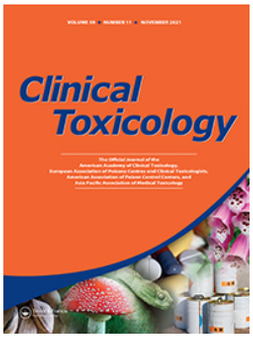

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SHORT COMMUNICATION

Intravenous phytonadione administered orally in reducing warfarin-related coagulopathy

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ABSTRACT

Introduction: The cost of phytonadione tablets has increased markedly and is significantly higher than the intravenous formulation. The intravenous formulation given orally is a potential alternative but has not been directly evaluated in comparison to the commercially available tablet. The objective of this study was to evaluate the efficacy of phytonadione intravenous solution given orally compared to commercially available phytonadione tablets for reversal of coagulopathy related to warfarin.

Methods: We conducted a retrospective, observational study of adult patients who received phytonadione tablets and the IV formulation orally for warfarin-related coagulopathy. The international normalized ratio (INR) was measured before and after phytonadione administration. The primary outcome was INR <1.5 at 24 h after phytonadione administration.

Results: From January 1, 2015 to August 1, 2018 a total of 200 patients were identified. In total, 58% ($n = 116$) patients received IV phytonadione solution given orally and 42% ($n = 84$) patients received the tablets. The primary outcome of INR <1.5 at 24 h was not significantly different between groups ($p = 0.321$).

Discussion: The IV phytonadione solution given by mouth and the tablet formulation performed similarly.

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Phytonadione; vitamin K; warfarin

Introduction

Phytonadione is used in the treatment of coagulopathy due to vitamin K antagonists. Phytonadione is commercially available in both oral and injectable formulations. In response to increased cost and decreased availability of oral phytonadione tablets, several institutions began compounding the intravenous (IV) formulation of phytonadione solution into an oral solution for the treatment of warfarin-related coagulopathy. Prior investigators have evaluated IV phytonadione given orally and have demonstrated its efficacy [1–4]. However, only one small prospective study has previously evaluated a comparison of efficacy between the tablets and the oral administration of the IV solution [5]. Given the small sample size of this study, further evidence is needed. The objective of this study was to evaluate the efficacy of phytonadione IV solution given orally compared to phytonadione tablets for reversal of coagulopathy related to warfarin.

Methods

This was a single-center, retrospective, cohort study performed at a 945-bed academic medical center and approved by the institutional review board. Adult patients were retrospectively identified by pharmacy orders for phytonadione orally in the electronic medical record from January 1, 2015 to August 1, 2018. The institution formula for compounding this product consisted of using 1 mL of the 10 mg/mL solution for injection and 100 mL of simple syrup to make a 100 mcg/mL oral suspension. This suspension was dispensed in a plastic amber bottle with a 90 day beyond use date and stored at room temperature [6].

For inclusion, patients must have had an INR value within 12 h before phytonadione administration and at least one INR value following the administration of phytonadione. Exclusion criteria included documentation of liver disease or dysfunction, concomitant administration of phytonadione *via* intravenous or subcutaneous route, administration of other anticoagulant agents, age <18 years, or pregnancy.

Chart review and data collection was performed by abstracters trained by the project leader. A kappa score was not calculated. Data were collected and managed utilizing the REDCap data capture tool. The administration of the first dose of phytonadione for the visit was considered the index dose. All INR values for the subsequent 48 h after the index dose were collected. The lowest INR obtained within 24 h following the index dose was considered the INR at 24 h. INR <1.5 at 24 h after phytonadione administration was chosen as the primary outcome as it is a clinically relevant level at which most providers at this institution will conduct procedures or interventions.

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Descriptive statistics were performed to evaluate the demographic characteristics of the patient population. For categorical variables, frequencies and column percentages (%) were reported and *p*-values were calculated using χ^2 and Fisher's exact tests, as appropriate. Continuous variables were tested for normality using the Shapiro-Wilk normality test. Normally distributed continuous variables were reported using means and standard deviations (SD) and p-values were calculated using Welch two-sample t-tests; otherwise, medians and first/third quartiles [Q1,Q3] were reported and p-values were calculated using Mann-Whitney *U* tests. Outcome analyses were performed after adjustment for baseline INR. Statistical significance was set at $p \leq 0.05$.

Results

During the study period, 288 patients were assessed for inclusion. A total of 88 patients were excluded for liver dysfunction or disease, concomitant phytonadione administration *via* intravenous or subcutaneous route, or age <18 years at the time of treatment. Table 1 describes the baseline demographic data of the study population. In the oral tablets group, the baseline INR was lower and these patients received higher doses of phytonadione. After adjustment for baseline INR, the primary outcome was similar between groups. Other findings are shown in Table 2.

