Warfarin Overdose: A 25-Year Experience

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Abstract Warfarin, a vitamin K antagonist, is widely used for the prophylaxis and treatment of thromboembolic disease. While guidelines exist for management of a supratherapeutic international normalized ratio following therapeutic warfarin use, these guidelines are not designed for management of the acute warfarin overdose. There is a paucity of literature describing the latter. The primary objective of this manuscript is to characterize the coagulopathy and describe the bleeding events that occur after a warfarin overdose. A secondary goal is to describe the amount of vitamin K administered to patients presenting with warfarin overdoses. A retrospective chart review of patients admitted with an acute warfarin overdose at two tertiary care medical centers in the USA was conducted. Clinical characteristics were abstracted, and bleeding categories (major, minor, trivial) were defined a priori. Twenty-three patients were admitted during the time period; males accounted for 15/23 (62.5 %) subjects. The median (interquartile range (IQR)) age was 43 (32–48.5) years. Seventeen subjects received vitamin K, with a median (IQR) dose of 15 (10–50) mg. The

maximal total amount of vitamin K administered to a single patient during the index hospitalization was 110 mg. Three bleeding events occurred; one classified as major, and two as minor. All patients made a full recovery. In this case series of acute warfarin overdose, nearly all patients developed a coagulopathy, and nearly three-quarters of patients received vitamin K. Bleeding events occurred in a minority of patients.

Keywords Warfarin · Overdose · Vitamin K · Vitamin K antagonist · Coagulopathy

Background

Warfarin is widely used to prevent thrombus formation resulting from mechanical heart valves as well as in conditions including atrial fibrillation and dilated cardiomyopathy. In addition, warfarin is used to treat formed thrombus including those in the deep veins [1, 2]. As a vitamin K antagonist, warfarin inhibits the cyclic conversion of vitamin K 2,3 epoxide to vitamin K quinone as well as the conversion of vitamin K quinone to vitamin K quinol, the active moiety. This inhibition prevents the gamma carboxylation of the vitamin K-dependent clotting factors, ultimately leading to their depletion [3, 4]. Because of its narrow therapeutic index, maintaining anticoagulation in the therapeutic range can be difficult. Consequently, over-anticoagulation is common [5].

Several guidelines have been developed for management of the patient with a supratherapeutic international normalized ratio (INR) [6, 7]. These guidelines are designed for patients who are taking warfarin therapeutically, who later develop a supratherapeutic INR. While not explicitly stated, they are not designed for the management of patients with an acute overdose of vitamin K antagonists. Such overdoses are relatively rare, with most published cases consisting of a case report or a small case series [8–12]. Large case series involving warfarin overdose have not been published.

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The primary purpose of this study is to characterize the coagulopathy and describe bleeding events that occur following a warfarin overdose. A secondary goal is to describe the amount and pattern of vitamin K administration in patients with warfarin overdose.

Methods

This retrospective study was conducted at two tertiary care medical centers which serve as referral centers for poisoned patients. At both of these hospitals, patients with a known or suspected poisoning requiring admission are routinely admitted to the toxicology service, which maintains a registry of all patient encounters. Patients were identified via a review of each respective registry. The study received approval from the institutional review board from both participating hospitals.

Study Subjects

All subjects who were admitted with a reported warfarin overdose between 1 January 1987 and 31 July 2012 were eligible for inclusion. Patients without a history of an acute overdose and those with supratherapeutic INRs following therapeutic use were excluded.

Data Collection

Data abstracted from the medical records included demographic information, all prothrombin times (PTs), and INRs during the initial hospitalization, reason for ingestion, reason for anticoagulation (if the warfarin belonged to the patient), and the amount and routes of vitamin K administered. If follow-up PTs and/or INRs were available in the medical center's computer system during the week after admission (e.g., during the inpatient psychiatric stay), those results were also abstracted. In addition, the amount of warfarin reported to have been ingested (if documented), length of stay, and outcome, including the presence of any hemorrhagic or thrombotic complications during the index hospitalization, was recorded. Data were abstracted onto a predesigned data abstraction sheet and subsequently entered into a spreadsheet by one investigator at each study site (ML, AFP). Twenty percent of the charts was reviewed by a second reviewer (AMR) and a kappa statistic was performed for all categorical variables.

