Clinical Investigation

Influenza Vaccination and Theophylline Pharmacokinetics in Patients With Chronic Obstructive Lung Disease

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Total theophylline clearance rate was measured before and 24 hours after standard influenza vaccination in seven men with stable chronic obstructive lung disease. In four, total theophylline clearance rate was also measured 48 hours after vaccine administration. There was no significant change in the clearance rate after either time interval. These results do not support recent recommendations to monitor serum theophylline concentrations or reduce theophylline dosage during the 48-hour period following influenza vaccination. Nevertheless, pending further studies, patients maintained on a regimen of theophylline preparations should be followed clinically for theophylline toxicity for the first several days after receiving influenza vaccine.

Elimination of theophylline from the body occurs predominantly via oxidative metabolism by hepatic cytochrome P-450 microsomal enzyme systems.[1,2] Multiple factors are known to alter hepatic theophylline metabolism and thereby change steady-state serum theophylline concentration.[3] Certain acute viral infections of the upper respiratory tract may transiently depress the hepatic elimination of theophylline, leading to a toxic reaction in some patients.[4-8] This observation is consistent with previous investigations showing that a variety of agents that activate the immune system and stimulate interferon synthesis may also simultaneously depress cytochrome P-450-linked monooxygenase systems that metabolize drugs in the liver.[6,9-14]

Standard influenza vaccination has recently been reported to significantly impair the elimination of theophylline and certain other drugs metabolized in the liver.[15-17] Other investigations have not confirmed these observations, however.[18-20] Annual influenza vaccination is recommended for patients who have chronic obstructive lung disease,[21] many of whom receive maintenance theophylline therapy. It is therefore important to determine whether or not influenza vaccination adversely affects theophylline pharmacokinetics. We have investigated the effect of influenza vaccination on theophylline clearance rate in clinically stable persons who have chronic obstructive lung disease 24 and 48 hours following vaccination. Serum interferon levels were measured before and after vaccination to determine their relationship to any observed interaction.

Patients and Methods

Seven men were electively admitted to either the Salt Lake City Veterans Administration Medical Center or the Clinical Research Center of the University of Utah. The mean age of the men was 64 years (range, 57 to 79). All had chronic bronchitis as defined clinically by the American Thoracic Society[22] and chronic airflow obstruction according to standard spirometric criteria.[23] Five of the men were currently smokers (5 to 30 cigarettes per day) and two were ex-smokers who had not smoked during the past year. Before the study, all had been receiving maintenance theophylline therapy by mouth on a long-term basis. None were receiving corticosteroids either by inhalation or by mouth. Other routine drug therapy was continued during the study period.

Two persons had received influenza vaccine a year before the study. Three others had received influenza

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vaccine two, three and five years before the study, respectively. The remaining two persons had never been vaccinated for influenza. Subjects were admitted to the study only after they met the following criteria designed to assure clinical stability and to eliminate those factors known to alter theophylline elimination:[3]

- No clinical deterioration of their chronic obstructive lung disease, including upper and lower respiratory tract infections, in the two months before the study.
- No clinical evidence of right or left ventricular congestive heart failure.
- No intake of medications known to affect theophylline elimination (erythromycin, β-blocking medicines, cimetidine, allopurinol or phenobarbital). The only exception was a patient who had been taking cimetidine, 300 mg by mouth at bedtime, for the past year; this regimen was continued during the study.
- No biochemical evidence of active liver disease.

They were asked to maintain their usual caffeine intake and dietary habits. Informed written consent was obtained from each subject after the study had been fully explained in a manner approved by the Human Studies Committee of the Salt Lake City VA Medical Center and the Institutional Review Board of the University of Utah School of Medicine.

Study Design

Maintenance oral theophylline therapy was discontinued on the first day of the study period. A constant intravenous infusion of aminophylline ([formerly theophylline ethylenediamine] 85% anhydrous theophylline, GD Searle & Company, Chicago) was then administered via infusion pump (IMED 922, IMED Corporation, San Diego, Calif) for the duration of the study. The concentration of the aminophylline infusion was calculated such that during the 24-hour period the subject received his usual total 24-hour dose of anhydrous theophylline in 1,500 ml of 5% dextrose in water. Total theophylline clearance rate (TTCR) was calculated according to the equation[24,25]

$$\text{TTCR (ml/min)} = \frac{Q}{C_{ss}} \times \frac{1{,}000}{60}$$

where Q = rate of theophylline infusion (mg per hr) and C_{ss} = steady-state serum theophylline concentration (μg per ml). Steady-state with respect to serum theophylline concentration was accepted when serum theophylline concentrations, measured 24, 25 and 26 hours after an intervention—that is, initiation of intravenous aminophylline infusion and administration of influenza vaccine—were within 1 to 2 μg per ml of each other and showed no consistent upward or downward change in the three serial samples.[25] In the average person, the mean difference among the three serially measured theophylline concentrations was 0.48 μg per ml. C_{ss} was calculated as the mean of the three samples.

