



Epidemiological features of warfarin overdose and efficacy of prothrombin complex concentrates

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ABSTRACT

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The aims of this study were to investigate the epidemiological features of warfarin overdose and evaluate the efficacy of prothrombin complex concentrate (PCC) for overdose treatment. The hospital records of 106 patients admitted to the emergency department (ED) for warfarin overdose during a two-year period were evaluated retrospectively. Demographic and epidemiological data as well as treatments were recorded. The data from 15 patients administered PCC were compared with those of other patients. The patient population consisted of 53 (50%) males and 53 (50%) females with a mean age of 70.2±14.5 years. Forty-five (42.4%) patients were admitted to the ED with bleeding disorders; 61 (57.6%) patients were admitted for other symptoms such as headache, syncope, trauma related injuries. Atrial fibrillation (n=50, 47.1%) was the most common indication for treatment with a vitamin K antagonist (VKA). Other common indications were transient ischemic attack, stroke (n=43, 40.5%) and valvular heart disease (n=17, 16%). Vitamin K was the preferred treatment for VKA reversal in 32 (30.2%) patients. Fresh-frozen plasma (FFP) was preferred in 23 (21.7%) patients. Fifteen (14.1%) patients required acute reversal of VKA with PCC. The anticoagulant drug was discontinued in 58 (54.7%) patients. Erythrocyte suspension (ES) and thrombocyte suspension (TS) transfusion rates were higher in the PCC-administered group; hospitalization rates were also higher in this group. ED length of stay (LOS) was shorter in this group. Initial international normalized ratio (INR) levels were significantly higher in the PCC group (5.68±3.74 versus 13.17±5.15). As the elderly population increases, warfarin and VKA-related complications will be a more significant portion of ED practice. ED physicians should be experienced in acute reversal of VKA with PCC, and be familiar with the possible complications of FFP and PCC.

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1. Introduction

Drug overdose-related symptoms are an important part of emergency department (ED) admissions. Drug overdose-related side effects are more common than suicidal drug intoxications. Drug overdosing is generally related to narrow therapeutic index of the relevant drug. A recent study revealed that drug side effect-related ED admissions comprised 3.6% of admissions in the elderly; 33.3% of these admissions were due to warfarin, digoxin and insulin (Budnitz et al., 2007). A previous study also revealed that 65.7% of all drug intoxications that resulted in to ED admissions were drug overdoses. The most common drugs were warfarin, insulin,

antiplatelet and oral hypoglycemic agents (Budnitz et al., 2007).

Warfarin is the main vitamin K antagonist (VKA) used as oral anticoagulant, warfarin overdose is the most common cause of drug overdose admissions to ED, (Budnitz et al., 2011). Acenocumarol, phenprocoumon, fluindione and tecarfarin are other vitamin K antagonist derivatives of coumarins (Ellis et al., 2009; Altunbaş et al., 2013). Following oral intake, warfarin is absorbed from the gastrointestinal system and binds to plasma albumin. Warfarin acts as an anticoagulant via inhibition of vitamin K-dependent monitoring to estimate the international normalized ratio

(INR) is required. Inadequate doses increase the potential of thromboembolism, and excessive anticoagulation increases bleeding complications (Kamali and Wynne, 2010).

Recent treatment options for reversal of overdosing with vitamin K antagonists (VKA) include vitamin K, fresh-frozen plasma (FFP), recombinant activated factor VII (rFVIIa) and prothrombin complex concentrate (PCC; factors II, VII, IX and X). Reversal of prothrombin time to normal levels with vitamin K lasts 12-24 hours. Reversal of INR to normal values takes an average of 30 hours with FFP, and is associated with volume overload (Demeyere et al., 2010; Dentali et al., 2011; Patanwala et al., 2011). No studies have evaluated the efficacy of PCC in Turkey. Thus, we tried to determine the epidemiological features of vitamin K antagonist-related ED admissions and the efficacy of treatment options for the reversal of VKA overdosing.

2. Materials and methods

The records of 106 patients that were admitted to the ED for warfarin overdose during a two-year period were evaluated retrospectively. Demographic and epidemiological data, as well as treatments, were noted on standard study forms. Data from 15 patients administered PCC were compared with those of the other patients.