Study Definitions

Bleeding was classified as major, minor, or trivial, according to the following definitions, which were created a priori. Major bleeding was defined as fatal bleeding, bleeding associated with hemodynamic instability, bleeding for which an invasive intervention (e.g., endoscopy) was performed,

bleeding for which one or more units of packed red blood cells were transfused, or bleeding into an enclosed space (e.g., retroperitoneal or intracranial). Minor bleeding was defined as any bleeding resulting in a prolonged observation but for which no specific intervention other than administration of vitamin K was performed. Trivial bleeding was defined as bleeding not leading to prolonged observation or intervention (other than vitamin K). Such bleeding would include oozing from puncture wounds, and self-limited bleeding not requiring intervention (e.g., epistaxis or hemorrhoidal bleeding). Coagulopathy was defined as an $\text{INR} \geq 1.4$.

Subjects with a PT or INR that exceeded the reporting limits for the laboratory were considered to have a PT of 100 s and an INR of 10, respectively. For those patients not taking warfarin prior to the ingestion (and hence presumably with normal concentrations of the vitamin K-dependent clotting factors), the time to the development of a coagulopathy was determined. In such cases, a coagulopathy was defined a priori as an $\text{INR} \geq 1.4$.

Data Analysis

Medians and interquartile ranges were calculated after determining that the data were non-normally distributed.

Results

During the study period, a total of 23 patients were admitted following reported warfarin overdose. Men accounted for 15/23 (65 %) subjects. The median (interquartile range) age was 43 (32–48.5) years (Table 1). The reasons for anticoagulation are described in Table 2. In 5/23 (22 %) cases, the warfarin did not belong to the patient. The reason for warfarin overdose was documented to be suicide attempt in 21 patients, exploratory ingestion in one 2-year-old patient who ingested 25 mg of a relative's warfarin and unknown in one patient. Of those with a known time of ingestion, the median (interquartile range (IQR)) time from ingestion to presentation was 2 (1.5–3.6) h. The time of ingestion was unknown, or the ingestion

Table 1 Subject characteristics

Variable	
Men	15/23 (65 %)
Age [median (IQR)], in years	43 (32–48.5)
Ingested dose by history [median (IQR)], in mg	100 (75–216)
Initial PT [median (IQR)], in seconds	18.6 (13.8–46)
Initial INR [median (IQR)]	1.6 (1.1–4.5)
Maximal PT [median (IQR)], in seconds	57.8 (28.6–96.7)
Maximal INR [median (IQR)]	5.8 (2.75–9.8)

PT protime, INR international normalized ratio, mg milligrams

Table 2 Reason for anticoagulation

	Reason	Number
<i>DVT/PE</i> deep vein thrombosis/pulmonary embolism, <i>VTE</i> venothromboembolism	Current DVT/PE	1
	Past VTE	11
	Mechanical heart valve	2
	Atrial fibrillation	1
	Miscellaneous/unknown	3
	Does not belong to patient	5

occurred over multiple days in 7/23 (30 %) patients. In the four patients with a known time of ingestion who were not taking warfarin prior to the acute overdose, the initial coagulation parameters were normal and the INR did not rise above 1.3 for at least 16 h (Table 4).

The initial median (IQR) PT and INR were 18.6 (13.8–46)s and 1.6 (1.1–4.53), respectively, while the maximal median (IQR) PT and INR were 57.8 (28.6–96.7)s and 5.8 (2.75–9.8), respectively (Table 1). Documented PT and INR values following presentation to the hospital as well as doses and timing of the administration of vitamin K are detailed in Table 3.