After baseline total theophylline clearance rate was determined, each person received intramuscularly an injection of 0.5 ml of inactivated subvirion trivalent influenza vaccine (Wyeth Laboratories, Philadelphia; lot 212001; expiration date June 1982). The intravenous aminophylline infusion was continued and the total theophylline clearance rate was measured 24 hours after the vaccination in the seven men. In four, the total theophylline clearance rate was also determined 48 hours following administration of the influenza vaccine. Patients were monitored for vital signs and clinical theophylline toxic reaction every eight hours during the course of the study period.

TABLE 1.—*Total Theophylline Clearance Rate (TTCR) Before and 24 Hours After Influenza Vaccination in Seven Men With Chronic Obstructive Lung Disease*

Subject	*Age (years)*	*Aminophylline Infusion Rate (mg/kg/24 hr)*	*Prevaccination TTCR (ml/kg/min)*	*24 Hour Postvaccination TTCR (ml/kg/min)*	*Difference in TTCR (ml/kg/min)*
1	59	21.6	1.2	1.7	−0.5
2	61	18.2	1.3	1.0	0.3
3	69	20.0	1.8	1.8	0.0
4	60	13.2	1.3	1.2	0.1
5	61	11.3	0.8	0.7	0.1
6	57	12.8	1.1	1.3	−0.2
7	79	22.0	0.7	0.7	0.0
Mean	64	17.0	1.2	1.2	−0.03
SD	8	4.5	0.4	0.4	0.26

SD = standard deviation

Theophylline assay was done using the quantitative Enzyme-Mediated Immunoassay Technique (EMIT; Syva Inc, Palo Alto, Calif).[26] In our laboratory, the measurement of serum theophylline concentration has a coefficient of variation of ±3.0% at serum theophylline concentrations of 5 to 15 μg per ml.

Serum interferon titers were measured immediately before influenza vaccination and repeated at intervals of 8, 16, 24 and 48 hours and 7 to 10 days following vaccination. An automated, quantitative cytopathic-effect reduction assay for interferon was used.[27] The interferon titer was recorded as the reciprocal of the dilution producing 50% reduction in encephalomyocarditis virus cytopathic effect formed in the microassay system. The National Institutes of Health human leukocyte interferon standard (6023-901-527) with a reported titer of 20,000 units has an average titer of 23,000 units in the automated assay.*

Student paired *t* test was used to examine differences in the total theophylline clearance rate, serum theophylline concentration and interferon titers before and after influenza vaccination of each subject. For all statistical testing, *P* less than .05 was used as the minimal level of significance.

Results

The mean prevaccination total theophylline clearance rate for subjects 1 to 7 was 1.2±0.4 ml per kg of body weight per minute (mean±SD; Table 1); mean steady-state serum theophylline concentration was 9.0 ±3.9 μg per ml (mean ± SD). The mean difference

*Jon Green, MD, Division of Infectious Diseases, performed the interferon assays.

TABLE 2.—*Total Theophylline Clearance Rate (TTCR) Before and 48 Hours After Influenza Vaccination in Four of Seven Men in Study*

Subject	Age (years)	Aminophylline Infusion Rate (mg/kg/24 hr)	Prevaccination TTCR (ml/kg/min)	48 Hour Postvaccination TTCR (ml/kg/min)	Difference in TTCR (ml/kg/min)
4	60	13.2	1.3	1.1	0.2
5	61	11.3	0.8	0.7	0.1
6	57	12.8	1.1	1.3	−0.2
7	79	22.0	0.7	0.7	0.0
Mean	64	14.8	1.0	1.0	0.03
SD	10	4.9	0.3	0.3	0.17

SD = standard deviation

in the total theophylline clearance rate before and 24 hours following influenza vaccination was -0.03 ± 0.26 ml per kg per minute (SD), which is not significant (paired t test, $P = .778$). Similarly, the mean difference in total theophylline clearance rate before and 48 hours after influenza vaccination in subjects 4 to 7 was not significant (0.03 ± 0.17 ml per kg per minute [SD], $P = .789$; Table 2).

Serum interferon was not detected in any of the seven persons before influenza vaccination or at intervals of 8, 16, 24 and 48 hours and 7 to 10 days following vaccination.

No adverse reactions to influenza vaccination or theophylline infusion were encountered during the study.

Discussion

A variety of agents that activate the immune system simultaneously depress drug-metabolizing, cytochrome P-450-linked monooxygenase systems in the liver.[6,9-14] As a result, these agents may have the potential to alter the therapeutic and toxic activities of certain drugs metabolized by the liver. The agents, which include certain acute infections (viral, bacterial and parasitic), vaccinations (pertussis and bacille Calmette Guérin) and synthetic polynucleotides, all have in common the ability to induce production of interferon. The passive transfer of interferon may depress hepatic cytochrome P-450 drug metabolism in experimental animals.[12] Based on these findings, it has been hypothesized that interferon production may contribute significantly to the observed depression of drug metabolism in these studies, though other immune mechanisms may also play important roles.[6]

