

Introduction:

- ❖ Acetaminophen is one of the most popular analgesic agents and generally considered safer than NSAIDs. Its use is more common in older populations, many of whom are on anti-coagulation.
- ❖ Adverse drug-drug interaction between acetaminophen and warfarin has been described in the literature. The resultant supratherapeutic INR may result in life-threatening bleeding.
- ❖ Despite the potentially dire consequences, the interaction may be widely underappreciated.
- ❖ We present one such case of this potentially mortal interaction.

Case:

80-year-old male presented to the hospital with right lower extremity (RLE) pain.

History

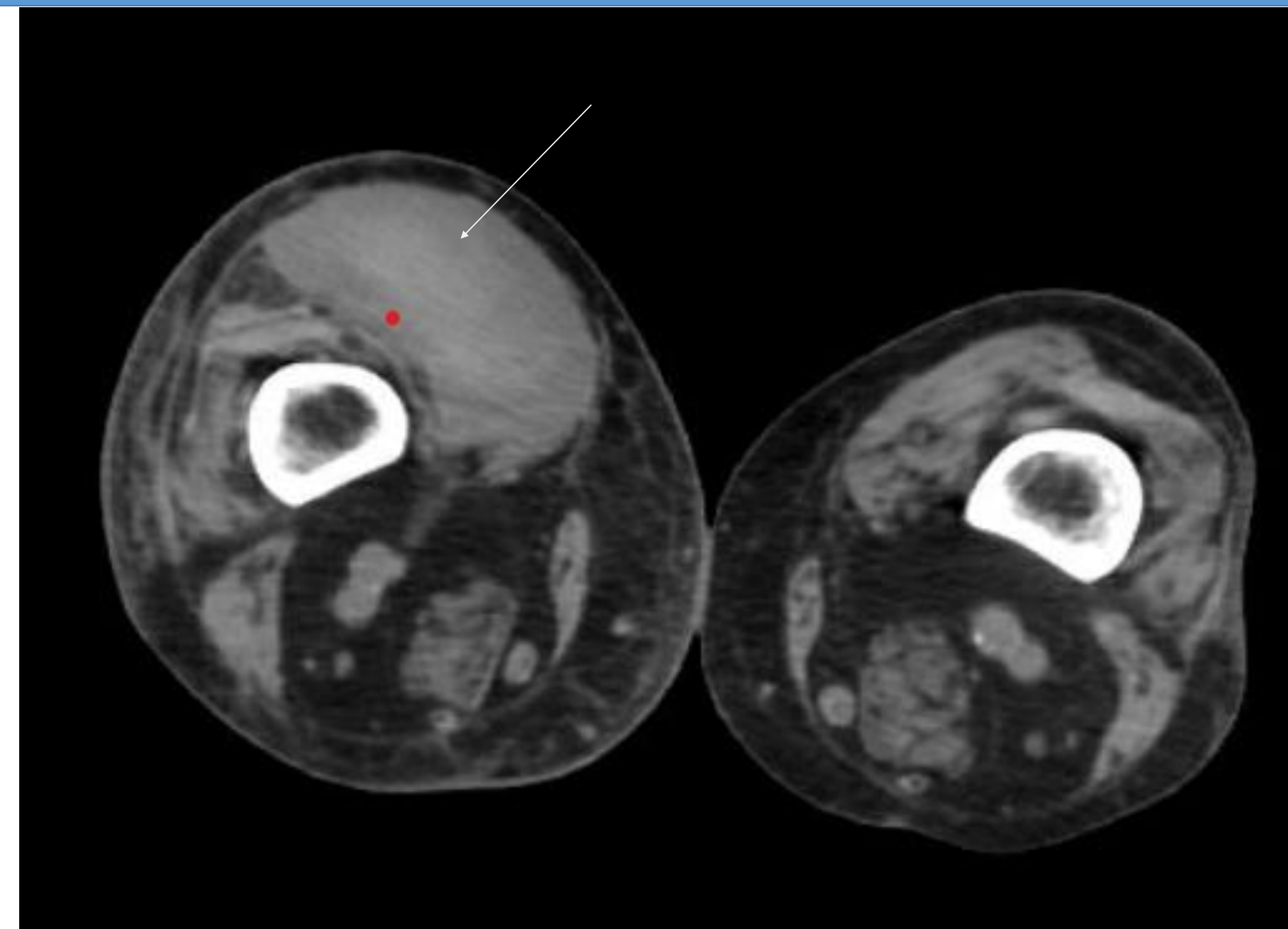
- **HPI:** The patient tripped on a mat 2 weeks ago and landed on his right knee. He felt well at the time and was able to mobilize. Hence, **he self-medicated with store-bought Extra strength Tylenol (Acetaminophen) and used 1 gram every 6 hours.** Over the next 10 days, his RLE became more painful, swollen, and bruised. He could no longer mobilize, which prompted a hospital visit.
- **PMH:** Atrial fibrillation controlled on oral Metoprolol, and **he was on warfarin for many years with no recent change in dosage and consistent therapeutic INR** including the last INR check 1 month ago

Physical exam

- **Vitals:** Within normal limits except for an irregular pulse rate of 104/min
- **Exam:** Diffuse right lower extremity swelling with patchy ecchymoses, especially over the thigh region, and multiple bruises on the trunk

