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Discontinuation of oral anticoagulation preceding acute ischemic stroke - prevalence and outcomes: Comprehensive chart review

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Abstract

Introduction—Oral anticoagulants (OAC) are the therapy of choice to prevent thromboembolism in patients at risk. Discontinuation of OAC prior to elective medical and surgical procedures may reduce the risk of bleeding, but may expose patients to increased risk of thromboembolism and ischemic stroke. The current public health burden of ischemic strokes associated with OAC discontinuation is unknown. We aimed to study the prevalence OAC discontinuation in patients who presented with acute ischemic stroke as well as the outcomes of these strokes.

Methods—Retrospective cross-sectional study by intensive chart review of all acute ischemic stroke patients over 6 months in a large tertiary care community hospital.

Results—A total of 431 patients with acute ischemic stroke were admitted during study period, of which 11 (2.6%) had OAC discontinuation within 120 days prior to the index admission. Several strokes occurred after relatively brief discontinuations. The patient group with discontinuation was older, had higher comorbidities and also had a clinically significant stroke and resulting higher mortality and morbidity.

Conclusion—About 2.6% or 1 in every 38 of all ischemic strokes occurred after OAC discontinuation. Strokes occurring after OAC discontinuation also have higher mortality and morbidity. Our data suggest that any planned discontinuation of OAC, however brief, should be carefully considered.

Keywords

Acute ischemic stroke; anticoagulation interruption; outcomes

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Declaration of interests

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Introduction

Long-term oral anticoagulation (OAC) is often the therapy of choice to reduce the risk of thromboembolism in several patient groups. In patients on OAC, continuation of anticoagulation during surgical and invasive medical procedures may increase the risk of bleeding and discontinuation of anticoagulation prior may increase the risk of thromboembolic events. General and specialty specific guidelines exist to guide clinicians in balancing these risks (e.g. gastrointestinal [1], general [2], anesthesia [3] and dental [4]).

Previous studies have shown that major thromboembolic complications, especially ischemic stroke, occur in approximately 1% of patients who underwent temporary discontinuations of OAC [5–7] before an invasive procedure. But the public health burden of this surprisingly high complication rate has not been assessed to our knowledge. In this study, we extensively reviewed the entire in-patient chart of all stroke patients admitted to our community-based academic medical center during a 6-month period. The aim of the study was to identify the prevalence of recent discontinuation of OAC in patients with acute ischemic strokes and to assess the neurologic outcomes of the event based on their follow-up modified Rankin scale score (mRS).

Methods

In a single center, cross-sectional cohort study, all patients age 18 or greater who presented with acute ischemic stroke between 1 January 2012 and 30 June 2012 were reviewed. An intense chart review study was conducted at a community-based academic medical center with over 1200 beds in the system. The study was approved by Institutional Review Board. Hemorrhagic stroke patients were excluded from the study.

Data collection

Eligible patients were identified by electronic query of hospital electronic medical records with International Classification of Diseases 9 codes of ischemic stroke (434.0, 434.1 and 434.9). All pertinent medical records including admission notes, consult notes, daily progress notes, discharge summaries, nursing notes, previous medical records were reviewed manually to identify prior use of OAC. Since we have found documentation of previous OAC use inconsistently noted in stroke patients, we reviewed every page of the hospital records. If OAC use was noted or suggested or a recent procedure was carried out, all records, including outpatient records, were further reviewed to confirm any discontinuation prior to the index admission. The reasons for discontinuation and the interval from discontinuation to stroke were verified by two investigators and reviewed by the research group prior to inclusion. Electronic medical record query was used to identify patient demographics, past medical history, clinical outcomes and the mRS for each patient.

Definitions

OAC discontinuation: Patients who were treated with OAC medications including vitamin K antagonists, direct thrombin inhibitors and factor X inhibitors for at least 1 month whose medication was stopped for more than 3 days for vitamin K antagonists or more than 2 days

for other medications. Patients who were on bridging therapy were not counted as discontinued anticoagulation.

Days of OAC discontinuation: were calculated from the day the discontinuation was first documented to the onset of stroke symptoms.

Groups

Group 1: Patients with ischemic stroke who had OAC discontinuation prior to presentation.

Group 2: Patients with ischemic stroke and were not on OAC or who had no discontinuation of OC prior to presentation.

