**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.

- **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.

**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 acetaminophen. 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 > 6.0.
  - 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 high.

- **In patients on warfarin, concurrent use of acetaminophen may cause pharmacodynamic interaction to increase the INR which increases the potential for life-threatening bleeding. 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.**

**Conclusion:**

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

**References:**