Ten patients presented without coagulopathy (INR<1.4). Nine of these ten developed a coagulopathy. Four subjects presented with a mild coagulopathy, below the lower limit of therapeutic anticoagulation (INR<2.0). Six subjects whose initial INR was less than 2.0 were managed with observation alone (without vitamin K), with the highest INR reaching 3.5 in this subgroup. Four of the ten subjects who presented without coagulopathy were treated with vitamin K after a rise in INR was noted, although the thresholds for treatment with

Table 3 Characteristics of those patients presenting with a subtherapeutic INR

	Initial INR<1.4 ^a	Initial INR 1.4–2.0 ^a	Max INR	Administration of vitamin K
		1	4.7	Yes
3			1.5	No
4			3.5	No
6			1.2	No
7			3.3	No
		8	5.8	Yes
		10	6.6	Yes
11			1.6	Yes
13			1.7	No
18			3.2	Yes
19			4.4	Yes
		20	6.8	Yes
21			1.6	Yes
22			2.3	No

^a Subject number

vitamin K and the doses used varied widely (Table 3). The remaining nine patients presented with a therapeutic INR (INR, 2–3; *n*=3), or a supratherapeutic INR (INR>3; *n*=6). Of the six patients with a supratherapeutic INR, the initial INR ranged from 3.3 to >10.8; all were treated with vitamin K.

A total of 17 patients (74 %) received vitamin K. Among those individuals who received vitamin K, the median (IQR) total dose administered was 15 (10–50)mg, and the median (IQR) number of doses administered was 3 (2–4). The maximal total amount of vitamin K administered to a single patient was 110 mg. A detailed description of vitamin K dosing in relation to the PT/INR can be found in Table 4.

Three patients experienced hemorrhagic events associated with their overdose. These were classified as major in one subject (1/23; 4.3 %) and minor in two subjects (2/23; 9 %). No subject experienced trivial bleeding. The major hemorrhagic event occurred in a 43-year-old man (case 17) who presented following a suicide attempt. He reported ingesting 168 mg of warfarin over 4 days. On arrival, he had epistaxis and an initial PT/INR>100 s/10. He was treated with 15 mg intravenous vitamin K. On the second hospital day, flank ecchymosis was noted, and a computerized tomography scan of the abdomen and pelvis revealed the presence of a retroperitoneal hematoma, prompting the administration of fresh frozen plasma and an additional 50 mg of vitamin K divided over three doses. A minor bleeding event occurred in a 32 year-old woman (case 5) on warfarin for a prior DVT, who presented following a reported ingestion of 90 mg of warfarin. The time of ingestion was unknown. Her initial and maximal PT/INR were 96.9 s/9.3 and >100 s/>10, respectively. She presented with epistaxis and was treated with a total of 15 mg of oral vitamin K divided over four doses. The other episode of minor bleeding occurred in a 40-year-old man (case 21) who presented 1.5 h after ingesting an unknown quantity of warfarin, escitalopram, and Comet™ cleaner (sodium hypochlorite, sodium hydroxide; pH 13). The warfarin was not prescribed to him. His initial and maximal PT/INR were 9.8 s/0.98 and 18.3 s/1.6, respectively. He had mild bleeding from the vocal cords and was treated with a total of 15 mg of intravenous vitamin K in two doses.

One patient (case 15) received fresh frozen plasma (FFP) in the absence of documented bleeding. A 60-year-old man was found unresponsive following an apparent overdose of clonazepam, warfarin, and digoxin. There was an initial concern that he might have experienced some trauma, based on forehead abrasions. Bystanders performed chest compressions, although cardiac arrest was never documented. Upon arrival of emergency medical services, the patient was intubated and found to be in a junctional rhythm. Digoxin concentration was 7.2 ng/mL, with PT/INR>100 s/10.8. A computerized tomography scan of the head was negative for bleeding, but the patient received FFP to correct the coagulopathy, in addition to 10 mg intravenous vitamin K.

