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Analysis of the trend in Oral Anticoagulation Overdose

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Abstract

Aim

The aim of this study is to observe trends in enquiries to the National Poisons Information Centre (NPIC) concerning oral anticoagulants over the past eleven years.

Methods

A retrospective review of all recorded cases involving anticoagulation enquiries to the NPIC from 2010 to 2020, inclusive, was conducted. Data included: name, type, patient demographics, location of incident, enquiry source, and type of incident, symptoms, poison severity score, and treatment.

Results

Four hundred and sixty five (*n*=465) oral anticoagulation enquiries were registered with NPIC from 2010 to 2020. Enquiries concerning anticoagulants occurred most frequently in the elderly age group (>65 years) in 47% (*n*=224). Most enquiries were from GP services at 46% (*n*=218). 1 in 10 calls involved a polypharmacy overdose. Accidental ingestion was more frequent (79%, *n*=105) in toddlers whereas therapeutic error occurred more frequently in elderly patients (76.1%, *n*=166). Majority of the cases (84%, *n*=396) had no symptoms at the time of the call. Only 44 (9.3%) cases received treatment. Less than 4% (*n*=17) required follow-up.

Conclusion

Anticoagulant overdose in elderly population is alarming. DOAC overdose's is concerning as specific antidotes are not widely available. Measures should be taken to reduce the risk of polypharmacy overdose.

Introduction

DOAC and Warfarin are two commonly prescribed oral anticoagulation agents for the prevention and treatment of thromboembolic diseases[1]. Both differ in mechanism of action. Warfarin is a Vitamin K antagonist and requires regular International Normalised Ratio (INR) monitoring[1]. There are two main classes of DOAC's: oral direct factor Xa inhibitors (i.e., rivaroxaban, apixaban, edoxaban, and betrixaban) and direct thrombin inhibitors (i.e. dabigatran). The US Food and Drug Administration (FDA) approved the first DOAC dabigatran in 2010 followed by rivaroxaban, apixaban, edoxaban, and betrixaban.

Increased prescription of DOAC's compared with Warfarin was observed since their authorisation[2]. Clinical trials report that DOAC's show non-inferiority to Warfarin[3,4,5].DOAC's have a more favourable safety profile compared to Warfarin[6,7,8]. Both oral anticoagulants are associated with an increased risk of bleeding however apixaban has been shown to have a safer profile than Warfarin in terms of major intra-cranial and gastrointestinal bleeding[9].

One of the major causes of oral anticoagulation toxicity is drug-drug interactions, which is often overlooked in clinical practice[10,11]. Other potential causes include accidental, therapeutic error or intentional overdose. The objective of this study is to assess the trend in oral anticoagulation overdose over the period of 11 years as reported by National Poison Information Centre, (NPIC), Beaumont Hospital, Ireland.

Method

A retrospective review of all enquiries to the NPIC concerning oral anticoagulants from 2010 to 2020 inclusive was conducted. The NPIC is the only poison centre in Ireland that provides advice to healthcare professionals, and members of the public. It also collects and analyses epidemiological data on acute poisoning. Trained Poisons Information Officers (PIO's) triage and give advice on over eleven thousand calls per year (NPIC Annual Report 2020). The PIO's log details of enquiries to a secure toxicological database[26]. Demographics (age, gender), enquiry source (hospital doctor, general practitioner, pharmacist, member of the public), incident location, circumstance of the case (accidental, intentional, therapeutic error) and poison severity scale score (PSS 0-4) were documented. The product(s) involved were also recorded.