Tests

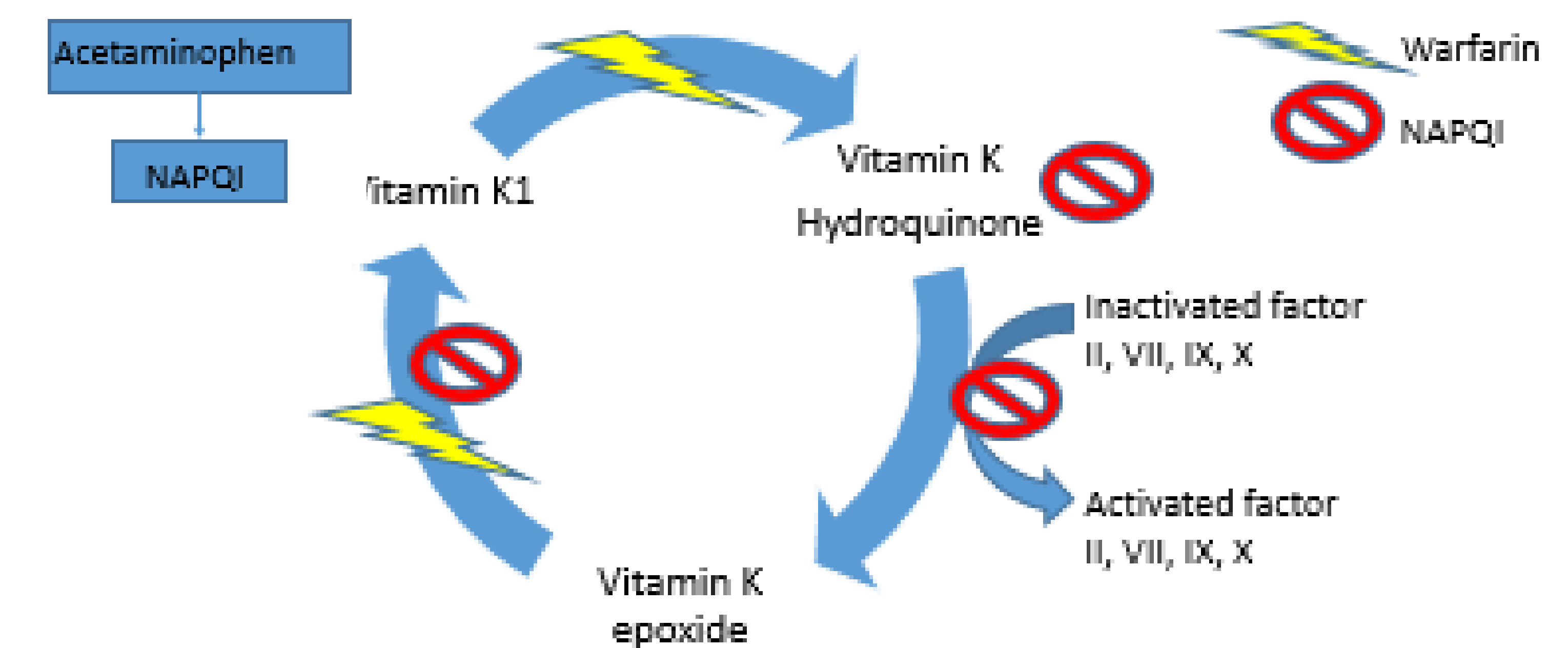
- **Labs:** **Initial INR was 22.21** confirmed twice. aPTT was 86.5 seconds and platelets were 460,000/ μ l
- **Imaging:** CT-RLE without contrast showed a **large hematoma in the right thigh measuring 16 x 9 x 4 cm³**



Clinical course:

- ❖ With the large hematoma and high INR, the patient was given 5000 units **Prothrombin Complex Concentrate with vitamin K 10 mg IV** and the INR was lowered to 1.12.
- ❖ Warfarin was discontinued and the hematoma was managed conservatively in conjunction with vascular surgery.
- ❖ The patient improved and was eventually discharged with anti-coagulation held for the next 2 weeks.
- ❖ **He was explicitly advised to discuss any new drug use including over-the-counter medications with his physician at the outset.**

Discussion:



- ❖ **COMMON-** In a study of 134,833 patients on long-term warfarin therapy, **22.7% were co-prescribed acetaminophen¹**. This does not include Over-the-counter acetaminophen use.
- ❖ **DANGEROUS-**
 - A case control study of 93 patients on warfarin suggested that concurrent **acetaminophen use was associated with up to 10-fold increase in risk of having INR > 6.0²**.
 - A systematic review of 7 RCTs found that acetaminophen caused a **dose-dependent increase in the INR** however trials withdrew patients for safety reasons if their INR became high³.
- ❖ **In patients on warfarin, concurrent use of acetaminophen may cause pharmacodynamic interaction to increase the INR** which increases the potential for life-threatening. In our patient, the INR rose to more than 20 with clinically significant bleeding.
- ❖ **Close monitoring of INR is needed for patients starting or ending acetaminophen courses.**^{3,4}

Conclusion:

This case serves as a reminder for an internist to remember this critical yet overlooked interaction and reinforce patient education!

References:

1. Wittkowsky AK, et al. Frequency of concurrent use of warfarin with potentially interacting drugs. *Pharmacotherapy* 2004;24:1668-74.
2. Hylek EM, et al. Acetaminophen and other risk factors for excessive warfarin anticoagulation. *JAMA* 1998;279:657-62.
3. Caldeira D, et al. How safe is acetaminophen use in patients treated with vitamin K antagonists? A systematic review and meta-analysis. *Thromb Res* 2015;135:58-61
4. Lopes RD, et al. Warfarin and acetaminophen interaction: a summary of the evidence and biologic plausibility. *Blood* 2011; 118: 6269-73