Patients under 18, pregnant females, missing data, other anticoagulant users or combined anticoagulant users were excluded from the study. Descriptive statistics with confidence intervals were used for continuous data. Categorical data were analyzed using χ^2 tests. Non-parametric data were analyzed using Mann Whitney-U tests. SPSS 17.0 was used for the statistical analysis.

3. Results

The patient population consisted of 53 (50%) males and 53 (50%) females with a mean age of 70.2 ± 14.5 years. There were no significant differences in age and gender among the vitamin K, FFP reversal of VKA, and PCC reversal of VKA groups. Vital signs of all patients are shown in Table 1.

Table 1. Patient vital signs

| | Minimum | Maximum | Mean \pm SD |
|------------------------------------|---------|---------|------------------|
| MAP (mmHg) | 42 | 126 | 97.19 \pm 13.5 |
| Core temperature (C ^o) | 36 | 38.2 | 36.6 \pm 0.34 |
| Pulse/minute | 43 | 150 | 88.12 \pm 16.3 |
| Respiratory Rate/minute | 10 | 25 | 14.32 \pm 1.81 |

MAP: Mean arterial pressure; SD: Standard deviation

Forty-five (42.4%) patients were admitted to the ED with bleeding disorders. Sixty-one (57.6%) patients were admitted to the ED for other symptoms. The most common symptoms were headache (n=18, 16.9%), hematuria (n=14, 13.2%) and epistaxis (n=13, 12.2%). Initial symptoms of patients are shown in Figure 1. In this study, one patient had intracranial hemorrhage (ICH).

Eighty-nine (84%) patients had accompanying chronic diseases, of which hypertension was the most common (Fig. 2).

Atrial fibrillation (n=50, 47.1%) was the most common indication for VKA treatment. Other common indications were transient ischemic attack, stroke (n=43, 40.5%) and

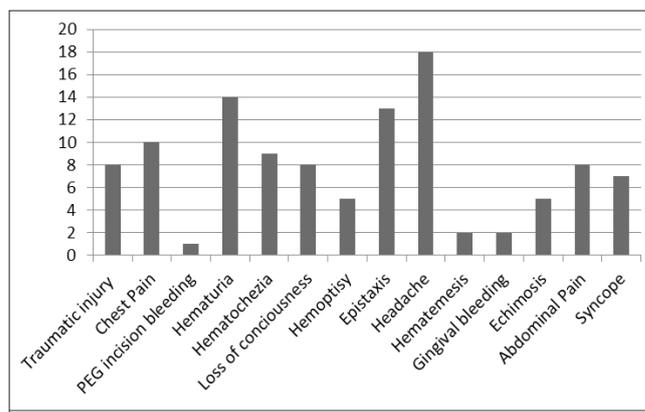


Fig. 1. Initial symptoms of VKA-receiving patients in the ED

valvular heart disease (n=17, 16%). Indications for VKA use are shown in Figure 3.

Vitamin K was the preferred treatment for VKA reversal, in 32 (30.2%) patients. FFP was preferred in 23 (21.7%) patients. Fifteen (14.1%) patients required acute reversal of VKA with PCC. Discontinuation of the drug was the chosen treatment in 58 (54.7%) patients. Ten (9.4%) patients required erythrocyte suspension (ES) transfusion, and one (0.9%) patient required thrombocyte suspension (TS) transfusion. Two patients in FFP group had anaphylaxis; none of the patients had hypervolemia or thrombosis in the study groups.

Initial mean INR levels were 5.68 ± 3.74 (min=2.05, max=22.29) in the vitamin K and FFP group and 13.17 ± 5.15 (min=4.60, max=25.93) in the PCC group. Initial INR levels were significantly higher in the PCC group. INR levels were in acceptable ranges in the first hour after acute reversal of VKA, and a moderate increase was identified in the third hour. The efficacy of PCC for reversal of VKA is shown in Figure 4.

