after vaccination, and in four healthy volunteers given the same dose of oxtriphylline 24 hours after vaccination the half-life of theophylline increased by an average of 122%. Two of the three patients showed signs of a toxic reaction to the drug. These results suggest that the elimination of theophylline is impaired to a clinically important degree after influenza vaccination and that the resulting levels of the drug can be toxic even when conventional therapeutic doses of theophylline are given.

Après la vaccination antigrippale l'élimination de la théophylline est abaissée. Chez trois patients recevant 200 mg d'oxtriphylline par voie orale (l'équivalent de 128 mg de théophylline) aux 6 heures les taux sériques de théophylline se sont élevés après la vaccination, et chez quatre volontaires à qui on administra la même dose d'oxtriphylline 24 heures après la vaccination la demi-vie de la théophylline s'est accrue de 122% en moyenne. Deux des trois patients ont manifesté des réactions toxiques au médicament. Ces résultats indiquent que l'élimination de la théophylline est altérée de façon cliniquement significative après une vaccination antigrippale et que les concentrations sériques du médicament qui en résultent peuvent être toxiques même avec l'administration des doses thérapeutiques habituelles de théophylline.

Decreased elimination of theophylline was recently demonstrated in six children with viral infections of the upper respiratory tract.[1] The cause was later suggested to be decreased hepatic biotransformation of theophylline by the mixed function oxidase cytochrome P-450 during the acute phase of the infection.[2] Several studies in animals had demonstrated the level of cytochrome P-450 and related drug elimination to be decreased following the activation of host defence mechanisms.[3-7] We tested this hypothesis further in humans and studied the alteration of theophylline elimination following vaccination against influenza.

Methods

The effect of influenza vaccination on serum theophylline levels during long-term therapy was studied in three patients aged 73, 79 and 47 years. Patients A and B were men and patient C was a woman. Each was recovering from an acute exacerbation of chronic obstructive lung disease. At the time of study the patients were well and ready for discharge. Before the study each had received by mouth 200 mg of oxtriphylline (equivalent to 128 mg of theophylline) every 6 hours for at least 7 days and the serum theophylline level was judged to have reached a steady state (the level was 5 to 10 μg/ml in two samples obtained 48 hours apart). A further serum level was determined immediately before vaccination with 0.5 ml of trivalent influenza vaccine (Fluogen, Parke–Davis, lot 919961B). Blood samples were obtained 12, 24, 48 and 72 hours thereafter, immediately before oxtriphylline was taken; throughout the study the patients continued to receive 200 mg of oxtriphylline every 6 hours as well as all treatment and medication given before vaccination. No dietary restrictions were imposed. Patient A was being treated with furosemide, which can cause falsely high theophylline levels by interfering with the assay; however, before vaccination, when furosemide was being administered, the theophylline levels had been less than 10 μg/ml. The furosemide dosage remained constant throughout the study. Although many other factors are known to alter theophylline clearance[8] the conditions in each patient were identical, as far as we could determine, both before and after vaccination.

Because two of the three patients became ill after vaccination four healthy adults, two men (subjects 2 and 3) and two women (subjects 1 and 4), were used to study the effects of influenza vaccination on the elimination of a single dose of theophylline taken by mouth. A 200-mg dose of oxtriphylline (Choledyl) was given, then blood samples were obtained after 1, 2, 4, 8 and 12 hours. Six days later each subject was vaccinated with 0.5 ml of the same lot of influenza vaccine; after 24 hours 200 mg of oxtriphylline was again given and blood samples were obtained as before. In all subjects the dietary intake of methylxanthine was restricted 15 hours before each dose of theophylline was taken and throughout the sampling period. No other dietary restrictions were imposed. No theophylline or other interference was apparent in blood specimens obtained before ingestion of the drug.

The investigations in both patients and volunteers were carried out following review and approval by the ethics committee of the Victoria General Hospital, Halifax.

Serum theophylline levels were determined by a slightly modified version of the method described by Jatlow.[9] The sensitivity of the assay was increased by back-extracting theophylline into 0.5 ml of 0.1 N NaOH and using microcuvettes to determine the spectrum. The levels determined 2 hours after ingestion of the drug were assumed to follow a one-compartment

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model for elimination,[8] which was used for data analysis in the volunteers. Elimination constants were calculated from the terminal slope of the elimination curve (log concentration v. hours), which was fitted by the method of least squares. Student's *t*-test was used to examine differences in the slopes of the regression curves before and after vaccination of each subject.[10] Mean values were compared with the paired-sample Student's *t*-test.