Table 4 Description of vitamin K administration and coagulopathy

Case	Hours post-ingestion ^a	PT	INR	Vitamin K	Hemorrhage
1	3	22.9	1.9		No
	11	24.9	2.2		
	18	31.8	2.9		
	22	36	3.4		
	27	46.7	4.7		
	34	26.6	2.3		
	48	24.8	2.1		
	73	35.6	3.4		
	74			5 mg PO	
2	90	25.7	2.2		No
	3	24.9	2.6		
	8	32.5	3.4		
	32	100	>10		
	35			5 mg PO	
	38	>100	>10		
	42	>100	>10		
	48			5 mg PO	
	49	>100	>10		
	57	>100	>10		
	60			5 mg PO	
	66	>100	>10		
	74			5 mg PO	
	75	>100	>10		
	81	81.7	8.3		
	94	54.2	5.6		
	102	43.1	4.5		
	137	43.7	4.5		
	161	51.2	5.3		
	186	50.0	5.1		
3	195	28.6	3.0		No
	2	13.3	1.0		
	16	17.6	1.4		
	22	18.5	1.5		
4	2	9.9	1.1		No
	10	10.7	1.1		
	17	15.9	1.7		
	25	22.7	2.4		
	47	33.4	3.5		
	71	24.8	2.6		
	76	14.8	1.6		
	93	11.5	1.2		
5 ^b	0	96.9	9.3		Yes
	2			5 mg PO	
	8			2.5 mg PO	
	14	>100	>9.6		
	22	89.6	8.5		
	28	88.6	8.5		
	35			5 mg PO	
	41			2.5 mg PO	
	43	50.4	4.8		

Table 4 (continued)

Case	Hours post-ingestion ^a	PT	INR	Vitamin K	Hemorrhage
	66	46.8	4.4		
	122	24.2	2.2		
	6 ^b 0	12.0	1.1		
	15	12.2	1.1		
	30	12.8	1.2		
7 ^b	0	11.2	1.0		No
	8	11.8	1.0		
	21	19.1	1.7		
	33	29.1	2.6		
	45	36.8	3.3		
	56	37	3.2		
	70	36.2	3.0		
	82	34	3.1		
	156	35.4	3.0		
	8	16.5	1.4		
	17	17.1	1.5		
	31	29.9	2.6		
	43	50.2	4.4		
	53			2 mg PO	
	55	64.3	5.8		
8	68	52.3	4.7		
	74			2 mg PO	
	89	60.2	5.4		
	94	56.5	5.0		
	105			2 mg PO	
	107			2 mg PO	
	121	54.2	4.8		
	134	51.6	4.6		
	159	40.8	3.6		
	174			2 mg PO	
	187	34.7	3.1		
	211	16.9	1.5		
	9	29.8	2.7		
	5	26.6	2.3		
	9	24.8	2.1		
	18	28.4	2.5		
	31	42.7	4.1		
	36			10 mg PO	
	43	29.1	3.7		
				20 mg PO	
	52	33.1	3.0		
	69	22.8	1.9		
	79	20.5	1.7		
	88	18.3	1.5		
	2	18.6	1.6		
	9	24.2	2.2		
	19	37.3	3.8		
	25	49.7	5.5		
	26			5 mg IV	
	30	31.0	3		

Table 4 (continued)