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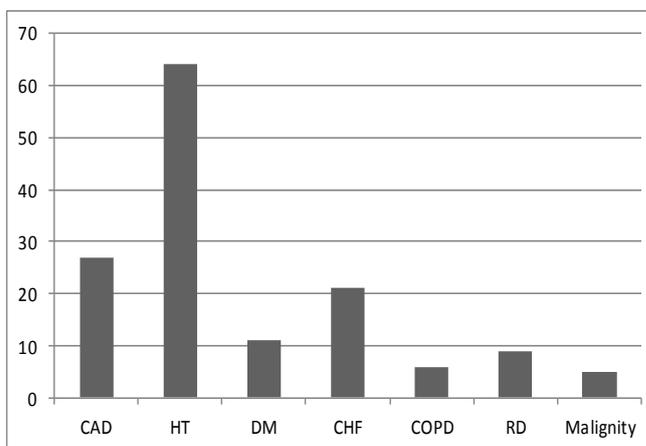


Fig. 2. Chronic disease distribution of VKA-receiving patients (n). (CAD: Coronary artery disease, HT: Hipertension, DM: diabetes mellitus, CHF: Congestive heart failure, COPD: Chronic obstructive pulmonary disease, CRF: Chronic renal failure)

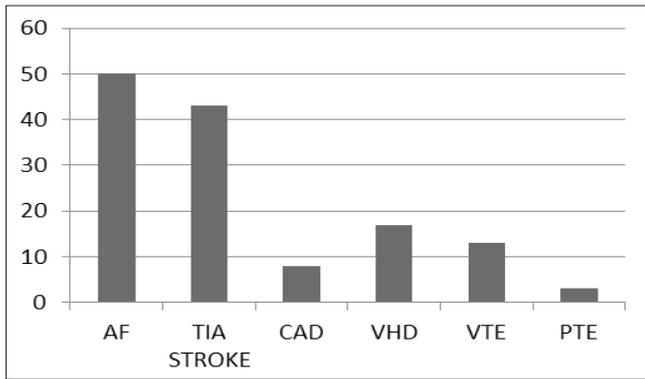


Fig. 3. Indications for VKA use (n), (VTE: Ventricular tachycardia extrasystole prophylaxis, CAD: Coronary artery disease, TIA: Transient ischemic attack, AF: Atrial fibrillation, PTE: Pulmonary thromboembolism, VHD: Valvular heart disease).

PCCs were used more commonly in patients with coronary artery disease (CAD) and AF ($p < 0.01$). Age, gender, vital signs, symptoms, and existing chronic disease did not differ significantly between the PCC-treated and the other groups. ED length of stay (LOS) in PCC group was significantly shorter than the vitamin K and FFP group ($p = 0.09$; Table 2). Four patients in the PCC group required ES, and one patient required TS transfusion.

4. Discussion

Common indications for anticoagulant treatment include atrial fibrillation, valvular heart disease, and prevention of venous thromboembolism (Streiff, 2011). Life-threatening bleeding complications may occur due to the narrow therapeutic range of warfarin (Phan et al., 2000; Libby and Garcia, 2002). The most serious bleeding complication is intracranial bleeding, with mortality rate of up to 50% in 30 days. In this study, one patient had intracranial hemorrhage (ICH). Previous studies revealed that an excessive increase in INR and older age increase the bleeding risk (Meer et al., 1993; Palareti et al., 1996). The incidence of warfarin-related bleeding complications is 0.25-1.1% annually (Butler and Tait, 1998). Acute reversal of VKA is important in patients with ICH and excessive anticoagulation. Inadequate doses increase the potential of thromboembolism, and excessive anticoagulation increases bleeding complications (Kamali and Wynne, 2010).

Incidental over therapeutic INR levels must be reversed by discontinuation of warfarin in EDs and outpatient periodic controls. A previous study revealed that discontinuation of the drug is adequate for 46% of these patients (Meeker et al., 2011). Our study showed a different rate (54.7%) for discontinuation of warfarin. The traditional options available for reversal of VKA are discontinuation of the drug, vitamin K, FFP and combination of vitamin K and FFP. Recent studies revealed that the PCC and vitamin K combination is more effective in reversal of VKA (Hickey et al., 2013).