Group 3: Patients with ischemic stroke and who were on OAC without discontinuation or who were on bridging therapy for high-risk interruptions.

Outcome measures

Length of stay was obtained from hospital Admission, Discharge, Transfer system by electronic query. Any in-hospital death was recorded only after confirmation with a death certificate in the medical record. The degree of disability was determined by the patient's mRS.

Statistics

Descriptive statistics were used for all baseline variables, with means and standard deviations for normally distributed variables, medians and interquartile ranges for non-normally distributed variables and rates and proportions for discrete outcomes in each group. Chi-square or Fisher's exact test for proportions, Student *t*-test for parametric and Mann-Whitney U-test for non-parametric tests were used to compare both groups.

Results

A total of 465 strokes were reviewed and 431 patients met the inclusion criteria of non-hemorrhagic stroke within the 6-month period and their charts were intensively reviewed. Of these, 11 (2.6%) patients had OAC discontinuation prior to the index admission, Group 1. There were no patients who were on continuous OAC therapy or who were on bridging therapy (group 3). The remaining 420 patients were included as group 2. The analysis was limited to two groups and baseline characteristics and clinical outcomes were shown in Table 1.

Overall, stroke patients who had OAC discontinuation (Group 1) were older than non-discontinuation patients (Group 2) (81.64 ± 7.12 vs 70 ± 14.27 years). All patients in the discontinuation group were Caucasians and 66.7% were male compared with 71% Caucasian and 49% male in non-OAC group. The average CHADS2 and CHA2DS2-VASc scores for group 1 were 3.3 ± 1.1 and 4.7 ± 1.0 , respectively. The length of stay was similar among both groups (5.73 ± 10.1 vs 4.75 ± 3.1 days). A total of eight (73%) patients with stroke who had OAC discontinuation were on warfarin and three (27%) were on dabigatran.

The International Normalized Ratio (INR) in OAC discontinuation patients was near normal at the time of admission/time of the neurologic event (1.3 ± 0.18).

Indications for OAC use in Group 1 include atrial fibrillation (AF) in all patients and three patients had an additional indication (Table 2). The reasons for anticoagulation discontinuation are summarized in Table 3 and individual patient data are presented in Table 4. Out of the 11 patients, 4 (36%) patients had discontinuation of OAC because of GI procedures, 3 (27%) patients because of surgical procedures (biopsy, spinal injection) and 3 (27%) patients had permanent discontinuation of OAC as they were deemed high risk for continuation of OAC. All patients who were on warfarin had subtherapeutic INR (1.6) on admission. Dabigatran was a relatively new medication during the study period, and 3 (27.3%) of the discontinuation patients who developed stroke were on dabigatran as the OAC agent. The length of discontinuation for those patients who were on dabigatran was between 3 and 9 days (Table 4).

Outcomes

Overall, 21 (4.9%) patients in the total study group died during hospitalization (Table 1). A significantly higher death rate was present in the OAC discontinuation group compared with OAC non-discontinuation group (27.3% vs 4.3%, $p = 0.001$). The average mRS scores in the OAC discontinuation group were 3.82 ± 2.1 and 45.5% were either dead or severely disabled (mRS of 5 or 6) on discharge.

Discussion

Our study provides the first comprehensive review to our knowledge of stroke admissions to assess the prevalence of events associated with OAC discontinuation and hence the public health burden of these events. The typical admission medication reconciliation process in the emergency room is often inadequate and inaccurate [8], especially in patients with acute cognitive disabilities such as stroke. Therefore, for accuracy of data, our team has conducted an extensive review of inpatient and outpatient medical records as well for any subtle clues of anticoagulation use.

Our analysis showed that 2.6% of ischemic stroke admissions were associated with OAC discontinuation. The average CHADS2 and CHA2DS2-VASc scores indicated that the stroke patients who had OAC discontinuation were high risk for anticoagulation discontinuation according to the current guidelines. The poor neurologic outcomes of these patients are consistent with previous studies which showed that embolic stroke is fatal or associated with a severe neurologic deficit in over 60% of patients with chronic AF [9,10]. In our study population, nearly half of patients, 45.5% who developed stroke in the setting of OAC discontinuation were either dead or severely disabled (mRS of 5 or 6). Despite a limited sample size, our results raise concerns that there is a significant underestimated public health burden of stroke in patients with OAC discontinuation, even brief temporary interruptions for procedures.