Results

The patients' serum theophylline levels increased by 219%, 89% and 85% within 12 to 24 hours after vaccination (Fig. 1). During this period patient A showed signs of a toxic reaction to theophylline, including nausea, diarrhea, malaise, cold sweats and chest pain. Patient B experienced malaise, disorientation and chest pain about 48 hours after vaccination. In patients B and C the serum theophylline levels were still high 48 and 72 hours after vaccination. Patient A became too ill to continue with theophylline therapy, so the 48- and 72-hour determinations were not made.

The elimination of a single dose of theophylline taken by mouth 24 hours after vaccination substantially decreased in the four healthy volunteers (Table I). The mean half-life of theophylline significantly increased and the mean clearance significantly decreased. The theophylline disappearance curves for one subject before and after vaccination are shown in Fig. 2.

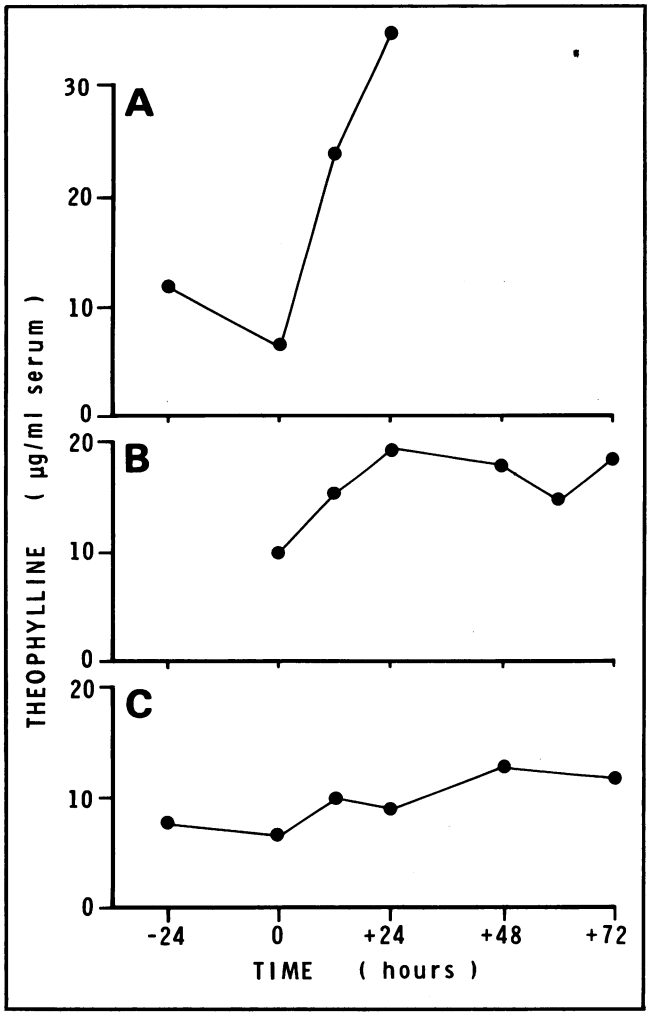

FIG. 1—Effect of influenza vaccination at time zero on serum theophylline levels in three patients receiving 128 mg of theophylline by mouth every 6 hours.

Discussion

After influenza vaccination the elimination of theophylline decreases: the serum theophylline levels rose in our three patients, and the theophylline half-life increased by an average of 122% in the four healthy volunteers. Although the duration of this effect is unknown, the theophylline levels remained high for at least 72 hours in patients B and C. Because in the first 24 hours after vaccination patients A and B showed signs of a toxic reaction to theophylline we ended our study of this group of patients.

The elimination of theophylline largely depends on biotransformation by hepatic cytochrome P-450; alterations in the rate of biotransformation can result in marked changes in the rate of elimination of the drug.[11] In animals the biotransformation of theophylline and related drugs in hepatic microsomes is decreased following the stimulation of host defence mechanisms by a number of agents, including bacillus Calmette–Guérin,[3] endotoxins,[4] interferon inducers,[5] *Corynebacterium parvum*,[6] viruses[7] and *Plasmodium*