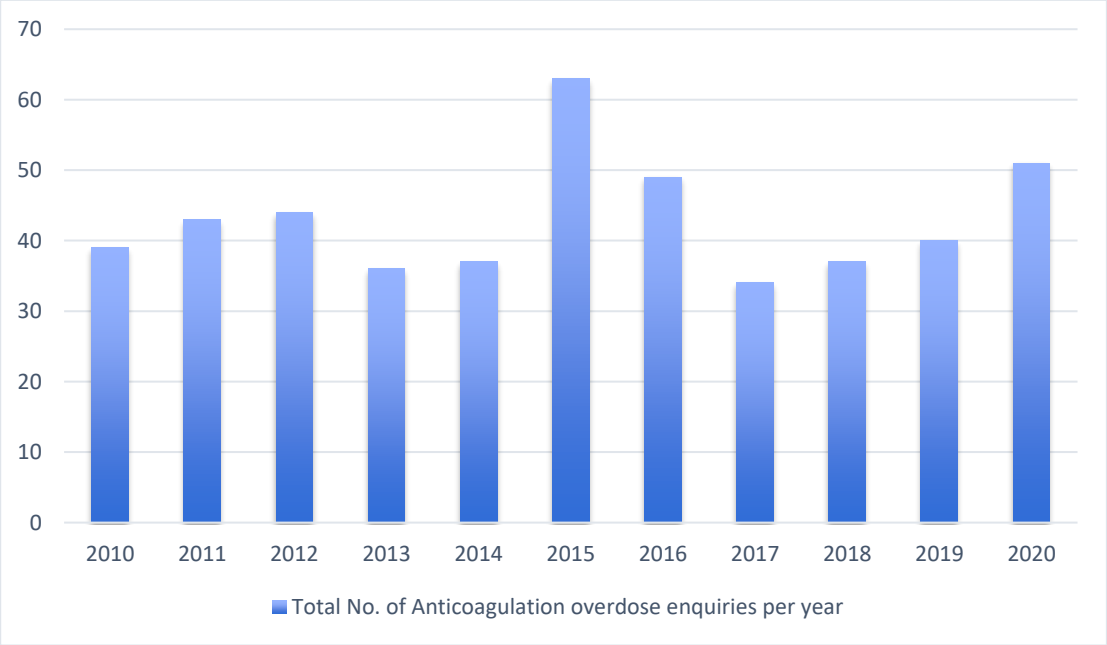
Data regarding anticoagulant enquiries to the NPIC from 1st January 2010 to 31st December 2020 was analysed. Details regarding gender, source of enquiry, number of drugs ingested, oral anticoagulation agent type, poison severity scale, circumstances of the case, treatment and follow-up plan were extracted from the NPIC electronic record. Patients were categorised into different age groups**.**

Extracted details from NPIC electronic record were analysed to compare the dataset for each year. Rate of each DOAC and warfarin overdose was calculated separately and then compared with each other over the period. Frequency of polypharmacy overdose (defined as ingestion of >4 drugs including oral anticoagulation) with different oral anticoagulation agents was calculated and compared to each other using the poison severity score. The above-mentioned rates were then stratified by age group and sex. Where applicable, statistical analysis was performed using tailed t-test. As a standard, minimum level of statistical significance was 5% ($p<0.05$). Ethics approval was not required, and the lead of the database approved the release of data for publication.

Results

A total of four hundred and sixty-five (*n*=465) oral anticoagulation enquiries were registered with NPIC from 2010 to 2020. Total number of poisonings enquires each year is illustrated in Graph 1, with the peak number of calls occurring in 2015.

Graph 1: Total number of Anticoagulation Overdose enquiries each year.



Nearly half of the anticoagulation enquiries occurred in the elderly age group (>65 years) (47%, *n*=224) with a peak incidence in 2015 (n = 38). There was a 2.8-fold increase in the number of overdose enquiries in the elderly from 10 in 2010 to 28 in 2020. This compares to a 4.7 fold decrease in anticoagulant overdose enquiries in the toddler age group from 19 in 2010 to 4 in 2020. Only 2.5% (*n*=12) of the total calls involved infants (under 1 year old), 4.22% (n=20) in the 5-18 year age group,

and 23% in the 18-65 year age group. A higher percentage of anticoagulation enquiries was observed in toddlers (21.35%, *n*=101) compared to infants and the 5-18-year age group (p<0.001). As shown in Table 2.