Stroke is the fourth leading cause of mortality and the number one cause of permanent disability in the USA. There are estimated 795,000 strokes per year in the USA, of which

87% (691,650) were ischemic and resulted in 130,000 deaths. Acute stroke healthcare costs an estimated 36.5 billion dollars per year and rising [11]. By simple extrapolation of the data from our study, OAC discontinuation would be associated with 17,652 strokes, 3200 deaths, 9800 disabled patients and nearly \$930 million in healthcare cost per year, assuming similar results nationwide. These costs may be even higher because current literature shows that direct costs in patients with AF-related stroke are higher than non-AF-related stroke [12].

Our review showed that in some patients who were supposed to resume OAC immediately after a brief discontinuation for medical and surgical procedures, their admission INR was subtherapeutic. This suggests that inadequate monitoring and/or follow-up and coordination of anticoagulation in these high-risk patients may result in longer discontinuation periods than clinically indicated or intended.

In clinical practice, interruptions to OAC therapy are not uncommon. In such events, there are risk predictors and patients with high risk are often suggested bridging therapy. According to the current American College of Cardiology guidelines, the assumed risk of OAC interruption is generally accepted for up to 1 week in the periprocedural period. However, in our series, several strokes occurred despite relatively brief “acceptable” discontinuation of OAC that conformed to guideline recommendations. The underestimation of risk results from the assumption that the yearly risk of thromboembolic complications for patients with certain conditions can simply be divided by the number of days off the medication. This is an oversimplification of the complex pharmacology associated with cessation of antithrombotic therapy, especially insofar as the procedures and surgeries leading to the discontinuation may increase thrombotic risk [13].

Current guidelines lack recommendations about the newer OAC including dabigatran. OAC usage data from the time period immediately precede our study show that the novel anticoagulants use was 19% [14]. Our data show 3 out of 11 (27.3%) of strokes associated with temporary interruption were from these newer agents, and that all of these events were associated with inappropriately long interruptions compared with package insert recommendations. Lack of familiarity with the pharmacokinetics of these new agents may be a public health problem. The manufacturer recommends interruption of 1–2 days with normal renal function, which was the case for our dabigatran-treated patients [15].

In our study, we found that the burden of stroke associated with OAC interruption may be higher than estimated by the simple extrapolation. Earlier studies also raised concerns about clinical rebound phenomenon [16,17] and tried biochemical explanation of warfarin interruption [18,19], although no definite conclusions can be drawn. However, recent data on anticoagulation interruption from novel anticoagulation studies also showed similar excess risk after discontinuation of OAC agents and real-world data from country level cohort suggested that the short-term risk of OAC interruption may be higher than expected [20,21]. Patients should be made aware of possible increased risk of thromboembolic events and their sequelae when an informed decision is made.

Limitations

Small sample size and lack of a control group limits the analysis, and although the data suggest association with stroke in patients who had OAC interruption, causality could not be proven. For patients who did not have OAC discontinuation, CHADS2 scores were not calculated, but would be less relevant since most of those patients did not have underlying AF. Further, we could not find any patients who had stroke while on bridging therapy. Therefore, the association of stroke in patients who had OAC interruption but undergoing a planned bridging therapy is unknown.

Conclusions

Stroke associated with OAC discontinuation is a significant public health burden. The major thromboembolic risk of OAC discontinuation may be higher than expected due to the complex nature of OAC therapy, and the risk of brief interruptions may not be simply extrapolated from the yearly risk of the underlying disease. Further studies are needed to identify vulnerable groups of patients.

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Table 1

Baseline characteristics and outcomes.