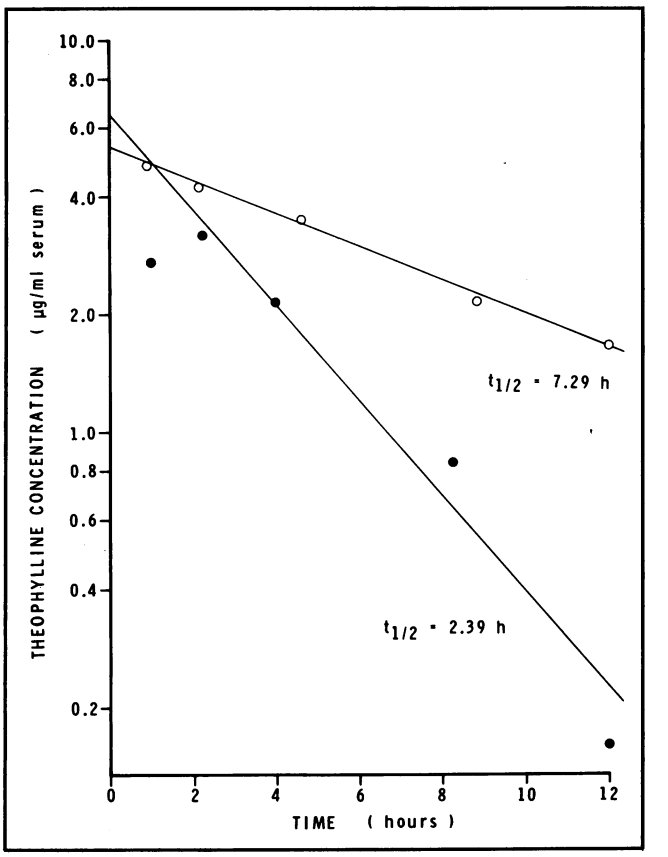

FIG. 2—Effect of influenza vaccination at time zero on elimination of single dose of theophylline taken orally 24 hours later by healthy volunteer. Black circles indicate control values and white circles values after vaccination.

Table I—Effect of influenza vaccination on theophylline elimination

Subject and time in relation to vaccination	Weight (kg)	Dose (mg/kg)	Theophylline elimination kinetics: Half-life (h)	Apparent volume of distribution (l/kg)	Clearance (mg/kg per hour)*
1					
Before	51.8	2.47	4.17	0.33	56.1
After			6.54†	0.32	35.2
2					
Before	72.7	1.76	2.99	0.09	20.7
After			9.63†	0.10	7.0
3					
Before	70.5	1.81	2.39	0.27	78.3
After			7.29†	0.34	30.6
4					
Before	48.6	2.63	3.64	0.27	51.3
After			5.72†	0.24	28.8
Mean ± standard error					
Before			3.30 ± 0.39	0.24 ± 0.05	51.6 ± 11.9
After			7.30 ± 0.84‡	0.25 ± 0.05	25.4 ± 6.3‡

*Calculated from apparent volume of distribution (Vd) and half-life ($t_{\frac{1}{2}}$) as follows: Vd X 0.693 ÷ $t_{\frac{1}{2}}$.
†Slope of terminal phase of elimination curve significantly different ($P < 0.05$) from corresponding control slope.
‡Significantly different ($P < 0.05$) from corresponding control mean.

berghei.[12] This decrease can have a marked effect on drug elimination rates, as demonstrated by a fourfold increase in the half-life of phenytoin in rats following treatment with *Bordetella pertussis* vaccine or the synthetic polynucleotide poly-rI·rC.[13] We therefore propose that the reduced elimination of theophylline in humans that we and Chang and collaborators[1] have observed results from decreased levels of cytochrome P-450 and a reduced capacity of the liver to metabolize theophylline.

Our study has demonstrated that the elimination of theophylline is significantly impaired after vaccination against influenza, and that the resulting theophylline levels are dangerous to patients receiving long-term theophylline therapy. This suggests that influenza vaccination of patients with chronic obstructive lung disease who are receiving maintenance oral theophylline therapy should be considered only if the serum theophylline levels can be carefully monitored.

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Who should receive influenza vaccine this fall?

"a) persons of any age who have such conditions as
1 acquired or congenital heart disease associated with pulmonary congestion
2 chronic pulmonary disease, associated with compromised respiratory functions
3 chronic renal disease, especially with azotemia
4 chronic metabolic disease such as diabetes mellitus
5 immunodeficient or immunosuppressed conditions including malignant tumours, leukemia, etc., under therapy
6 chronic severe anemias such as sickle cell disease.
b) older persons, particularly those over 65 years of age."

—National Advisory Committee on Immunization: "A Guide to Immunization for Canadians", available free from bureau of epidemiology, DNH&W, Ottawa, Ont. K1A 0L2.