Case	Hours post-ingestion ^a	PT	INR	Vitamin K	Hemorrhage
35		29.3	2.8		
45		43.1	4.6		
50				5 mg IV	
55		43.0	4.5		
61		50.0	5.5		
66				5 mg IV	
69		42.3	4.4		
77		48.1	5.2		
81				5 mg IV	
85		35.7	3.6		
94		40.0	4.1		
100		46.1	5		
105				5 mg IV	
106		38.6	3.9		
116		37.5	3.8		
127		39.2	4		
136		57.8	6.6		
142				5 mg IV	
150		51.8	5.7		
154				5 mg PO	
157				5 mg PO	
163		63.0	7.3		
164				5 mg PO	
166				5 mg PO	
172		37.9	3.8		
177		31.6	3		
188		28.6	2.7		
198		27.7	2.6		
208		21.6	1.9		
221		21.7	1.7		
11	11	N/R	1.2		No
	15	18.0	1.3		
	16			20 mg IV	
	31	18.0	1.5		
	37			10 mg IV	
	44	18.8	1.6		
	45			40 mg PO	
	48			20 mg PO	
	56	19.7	1.6		
	60			20 mg PO	
12 ^b	0	29.2	2.5		No
	4	34.8	3.7		
	10	44.9	4.8		
	15	59.7	6.4	10 mg PO	
	19			20 mg PO	
	23	45.3	4.9		
	27	93.3	8.7		
	30			20 mg PO	
	33	22.5	2.8		

Table 4 (continued)

Case	Hours post-ingestion ^a	PT	INR	Vitamin K	Hemorrhage
38		22.0	2.3		
48		14.0	1.4		
54		14.3	1.4		
62		13.9	1.4		
73		14.1	1.4		
80		14.5	1.5		
86		14.9	1.5		
96		16.1	1.6		
104		17.6	1.8		
13	5	10.4	1.0		No
	11	10.4	1.0		
	20	12	1.2		
	26	12.7	1.3		
	32	15.4	1.6		
	36	15.6	1.6		
	42	16.7	1.7		
	48	14.9	1.5		
	63	12.7	1.3		
	76	11.4	1.1		
14	15	81	7.6	20 mg IV	No
	17	>100	>10		
	20			20 mg IV	
	22			40 mg PO	
	24	17.9	1.9		
	28	13.8	1.7		
	41	13.3	1.3		
	55	13.8	1.4		
	79	11.4	1.1		
	103	11.4	1.1		
15 ^b	0	>100	>10.8		No
	2	>100	>10.8		
	5	>100	>10.8	10 mg SQ	
	10	9.6	0.9	5 mg SQ	
	24	10.8	1.0		
	33	10.7	1.0	5 mg SQ	
	57	10.4	1.0		
	81	10.9	1.0		
	105	10.6	1.0		
16	5	34.2	3.3	2.5 mg PO	No
	8	41.2	4.4		
	16	58.8	6.3		
	20	78.5	8.4		
	27	90.6	9.7	2.5 mg PO	
	29			5 mg PO	
	31	>100	10.8		
				10 mg PO	
	38	48.1	4.6		
	45	53.8	5.8		
	49			2.5 mg PO	

Table 4 (continued)

Case	Hours post-ingestion ^a	PT	INR	Vitamin K	Hemorrhage
	51	39.0	4.2		
	58	31.2	3.3		
	65	23.8	2.5		
	74	20.1	2.1		
	83	18.5	1.9		
	101	17.3	1.8		
	124	17.5	1.8		
	149	19.7	2.1		
17^b	0	>100			Yes
	5	>100		15 mg IV	
	8	25.8	2.4		
	13	22.2	2.0	10 mg IV	
	16			20 mg IV	
	20	15.5	1.2		
	26	16.3	1.3		
	32	16.5	1.3		
	38	18.0	1.5		
	45	16.1	1.3	20 mg IV	
	48	14.8	1.2		
	54	14.2	1.1		
	60	13.8	1.1		
	69	14.0	1.1		
	80	15.5	1.2		
	111	17.3	1.4		
18	8	15.7	1.2		No
	17	20.3	1.		
	20	20.6	1.8		
	27	26.3	2.4		
	38	33.1	3.2		
	40			10 mg IV	
	43	18.5	1.5		
	51	15.8	1.3		
	68	12.7	1.0		
19	5	13.8	1.1		No
	11	14.1	1.1		
	23	17.8	1.5		
	27	22.5	2.0		
	49	42.3	4.4		
	54			2.5 mg PO	
	59	45.3	4.8		
	61			2.5 mg PO	
	74	43.0	4.5		
	97	41.3	4.3		
	130	43.8	4.6		
	154	39.4	4.0		
	178	30.7	3.8		
	202	29.6	2.8		
20	1	19.3	1.6		No
	24	20.3	1.7		