Theophylline elimination occurs largely via oxidative metabolism in hepatic cytochrome P-450 systems.[1,2] Recent investigations suggest that some infections and other types of immune stimulation may depress theophylline elimination.[4-8,15,16] Certain respiratory tract viral infections have been shown to acutely prolong plasma theophylline half-life by 68% in one study (influenza A and adenovirus)[4] and to increase serum theophylline concentration by a mean of 16.5 μg per ml in another study (influenza B).[5]

Standard influenza vaccination with inactivated vaccine has also been reported to decrease the elimination of theophylline and the hepatically metabolized drug, aminopyrine.[6,15-17] In four healthy volunteers, Renton and co-workers found a mean 51% reduction in serum theophylline clearance 24 hours following inactivated whole virion influenza vaccination. They also measured serum theophylline concentrations before and after influenza vaccination in three patients with chronic obstructive lung disease and found increases of 219%, 89% and 85%, respectively, within 12 to 24 hours of vaccination.[6,15] Walker and associates reported the case of a pediatric patient who had a 70% increase in serum theophylline concentration five hours following subvirion influenza vaccination.[16] Similarly, in another recent study hepatic metabolism of aminopyrine was reduced by a mean 46% a week following influenza vaccination in healthy volunteers.[17] On the basis of these reports, some authorities have suggested that consideration be given to omitting or decreasing theophylline dosage for 24 hours following influenza vaccination.[28]

The present investigation does not confirm a clinically significant effect of influenza vaccination on theophylline elimination. In seven elderly men with chronic obstructive lung disease, we found no alteration in total theophylline clearance rate 24 hours following influenza vaccination. In four of these persons, there was also no change in total theophylline clearance rate 48 hours after administration of the vaccine. Three additional investigations reached a similar conclusion.[18-20] However, these studies are limited by their use of sustained-release theophylline preparations and measurement of isolated serum theophylline concentrations rather than theophylline elimination values. There may be great dose-to-dose intrasubject variation in the absorption profile of sustained-release theophylline medicines.[29] This results in considerable dose-to-dose variability in serum theophylline concentrations measured at a given interval following theophylline ingestion. Still, in 12 clinically stable asthmatic adults receiving oral maintenance therapy with a sustained-release theophylline preparation, Fischer and colleagues noted no significant increase in serum theophylline concentration 24 hours, 72 hours and one and two weeks following influenza vaccination.[20] A single subject in this study did show a 10 μg per ml increment in serum theophylline concentration 24 hours after vaccination associated with symptoms of toxic reaction to theophylline. The other two preliminary studies found no significant change in serum theophylline concentration 24 hours following influenza vaccination in a total of 16 persons with stable chronic obstructive lung disease.[18,19]

There are several possible explanations for the disparate results of these studies. First, different preparations of standard, inactivated vaccine may exert maximal effects on hepatic drug metabolism at different times.[30] The preparations used by Renton and Walker and co-workers[15,16] impaired theophylline elimination within 24 to 36 hours of vaccination, whereas the preparation used by Kramer and McClain[17] did not exert its maximum effect on aminopyrine metabolism

until seven days after vaccination. Against this hypothesis, Fischer and associates found no significant change in serum theophylline concentration up to 14 days after influenza vaccination.[20]

Another consideration is that only certain influenza vaccine preparations may be capable of inducing the synthesis of circulating interferon or of depressing hepatic drug metabolism, or both.[30] The inactivated influenza vaccine preparation used in this study did not induce production of measurable serum interferon at postvaccination intervals of 8, 16, 24 and 48 hours and 7 to 10 days. It is not clear, however, that interferon production is the mechanism by which inactivated influenza vaccine may depress the elimination of some hepatically metabolized drugs. Inactivated influenza vaccine is not likely to be a potent inducer of interferon production, which may require active influenza virus replication.[31-36]

Differences in study population also do not obviously explain the disparate results of the available studies of influenza vaccination and theophylline elimination. Age is apparently not a confounding variable, as studies reporting a depressant effect of influenza vaccination on theophylline elimination have included both younger[16,17] and older persons,[15] as have studies showing no effect.[18-20] Cigarette smoking also does not appear to be a significant factor. Five of seven persons in our study were smokers, whereas all of the subjects in the study by Fischer and colleagues[20] were nonsmokers. Neither study found an effect of influenza vaccination on theophylline elimination. Prior exposure to influenza vaccination does not seem to condition who will or will not have depressed theophylline elimination following vaccination. Two of our subjects had not previously received influenza vaccine, whereas the other five had been vaccinated within the past five years. Neither group showed a decrease in theophylline elimination.

Available studies do not support current recommendations to either monitor serum theophylline concentrations or omit or decrease theophylline dosage for the 24 to 48 hours following trivalent influenza vaccination.[28] In the absence of definitive information, vaccinated patients should be advised to report symptoms suggestive of toxic reaction to theophylline immediately to their physicians. Further studies are warranted to determine the frequency with which influenza vaccination may depress hepatic drug elimination as well as the timing, mechanism and conditioning factors for this interaction.

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