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Vitamin K supplementation in patients with cirrhosis

Cirrhosis can result from various underlying diseases affecting the liver. In the United States, viral hepatitis, alcoholic liver disease, and nonalcoholic fatty liver disease are among the most common etiologies. Historically, cirrhosis was believed to be irreversible, but today successful treatment of the underlying cause can potentially reverse cirrhosis in its early stages. Unfortunately, many patients will progress to end-stage liver disease with serious complications resulting in over 36,000 deaths each year in the United States.

A common complication of cirrhosis is altered hemostasis. Patients with cirrhosis have reduced production of both procoagulant and anticoagulant factors. Many patients with cirrhosis have a prolonged prothrombin time (PT) despite having “rebalanced” coagulation as a result of decline in both procoagulant and anticoagulant factors. It is common practice to administer vitamin K to patients with cirrhosis who have prolonged PT or international normalized ratio (INR). Doses are variable, but 10 mg given orally daily for several days or a one-time 10 mg injection are common regimens. Evidence supporting the use of vitamin K for these patients is lacking and recent data further question its necessity.

In a 2013 single-center, observational study 89 patients with hepatitis B, hepatitis C, cirrhosis, or hepatocellular carcinoma were administered 10 mg of subcutaneous vitamin K and compared with 39 healthy controls. Patients with a history of bleeding or thromboembolic disease were excluded. Laboratory parameters including PT, activated partial thromboplastin time (aPTT), thrombin time (TT), fibrinogen, Factor VII, protein C, and protein S were measured at baseline and 72 hours after the administration of vitamin K.

At baseline, patients with cirrhosis had significantly prolonged PT, aPTT, and thrombin time compared with healthy controls. Patients with hepatitis C had prolonged PT and thrombin time. Vitamin K significantly reduced both the PT (from 166.3 to 152.8 [values expressed as percentage of control plasma]; p=0.016) and aPTT (from 146.1 to 132.5; p=0.016) in patients with cirrhosis but had no effect on patients who had liver disease without cirrhosis. Vitamin K failed to significantly increase Factor VII or fibrinogen in any of the patients with liver disease. In addition, no increase in protein C or S was found. The authors concluded that although vitamin K administration provided small but significant improvements in PT and aPTT in patients with more severe liver disease, the overall efficacy was limited.

Unfortunately, there are a number of limitations to this study that hinder its generalizability to clinical practice. The use of a single center, small sample size, and observational design are primary concerns. In addition, the study administered vitamin K via the subcutaneous route which is known to result in erratic absorption; thus, other routes of administration may be more effective. Laboratory parameters were tested only once after vitamin K administration (3 days post-dose); measurements at different time points could alter the study results. Finally, no clinical outcomes were included in the study so it is unknown whether vitamin K administration would improve the outcomes of these patients.

More recently a retrospective, observational study of 276 patients sought to determine whether vitamin K administration improved the INR in patients with cirrhosis. Patients with cirrhosis who were administered vitamin K during the first 4 days of hospital admission for reasons other than warfarin reversal were included and matched with patients who did not receive vitamin K. Vitamin K was administered subcutaneously (16.9%), orally (36%), intravenously (13.1%), or by more than 1 route (33.8%). The median single dose was 5 mg (interquartile range [IQR] 1 to 20 mg) and over 4 days the median dose was 15 mg (IQR 1 to 50 mg).

Baseline INRs were similar in patients who did not receive vitamin K (1.66) to those who received vitamin K (1.95). Vitamin K administration was not associated with a decrease in INR (adjusted odds ratio 1.17, 95% CI 0.66 to 2.08; p=0.59) or a reduced risk of bleeding (adjusted odds ratio 4.90, 95% CI 0.56 to 43; p=0.15).

This study suffers from several limitations similar to the earlier study with added concerns related to the retrospective nature of the study. The use of a variety of vitamin K doses and routes of administration make it difficult to determine whether a particular dose or route is effective for normalizing the INR in these patients.