Table 4 (continued)

Case	Hours post-ingestion ^a	PT	INR	Vitamin K	Hemorrhage
	32	25.2	2.3		
	45	39.3	4.0		
	48			5 mg PO	
	51	50.4	5.6		
	54			2.5 mg PO	
	59	59.3	6.8		
	70	39.0	4.0		
	79	30.1	2.9		
	93	31.6	3.1		
	99	29.4	2.8		
	120	28.3	2.6		
	144	23.6	2.1		
	168	24.5	2.2		
	192	22.8	2.0		
21	1.5	9.8	0.98		Yes
	8	12.9	1.0		
	11			10 mg IV	
	16	15.4	1.3		
	18				
	20	15.6	1.3		
	37	14.5	1.2	5 mg IV	
	32	14.4	1.2		
	42				
	55	14.3	1.2		
	79	16.8	1.4		
	104	18.3	1.6		
22	3	14.3	1.2		No
	24	24.1	2.3		
	34	20.4	1.8		
	87	15	1.2		
23	16	42.0	4.4		No
	20	70.6	6.4		
	21			5 mg PO	
	25	48.1	5.3		
	33	25.7	2.8		
	42	22.0	1.9		
	55	22.2	2.0		
	66	21.9	1.9		
	78	24.1	2.0		

NR not reported

^a Rounded to nearest hour^b Represents a patient with an unknown time of ingestion or subacute ingestion. In these individuals, “time zero” represents arrival in the emergency department

Bold patient numbers indicate those patients who received fresh frozen plasma (FFP)

The median (IQR) length of stay was 3 (2–6) days. No patient developed a thrombotic complication during the hospital stay. There were no deaths. Five patients ingested

warfarin which belonged to someone else. Of the remaining 18 patients, 13 patients restarted their warfarin prior to discharge from the hospital. The remaining patients were discharged off their warfarin. In most cases, in light of the recent ingestion, it was felt that the risk/benefit ratio favored not restarting warfarin acutely, and the patients were ultimately told to follow up with their primary care physician for evaluation of long-term anticoagulation options.

The kappa score for each categorical variable abstracted was greater than 0.8.

Discussion

Warfarin overdoses are relatively uncommon, yet are associated with the potential for significant morbidity. According to the National Poison Data System, in 2011, 785 patients were treated in health care facilities for intentional or unintentional warfarin ingestions [13]. The majority of these patients (692/785; 77 %) were classified as having “none” or “minor” toxicity. Nonetheless, “major” toxicity occurred in 18 individuals, with an additional two individuals having fatal ingestions. No specific guidelines exist to guide management of such patients. Alternatively, supratherapeutic anticoagulation associated with therapeutic use of warfarin is common, and guidelines have been established to aid clinicians in managing patients with high INRs in this setting [6, 7]. In these guidelines, in the absence of bleeding, vitamin K is considered optional for an INR exceeding 5 and is not clearly recommended until the INR exceeds 9. Even in those cases, in the absence of bleeding, the doses of vitamin K are typically low. Neither the guidelines sponsored by the American College of Chest Physicians (ACCP) [6] nor those sponsored by the Australian Society of Thrombosis and Haemostasis [7] specifically provide recommendations for the management of an acute warfarin overdose.

Following oral consumption, warfarin is rapidly absorbed across the gastrointestinal tract, with a maximal concentration occurring 90 min after ingestion [6]. The S-enantiomer of warfarin has a half-life of 29 h, while the R-enantiomer has a half-life of 45 h. In therapeutic dosing, the pharmacokinetic data are well described. The toxicokinetics following overdose, however, are relatively poorly described. Serial warfarin concentrations from four separate case reports involving acute overdose have been published. Among these patients, the elimination half-life ranged from approximately 21 to 53 h [8–11]. In their case report of a single patient, Renowden et al. reported a decrease in the elimination half-life of warfarin from 53 to 33 h after the addition of cholestyramine [11].

