

Controversies Surrounding Medication Interactions with the Influenza Vaccine

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Encouraging patients to receive an annual influenza vaccine is the best way to protect against influenza and its consequences, such as an increase in number of doctor visits, missed days of work, flu-related hospitalizations, and death.¹ Even with the well-known benefits of the influenza vaccine, only 43.6 percent of adults in the United States were vaccinated in 2015.²

However, prior to receiving the influenza vaccine, many patients, and even some influenza consent forms used in outpatient settings, ask questions related to the use of chronic medications such as warfarin, theophylline, and phenytoin. As a result of these inquiries, patients and providers who are taking and/or prescribing these medications may question if it is safe to receive and/or administer an influenza vaccine.

While it is necessary to ensure the safe use of the influenza vaccine including the potential impact it may have on other important medications, rarely do patients need to avoid the influenza vaccine due to medication interactions. This article aims to review the evidence surrounding these perceived influenza medication interactions.

Influenza Vaccine and Warfarin

An interaction between the influenza vaccine and warfarin was first described in the 1980s when an 81-year-old patient developed a gastrointestinal bleed ten days following the influenza vaccination while on chronic warfarin.³ Since that time, there have been multiple studies, with various results, aimed to determine if

the influenza vaccine increases the risk of bleeding. The CHEST anticoagulation guidelines reflect these various findings, classifying the influenza vaccine as an agent that both inhibits and potentiates warfarin's effect depending on the publication year. The most current CHEST anticoagulation guidelines do not include the influenza vaccine as a problematic medication.⁴ Kuo and colleagues reviewed seven different studies of varying methodology which makes it difficult for the researcher to compare outcome data.⁵ Regardless, six of the seven studies found no significant difference in bleeding risk and anticoagulant effects among patients who received the influenza immunization compared to those who did not. In the single study that found a significant difference, patients who had been on stable anticoagulation for three months were monitored 5-7 days before the immunization and again 7-10 days after. The study group had a mean increase in INR of 0.56 from baseline which was statistically significant, and two of these patients had a mild bleeding event. Current CHEST guidelines do not recommend warfarin dosing adjustments for an individual INR reading with a change of less than 0.5 in patients who have previously been stable on warfarin.⁴ Therefore, while this study did see an increase in INR with the influenza vaccine, this change was not clinically significant in the majority of patients. Based on the evidence, it is not necessary to screen patients of warfarin use prior to administering the influenza vaccine nor should warfarin use constitute a reason to avoid the influenza vaccine.

Influenza Vaccine and Theophylline

It has been hypothesized that the influenza vaccine decreases theophylline clearance through the suppression of microsomal enzymes or through a mediator such as interferon. This hypothesis was first made after theophylline level increases were seen following the administration of older variations of the influenza vaccine. While there have been a number of studies since this initial hypothesis (the majority concluding theophylline levels are unchanged after immunization) there are relatively few current studies addressing the potential interaction between the influenza vaccine and warfarin—two of the most current articles date back into the 1980s. In one such study, Hannan and colleagues administered theophylline to 16 healthy patients and subsequently drew blood levels at 15, 30, 45 minutes, and at 1, 2, 3, 4, 6, 8, 12, and 24-hour time intervals.⁶ After the initial blood draw period, patients were administered the whole virus influenza vaccine and repeated blood work as outlined above on days 2 and 6 after vaccine administration. Pharmacokinetic data demonstrated there were no significant changes in half-life, maximum concentration (C_{max}), area under the curve (AUC), or clearance, indicating it was unlikely that there would be increased risk of theophylline toxicity after the influenza vaccine administration. In a subsequent study, six healthy young adult individuals were given a five-day course of theophylline in two

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cycles.⁷ The influenza vaccine was administered on the fourth day of the second five-day cycle. Plasma theophylline concentrations were measured on days 4 and 5 of both cycles: No changes in trough, C_{max}, time to peak concentration, or AUC were seen. With the modernization of influenza vaccinations and literature revealing the unlikelihood of increased theophylline levels, theophylline use should not warrant avoidance of the influenza vaccine.

Influenza Vaccine and Phenytoin

The potential interaction between the influenza vaccine and phenytoin has been studied in a limited amount of patients and not extensively since the 1980s. Unfortunately, based on studies, no clear conclusion has been made as these studies have shown an increase, decrease, and no change in phenytoin levels. In a prospective study of 16 elderly patients treated with phenytoin who were administered trivalent influenza vaccine, there was a slight nonstatistically significant increase in serum phenytoin levels.⁸ When levels were assessed prior to vaccination, seven, and 14 days after administration, mean phenytoin levels of 11.3, 11.9, and 12.1 mcg/mL were seen respectively. In a subsequent study of 16 patients with epilepsy stabilized on phenytoin, no significant increases in serum phenytoin concentrations were seen on days 7 or 14 after the administration of the influenza vaccine.⁹ Four patients did experience

phenytoin increases ranging from 46-170 percent, and, in two of these patients, changes in phenytoin levels best correlated with the influenza vaccine. Although we see small variances in serum phenytoin levels, it is considered by most to be a minor drug interaction and the benefits of the influenza vaccination in most cases far outweigh the risk of the interaction.

Conclusion

Overall, none of the above potential influenza vaccine-medication interactions should preclude the administration of the influenza vaccine. It may be prudent to monitor INR values soon after the administration of the influenza vaccine for patients on warfarin at an increased risk of bleeding. Studies indicate theophylline levels do not need increased monitoring after the administration of the vaccine. It may also be prudent to monitor phenytoin levels in high risk patients on phenytoin within 1-2 weeks of administering the influenza vaccine; however, the evidence is conflicting.

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