The use of vitamin K in patients with cirrhosis is commonplace and, due to its mild adverse effect profile, arguments against its use are often minimized. However, recent evidence refutes its necessity. Unfortunately, these studies are observational in nature, have a number of limitations, and are unlikely to change clinical practice.

Seizing opportunities to reduce risk for tranexamic acid-associated seizure

Tranexamic acid (TXA) and aminocaproic acid (ACA) are the antifibrinolytic lysine analogues used to reduce bleeding in surgical procedures since the 1960s. These agents have primarily been studied in cardiovascular surgery, where 80% of surgical bleeding occurs. In a discussion on considerations to reduce perioperative bleeding and blood transfusion, the 2011 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines on coronary artery bypass graft surgery state that both TXA and ACA reduce blood loss and transfusion and do not appear to adversely influence mortality risk. Recently, some manufacturers of aminocaproic acid injection have experienced shortages, which may encourage the use of TXA while ACA is unavailable. However, increased use of TXA has led to questions regarding its neurological safety because of numerous reports of TXA-associated seizure.

Incidence and risk factors

The first identification of TXA-associated seizure was shortly after the 2008 withdrawal of the antifibrinolytic aprotinin which, similar to the current ACA shortage, diverted use of antifibrinolytic agents to TXA. Postoperative generalized convulsive seizures were observed in patients who had no evidence of cerebral ischemia. Further study in animal models indicated that seizure may be induced by TXA through its actions as a glycine antagonist, generation of cerebral ischemia, and disinhibition of gamma-aminobutyrate type A receptors. A dose-dependent risk of seizures was identified with TXA, and because of variability in dosing at the time, a consensus conference was convened that resulted in a recommendation for a maximum TXA total dosage of 50 to 100 mg/kg in patients over 50 years of age who undergo on-pump cardiac surgery.

Systematic analyses describing TXA-associated seizures vary in level of evidence, as do their reported seizure incidence rates, which range from 0% to 7.6%. The largest dataset comes from a retrospective analysis of data from 11,259 patients who underwent cardiopulmonary bypass. Seizures were reported in 0.9% of patients receiving TXA, which was an independent predictor of seizure (odds ratio [OR], 14.3; 95% CI, 5.5 to 36.7). More rigorous study in a prospective observational cohort that diagnosed seizures with continuous electroencephalogram monitoring reported a 3% incidence rate, although the study was relatively small (n=101) and single-center. Seizures were reported in these analyses predominantly between 5 and 8 hours after surgery, although cases have been reported at up to 15 hours postoperatively. Compared to ACA, seizures have been approximately twice as frequent with TXA.

Patients who experience TXA-associated seizure may be at greater risk of morbidity and mortality. One single-center retrospective cohort reported worse outcomes among patients receiving TXA during cardiac surgery who experienced seizures. Compared to patients without seizures, there were significant increases in length of intensive care unit stay (329.2 vs 98.8 hours), and in-hospital mortality (19.1% vs 3.7%). Increased incidence of sepsis, stroke, and atrial fibrillation has also been reported with TXA-associated seizure. Similar findings have been reported from other analyses regarding increased mortality rates (9.7% to 14.3% of seizure cases vs 1.4% to 3.6% of controls).

In addition to TXA itself, other significant predictors of seizure in these studies included female sex, redo surgery, ascending aortic disease, and congestive heart failure (CHF), all of which increased odds of seizure by approximately 2- to 3-fold. Other variables significantly associated with increased seizure risk included age >70 years (OR, 1.9), renal impairment (defined as modification of diet in renal disease <59 mL/min/1.73 m2; OR, 1.87), and preoperative creatinine values >1.29 mg/dL (OR, 3.4), as described in a single-center case-control study.

Recommendations

Studies evaluating the risk of TXA-associated seizure have been limited by their single-center or retrospective nature, but current estimates place the incidence at up to 7.6%, and risk may be increased in females and patients who are elderly or who have comorbid conditions such as renal dysfunction or CHF. Clinicians switching to TXA during an ACA shortage should ensure appropriate doses of TXA are used and should monitor patients with increased risk for seizure, particularly within the first postoperative day.