In general, the vitamin K antagonists will not produce a significant rise in the INR until the factor VII level is approximately 30 % of baseline. Factor VII has a half-life of approximately 6 h [14]. In warfarin-naïve individuals, the PT/INR

would not be expected to rise for more than 12 h post-ingestion. However, in patients with preexisting factor VII deficiencies, coagulopathy occurs earlier [15]. As expected, patients in our study who were not chronically anticoagulated exhibited a rise in the INR more than 12 h after ingestion of warfarin. In the absence of vitamin K administration, the earliest rise observed in this series was 16 h. However, because of the small number of patients not chronically on anticoagulation, along with the inconsistent intervals in measuring the INR, determining an exact time when coagulopathy developed was not possible.

Patients who present with a supratherapeutic INR following therapeutic use are likely to present at a time when the INR reflects a steady-state warfarin concentration. Consequently, the INR is likely at or near its maximal value on presentation. In contrast, in the setting of acute warfarin overdose, there may be an ongoing absorption of warfarin after presentation to health care, and thus, the INR may continue to rise. In this series, except in the patients with an INR too high to measure on admission, the INR continued to increase in nearly every case.

Patients in this study received more vitamin K than would have been recommended using published treatment guidelines. While some patients in our series may have received more vitamin K than recommended to reverse or prevent worsening of coagulopathy, it is clear that other patients continued to have worsening coagulopathy despite doses of vitamin K in excess of 40 mg. This was likely due to the ongoing absorption of warfarin with continued inhibition of vitamin K 2,3 epoxide reductase and vitamin K quinone reductase, the enzymes responsible for adequate functioning of the vitamin K cycle.

There are no available guidelines in the published literature for the management of an acute warfarin overdose. Although there was marked variability in the doses, timing, and thresholds for administration of vitamin K in this series, there were some general consistencies in the management among treating physicians. Patients were observed without routine administration of vitamin K in the absence of coagulopathy or a rising INR. With a few exceptions, most patients were treated with vitamin K only after the INR exceeded the therapeutic range for warfarin anticoagulation. The majority of patients, in whom warfarin therapy was to be continued after discharge, received intermittent doses of vitamin K until the INR returned to therapeutic range.

It is impossible to predict how much vitamin K a patient will require to reverse or prevent coagulopathy after acute overdose since history of dose ingested is often unreliable, individual pharmacodynamics differ, and warfarin pharmacokinetics may change in overdose. In this series, intermittent doses ranging between 2.5 and 20 mg were given based on INR trends. The risk of giving too little vitamin K is the development of bleeding, while the risk of administering too

much vitamin K is “overshooting” in a patient who requires therapeutic anticoagulation and putting the patient at risk for thrombosis. For those subjects who are deemed to be at high risk for development of a thrombotic complication with complete reversal, two potential options exist. The first is either no reversal or partial reversal, with subsequent treatment of hemorrhagic complications should they occur. Alternatively, patients who achieve full reversal can be administered heparin until warfarin is reinstituted and a therapeutic INR is again achieved. No evidence-based data support one approach over the other for the management of patients with a warfarin overdose. In our practices, we consider full reversal of coagulopathy with subsequent administration of heparin a less desirable option because it prolongs the hospital stay, while the patient is converted back to warfarin therapy, and it also places the patient at risk for additional medication errors and complications. None of the patients in this series developed thrombotic complications; however, 12 patients on warfarin prior to the overdose did have at least one subtherapeutic INR following treatment with vitamin K. Importantly, of those 12 subjects, five were subtherapeutic on arrival, and warfarin was discontinued in an additional patient.