Table 2. Length of stay(hours) in the ED

| | N | Minimum | Maximum | Mean±SD |
|----------------|-----|---------|---------|------------|
| PCC | 15 | 1 | 12 | 2.93±3.035 |
| Vitamin K, FFP | 91 | 1 | 8 | 3.75±1.780 |
| Total | 106 | 1 | 12 | 3.63±2.006 |

INR levels may increase in patients who are treated with PCC without vitamin K administration. Recent studies recommend the combination of vitamin K with four-factor PCC (Guyatt et al., 2012).

AF and stroke were the most common indications for VKA in previous studies (Garcia et al., 2006; Majeed et al., 2012). Our study showed similar results for the major indications of VKA. In this study, only 45 (42.4%) of all patients were admitted to the ED with bleeding disorders. Sixty-one (57.6%) patients were admitted to the ED for other symptoms. A considerable number of VKA-receiving patients were admitted to the ED for non-VKA-related symptoms, and excessive VKA was diagnosed incidentally by laboratory findings. ED physicians must control the INR levels in all warfarin-receiving patients. Some studies have reported thromboembolic complications of VKA reversal with PCC (Lankiewicz et al., 2006; Bagot et al., 2007; Ratnaweera et al., 2007; Warren and Simon, 2009; Pabinger et al., 2010). However, these are retrospective studies of few cases. A recent study revealed no complications in 256 patients, while another revealed that PCC-related thromboembolic events were related to underlying chronic diseases (Sørensen et al., 2011; Desmettre et al., 2012). There were no reported complications in our PCC-administered group. In Turkey, many physicians use FFP as the first treatment option. Plasma transfusion for full reversal of VKA is associated with risks of volume overload and transfusion-related acute lung injury (Benhamou, 2007; Lin et al., 2013). In our study, vitamin K was the preferred treatment for VKA reversal in 32 (30.2%) patients. FFP was preferred in 23 (21.7%) patients. Fifteen (14.1%) patients required acute reversal of VKA with PCC. The low incidence of PCC treatment may be related to the high cost, uncertainty regarding thromboembolic complications or inadequate experience with PCC.

In our study, ES and TS transfusion rates were higher in the PCC-administered group. Hospitalization rates were higher and ED LOS was shorter in this group. Initial mean INR levels were 5.68 ± 3.74 in the vitamin K and FFP group and 13.17 ± 5.15 in the PCC group. Initial INR levels were significantly higher in the PCC group. These results suggest that PCC was used for VKA reversal only in the presence of serious bleeding complications. Recent studies revealed that PCC reversal of VKA is more effective in patients with serious bleeding and excessive anticoagulation (Erdoğan et

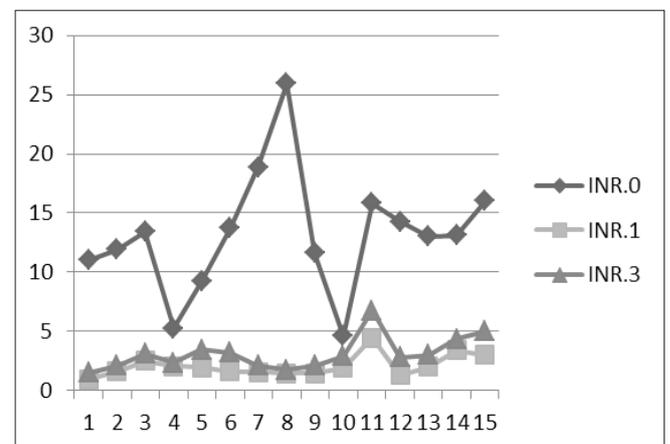


Fig. 4. Effect of PCC over INR after acute reversal of VKA. Figure shows each patient’s initial, first hour and third hours INR levels.

al., 2013; Preston et al., 2002). As the population of Turkey ages, warfarin and VKA-related complications will be a more significant part of ED practice. ED physicians must be experienced in acute reversal of VKA with PCCs and familiar with the possible complications of FFP and PCCs (Dentali et al., 2011; Patanwala et al., 2011).

As the elderly population increases, warfarin and VKA-related complications will be a more significant portion of ED practice. ED physicians must be experienced in acute reversal of VKA with PCCs. ED physicians must be familiar with possible complications of FFP and PCCs.

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