Table 2: Enquiries as per age group

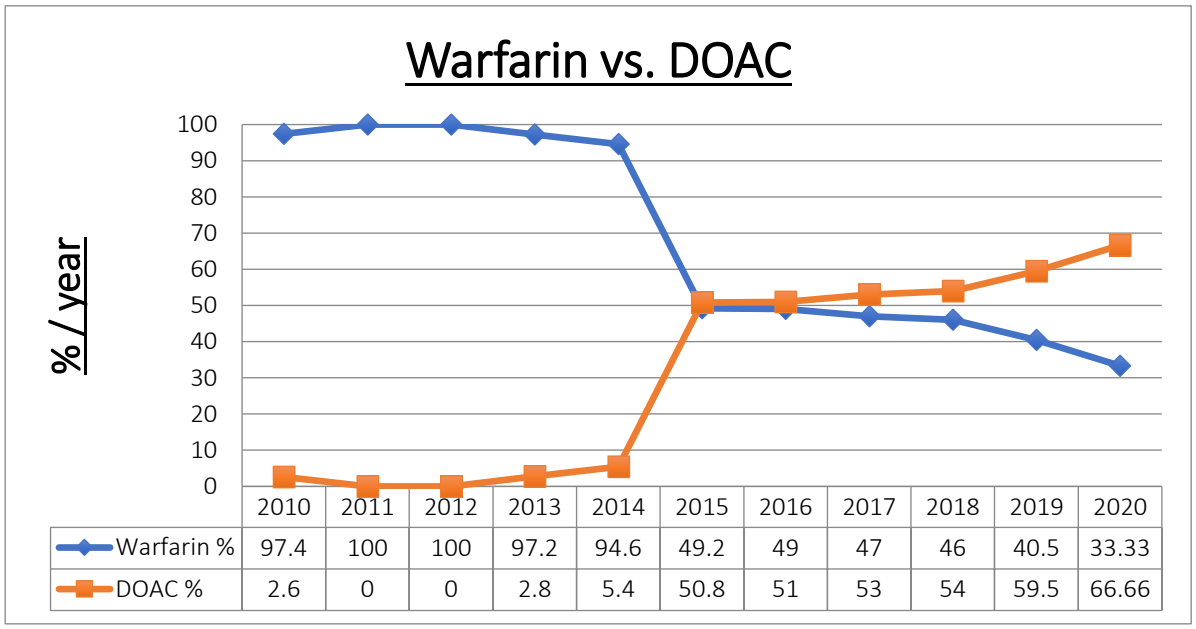
Age Group	Number of Enquiries	Percentage
Infant (0-1)	12	2.5%
Toddler (1-4)	101	21.35%
5 to 18-year-old	20	4.22%
18 to 65-year-old	110	23.25%
>65-year-old	222	46.93%
Total	465	

Male to female ratio was nearly 1:1 ratio. Polypharmacy overdose was observed in 1 in 10 enquiries (*n*=49). Majority of the polypharmacy overdoses occurred in the elderly patient 63.26% (*n*=31) (p=0.043), 28.5% (*n*=14) in 18 to 65-year-old and 6.12% (*n*=3) in the toddler age group. Nearly half of the enquiries were received from GP service (*n*=218) 46%, followed by hospital 29% (*n*=137), member of public 14.6% (*n*=69), community pharmacist 4.9% (*n*=23), nursing home 1.9% (*n*=9), other source 1.3% (*n*=6) and ambulance 0.6% (*n*=3).

There was a downward-trend of warfarin overdoses from 97.4% in 2010 to 33.3% in 2020 and an upward-trend of DOAC enquiries from 2.6% in 2010 to 66.6% in 2020 over 11 year-period as shown in Graph 2. Warfarin was the only anticoagulation overdose reported in 2011 and 2012. DOAC drugs such as apixaban, rivaroxaban and dabigatran came to Ireland market between 2011 to 2013. Bearing in mind that it may take some time for prescribing trends to stabilize, DOAC prescriptions started to rise in 2013 as per the data from Primary Care Re-imbursement Scheme (PCRS) Ireland. With the increased prescribing of DOAC's the NPIC enquires concerning Warfarin started to drop and DOAC