In this series, three patients (13 %) experienced bleeding, with only one event classified as major. Two of these patients presented late following their overdose, as evidenced by an initial PT/INR of 96.9/9.3 and greater than 100/10, respectively. Bleeding in the third patient was minor and appeared to be related to ingestion of a caustic agent rather than warfarin, as the patient had a normal PT and INR. Thus, one could reasonably conclude that warfarin overdose in this series was associated with bleeding only when INR exceeded 9. The ACCP guidelines only clearly indicate vitamin K when an INR is at least 10 [6]. Nonetheless, most of our patients received vitamin K when INR exceeded 3 due to concern for continued absorption and further inhibition of the vitamin K cycle and hence, worsening coagulopathy.

Previous studies in patients on chronic warfarin therapy who developed a supratherapeutic INR (without acute overdose) report major bleeding complications in 0.1–4.4 % of subjects [16–18]. In the current study, bleeding occurred in 13 % of subjects, with one subject experiencing major bleeding. Given the relatively small number of subjects, a direct comparison is not possible. Nonetheless, it seems reasonable to say that bleeding following warfarin overdose occurred at least as frequently, and possibly more frequently, than observed in patients presenting to outpatient anticoagulation clinics with supratherapeutic INRs.

Published literature describing the management of patients with an acute warfarin overdose is sparse and limited to case reports [9–11] and small case series [8, 12]. Nearly all cases involved the administration of vitamin K, while FFP was administered to approximately half of all previously published cases, despite the absence of bleeding [8, 12]. In previous case

reports, most patients were coagulopathic on admission. Nonetheless, only one of the previously published case reports presented with bleeding and that the case involved a patient who concurrently injected himself with heparin [9]. One of our subjects (case 11) received large doses of vitamin K in the absence of significant coagulopathy for unclear reasons. Only one patient, who was comatose with evidence of trauma, received FFP without bleeding, and the FFP was administered during the initial resuscitation out of concern for occult bleeding. The only other patient to receive FFP received it for a retroperitoneal hematoma.

The greatest limitation of this study is the retrospective design. Consequently, the conclusions are limited by the quality and completeness of the data in the medical record. In an effort to reduce such a limitation, the data abstracted were limited to continuous variables (e.g., PT or INR) and categorical variables which were subject to little interpretation bias (e.g., the presence or absence of bleeding). The use of such variables likely reduced, if not eliminated abstractor bias, and thus eradicated some of the limitations of a retrospective review [19]. In addition, the timing of laboratory assessment and administration of vitamin K were also not consistent among treating physicians. Consequently, it is not possible to determine specifically when the INR rose in warfarin-naïve individuals nor is it possible to determine the exact amount of vitamin K required for reversal.

It is possible that some patients with complications related to a warfarin overdose were not included in this series. For example, if a patient without known overdose presented with a supratherapeutic INR and an intracranial hemorrhage, the patient may have been admitted to a neurosurgical service rather than a toxicology service. In such cases, the patients would not be included in this case series. Such omissions would have led to an underestimation of the incidence of bleeding complications. It is possible, however, that sicker patients were selectively referred to our referral centers, which may have resulted in overestimation of the bleeding prevalence.

Subjects were not followed up after discharge from the hospital. Therefore, it is impossible to definitively know whether reversal of anticoagulation led to thrombotic complications after discharge. Of the 13 patients who were discharged on warfarin, six subjects had a subtherapeutic INR at the time of discharge. Of these six, two were subtherapeutic on initial presentation.

Conclusions

In this series of 23 patients with warfarin overdose, 21 presented with or developed coagulopathy. One major bleeding event occurred in a late-presenting patient with INR > 10 prior to initiating treatment. No thrombotic complications occurred in this series, and no subjects had fatal hemorrhage. The median

(IQR) total dose of vitamin K administered to patients in this series was 15 (10–50)mg with a maximal dose of 110 mg.

Conflict of Interest There are no financial, litigational, or other conflicts of interest to disclose.

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