Discussion

In this study, it was found the IV phytonadione solution administered orally achieved an INR <1.5 in a similar proportion of patients compared to the tablet formulation. Patients in this study had a baseline median INR in both groups relatively lower than reported in previous studies [1,2,4,7]. A large proportion of the patients in this study required reversal of anticoagulation for an emergent procedure (39.5%), while only one patient required reversal of anticoagulation due to a life-threatening indication.

Widespread shortages of phytonadione tablets have prevented retails pharmacies and institutions from ordering an adequate and affordable supply to provide to patients. Utilizing the IV formulation orally may be indicated in times of shortage and high cost. Institutions in the US participating in the 340B program may be able to procure phytonadione and provide it to their patients at a reduced cost. In addition increased product availability, using the IV formulation administered orally may be associated with significant cost savings [8]. The cost of commercially available phytonadione tablets tripled from 2014 to 2016 [8,9]. At the time of this publication, the wholesale acquisition cost of the tablets is $9.92 per mg, while the cost of the IV solution is $4.36 per mg (per UK HealthCare's primary wholesaler). Given the recent interest in this formulation due to the outbreak of synthetic marijuana contaminated with brodifacoum, the findings of this retrospective study of the use of intravenous phytonadione for warfarin related coagulopathy could be utilized in the management of these patients due to significant cost-savings and increased product availability [10]. For a patient requiring treatment with 88 grams of phytonadione over the course of 7 months due to brodifacoum exposure, this translates to a cost savings of approximately $489,280 using the IV formulation.

Limitations

Our study is limited in sample size and may not have been large enough to adequately detect a difference between treatment groups for the primary outcome. To eliminate the confounding variable of intravenous or subcutaneous phytonadione on INR, the exclusion of these patients may lead to a selection bias towards a population with less-severe bleeding events or mild elevations in INR. As the study design was retrospective, not all INR values were available at routine

Table 2. Correction of coagulopathy after adjustment for baseline INR.

Outcome	Estimate for: IV Orally vs. PO Tablets	95% CI	*p*-Value
INR < 1.5 at 24 h*	1.46	0.70–3.11	0.321
INR < 1.5 at 48 h*	1.69	0.92–3.17	0.096
INR at 24 h	−0.06	−0.53–0.42	0.812
INR at 48 h	−0.02	−0.47–0.44	0.948

*For binary outcomes, the estimates and 95% CIs are in terms of odds ratios.

Table 1. Baseline characteristics of study patients.

	Intravenous solution given orally (*N* = 116)	Oral tablets (*N* = 84)	*p*-Value
Age – Years, Median (Q1,Q3)	68.5 (53.8, 76.2)	67.0 (57.8, 73.2)	0.392
Female – *N* (%)	62 (53.4)	38 (45.2)	0.316
Baseline INR – Median (Q1,Q3)	4.3 (2.7, 7.2)	3.4 (2.3, 5.6)	0.020
Warfarin indication			
Atrial fibrillation – *N* (%)	55 (47.4)	46 (54.8)	0.377
Pulmonary embolism – *N* (%)	10 (8.6)	10 (11.9)	0.599
Deep vein thrombosis – *N* (%)	29 (25)	25 (30.0)	0.557
Valve replacement – *N* (%)	9 (77.5)	5 (6.0)	0.831
Other – *N* (%)	15 (12.9)	5 (6.0)	0.166
Reversal indication			
Emergent procedure – *N* (%)	42 (36.2)	37 (44.0)	0.331
Life-threatening bleeding – *N* (%)	1 (0.9)	0 (0)	1.00
Significant bleeding at any INR – *N* (%)	18 (15.5)	14 (16.7)	0.981
INR supratherapeutic without bleeding – *N* (%)	54 (46.6)	29 (34.5)	0.119
Other – *N* (%)	4 (3.4)	7 (8.3)	0.208
Total phytonadione dose within 24 h – Median, mg	5.0 (2.5, 5.0)	5.0 (5.0, 10.0)	0.001
Received blood products – *N* (%)	37 (31.9)	30 (35.7)	0.680
Packed red blood cells – *N* (%)	12 (10.3)	12 (14.2)	0.531
Fresh frozen plasma – *N* (%)	32 (27.5)	24 (28.6)	1.000

time points. This makes it difficult to compare exactly when a patient's INR may have met the primary outcome. Information regarding the patient's ingestion history prior to presentation was not collected, therefore differences in acute and chronic ingestions were not evaluated.

Conclusion

In this study, we found phytonadione intravenous solution administered orally performed similarly to the oral tablet formulation in correction of warfarin related coagulopathy. This was found both at 24 and 48 h after phytonadione administration. The high cost and limited availability of oral phytonadione tablets are a potential limiting factor for patients who require large doses and chronic therapy. Intravenous phytonadione solution compounded for oral administration is an effective alternative for patients.

Disclosure statement

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