Reducing waste of expensive drugs

Many drugs are dosed based on anthropometric characteristics, such as weight, body mass index, or body surface area, often because of their high safety risks or narrow therapeutic window. Not surprisingly, many of these drugs are used in treatment of cancer, immunologic, or rare diseases, and are therefore costly. A considerable obstacle in the responsible utilization of these drugs is their frequent requirement to be administered or discarded shortly after preparation. This often leads to waste of expensive medications because calculated doses do not correlate accurately with available product vial sizes. This problem is exacerbated by the use of many of these drugs for rare conditions, precluding the use of leftover drug in a reasonable timeframe.

A recent estimation of the cost of drug waste quantified the extent of this problem in cancer patients. The investigators corrected for common practices of vial sharing and combining different vial sizes to meet the required dosage to calculate a conservative estimate of the leftover drug amount for the top 20 cancer drugs in the US. The proportion of drug left over varied from 1% to 33%, and the potential revenue from this unused product in the US during 2016 was estimated at $1.8 billion.

Positions on vial repackaging and sharing

Ways to improve the lost opportunity and economic resources because of unused drug are unclear, and the most sweeping improvements may only come with regulatory pressure for manufacturers to change available product sizes. Guidance from organizations varies – Centers for Medicare and Medicaid permit the repackaging of doses from single-dose vials to multiple patients, as long as each repackaged dose is used for a single patient and handled and stored appropriately. In contrast, the Centers for Disease Control and Prevention recommend that vials labeled as single-dose or single-use vials should only be used in a single patient because of their frequent lack of preservatives.

Experience with dose-rounding protocols to avoid waste

Despite conflicting recommendations from these organizations, efforts to curb the problem of waste of costly drugs have been implemented. One institution evaluated the potential effects of rounding chemotherapy doses down by 5% or 10% with utilization of the nearest vial size. It is generally accepted that this amount of dose rounding is justified in metastatic disease because the balance between drug efficacy and safety differs from that in settings of curative treatment. Data on use of bevacizumab, trastuzumab, and cetuximab over a 4-month period showed that a 5% dose reduction produced a total savings of $60,468, while a 10% reduction produced a savings of $112,585. The decreases in waste amounts ranged from 16% to 61% and 38% to 97% using each method, respectively. Another analysis of dose rounding of ipilimumab used in 22 adult metastatic melanoma patients administered doses rounded to the nearest 50-mg vial size. The authors calculated a maximum potential cost savings with this strategy of $155,400.

Similarly, one institution evaluated the potential cost savings with a dose-rounding protocol for rituximab used in hematologic and oncologic indications that would administer doses rounded to the nearest vial size. Over a 2-year period, 99% of 2,028 actual rituximab doses could have been rounded to the nearest 100-mg vial size and remained within 10% of the ordered dose. Sixty-six percent of all doses would have remained within 5% of ordered doses. Upon survey, all responding physicians were comfortable with the dose deviation from at least one of these rounding protocols. The authors estimated a yearly savings of $37,000 with downward dose-rounding, while rounding doses upward would have increased cost by approximately $43,000. A similar study at another institution evaluated potential dose deviation and cost savings with the biologic cancer agents aldesleukin, bevacizumab, cetuximab, denileukin diftitox, gemtuzumab, rituximab, and trastuzumab. The authors found that a protocol approved by a medical oncology group that rounded doses within 10% of the ordered dose was applied to 42% of 126 ordered doses of these drugs, equating to a potential cost savings of $24,434 over a 3-month period. Annually, this had potential to reduce the expenditure of these products by 12%. However, lack of protocol adherence led to an actual savings of only 65% of that predicted.

Conclusion

The use of protocols to address waste and cost associated with expensive medications has been explored in order to maintain institutions' ability to provide sustainable care and encourage responsible utilization of costly drugs. Larger studies of dose-rounding protocols may shed light on their effects on drug safety and efficacy, but currently published literature demonstrates the potential for cost savings without compromising prescribers' level of comfort with rounded doses of expensive medications.

Authors/Editors: Courtney D. Krueger, PharmD, BCPS
Ryan Rodriguez, PharmD, BCPS