		Anticoagulation discontinuation status		
		Group 1 (yes) <i>n</i> = 11	Group 2 (none) <i>n</i> = 420	<i>p</i> -Value
<i>Age (years)</i>				
Mean ± SD		81.64 ± 7.12	70 ± 14.27	0.004 ^a
Median (IQR)		82 (79.5–84)	72 (60–81)	0.023 ^b
<i>Gender</i>				
Male		7 (66.7%)	205 (48.8%)	0.158
Female		4 (33.3%)	215 (51.2%)	
<i>Race</i>				
Caucasian		11 (100.0%)	299 (71.2%)	0.135
African American		0 (0.0%)	101 (24.0%)	
Others		0 (0.0%)	20 (4.8%)	
<i>Length of stay (days)</i>				
Mean ± SD		4.75 ± 3.13	5.73 ± 10.10	0.429 ^a
Median (IQR)		4.20 (2.67–5.51)	3.44 (1.92–5.95)	0.337 ^b
<i>Days of anticoagulation discontinuation</i>				
Mean ± SD		21.6 ± 33.44	N/A	
Median (IQR)		9 (5–12.5)		
<i>mRS score</i>				
Mean ± SD		3.82 ± 2.10	N/A	
Median (IQR)		4 (2.5–5.5)		
<i>INR on admission (if on warfarin)</i>				
Mean ± SD		1.26 ± 0.17	N/A	
Median (IQR)		1.2 (1.175–1.325)		
<i>CHADS₂ score</i>				
Mean ± SD		3.45 ± 1.21	N/A	
Median (IQR)		3 (2.5–4.5)		
<i>CHA₂DS₂-VASc score</i>				
Mean ± SD		4.9 ± 1.0	N/A	
Median (IQR)		5 (4–6)		
Discharge status	Home	2 (18.2%)	198 (47.1%)	0.001
	Dead	3 (27.3%)	18 (4.3%)	
	Rehabilitation	6 (55.5%)	204 (48.6%)	

Chi-square test,

^aStudent *t*-test,^bMann–Whitney U–test.

Abbreviations: IQR = Interquartile range; N/A = Not applicable; SD = Standard deviation.

Table 2

Indications and agents of oral anticoagulants use in patients who developed stroke.

Indication	Frequency	Anticoagulant agent	Frequency
Atrial fibrillation	11 (100%)	Warfarin	8 (73%)
Mechanical heart valves	1 (9%)	Dabigatran	3 (27%)
Ischemic cardiomyopathy	1 (9%)		
Recurrent pulmonary embolism/Factor V Leiden mutation	1 (9%)		

Table 3

Reasons and duration of oral anticoagulation discontinuation.

Reason	No. of patients	Average time from discontinuation to stroke (in days)
Gastrointestinal procedures	4 (36%)	5.75
Surgical procedures and biopsy	3 (27%)	6.33
Permanent discontinuation	3 (27%)	18
Other	1 (9%)	10
All	11 (100%)	9.7

Table 4

Details of patients who had acute ischemic stroke after OAC discontinuation.

Patient	CHADS ₂ score	CHADS ₂ -VASC score	OAC indication	OAC agent	Reason	Days OAC interrupted	Admission INR	LoS	mRS	Guideline adherence
1	2	4	AFib	Warfarin	Colonoscopy	5	1.4	2.1	6	Yes
2	5	6	AFib	Warfarin	Colonoscopy	8	1.1	11.7	5	No
3	5	6	Mechanical AVR, AFib	Warfarin	Hemorrhagic stroke	10	1.6	3.3	6	N/A
4	4	6	AFib	Warfarin	Spine injections	7	1.2	3.9	4	No
5	3	5	AFib	Warfarin	Surgical	10	1.1	5	5	No
6	4	5	AFib	Dabigatran	Colonoscopy	4	1.2	1.6	0	<i>a</i>
7	2	3	AFib	Dabigatran	EGD	9	1.6	8.5	6	<i>a</i>
8	3	5	AFib, ICM	Dabigatran	Minor Surgery	3	1.4	6	2	<i>a</i>
9	3	4	AFib, PE, Factor V Leiden	Warfarin	Permanent discontinuation	15	1.2	4.2	4	N/A
10	5	6	AFib	Warfarin	Permanent discontinuation	60	1.2	1.1	1	N/A
11	2	4	AFib	Warfarin	Permanent discontinuation	110	1.3	4.8	3	N/A

^a Guidelines do not address adequately, however, the duration of interruption exceeds recommendation from “Highlights of Prescribing Recommendations” (package insert [15]).

Abbreviations: AFib = Atrial fibrillation; AVR = Aortic valve replacement; EGD = Esophagogastroduodenoscopy; F = Female; LoS = Length of stay (in days); M = Male; mRS = Modified rankin scale score; N/A = Not applicable; OAC = Oral anticoagulants.