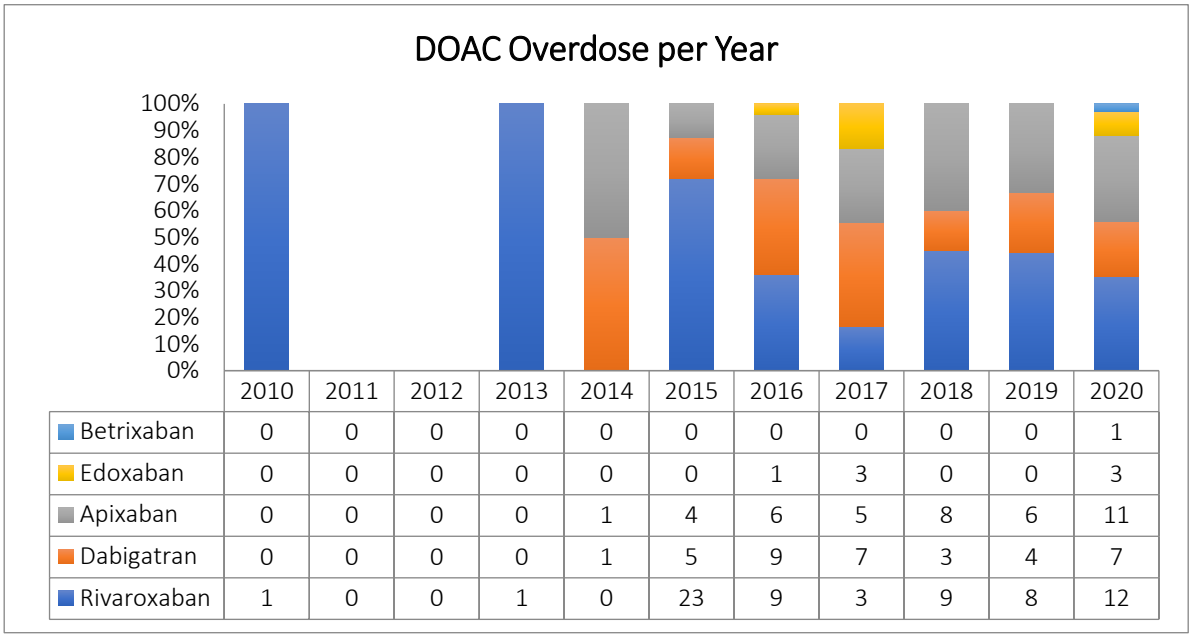
enquiries started rising from 2014 (Graph 2). Dabigatran came to the Irish market in 2015, and there was sharp increase of DOAC overdoses to 50% (*n*=63) compared to Warfarin at 49% (*n*=31). Rivaroxaban was the most common DOAC enquiry 72% (*n*=23) followed by dabigatran 15.6% (*n*=5) and apixaban 12.5% (*n*=4). In 2016, rivaroxaban lost its dominance and DOAC overdose was more broadly distributed with, rivaroxaban 36% (*n*=9), dabigatran 36% (*n*=9), apixaban 20% (*n*=5), edoxaban 4% (*n*=1) (see graph 3). Edoxaban was made available to the patients in September 2015 as per PCRS data. The gap between Warfarin and DOAC overdose enquiries started to increase from 2017. In 2020, there were 17 Warfarin and 34 DOAC overdose enquiries.

Graph 2: Warfarin versus DOAC Overdose each year.



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Warfarin %	97.4	100	100	97.2	94.6	49.2	49	47	46	40.5	33.33
DOAC %	2.6	0	0	2.8	5.4	50.8	51	53	54	59.5	66.66

Graph 3: Type of DOAC Overdose Each Year



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Betrixaban	0	0	0	0	0	0	0	0	0	0	1
Edoxaban	0	0	0	0	0	0	1	3	0	0	3
Apixaban	0	0	0	0	1	4	6	5	8	6	11
Dabigatran	0	0	0	0	1	5	9	7	3	4	7
Rivaroxaban	1	0	0	1	0	23	9	3	9	8	12

Majority of cases had no symptoms at the time of call, 84% (*n*=396), 8% (*n*=38) had minor, 3% (*n*=14) patients had a moderate poison severity score, with most of them 64.3% (*n*=9) associated with Warfarin although this was not statistically significant. Type of DOAC in moderate category poisoning was apixaban in all 5 cases. Only 1% (*n*=5) had severe poisoning of which 3 were Warfarin and 2 were DOAC's (1 rivaroxaban, 1 apixaban) (p=0.32).

429 (91%) out of 473 patients did not receive treatment prior to contacting NPIC with 7 of these patients designated as moderate to severe poisoning. 44 (9.3%) had treatment prior to the NPIC call with 13 of these designated as moderate to severe poisoning. Out of those 44 patients, 35 received supportive treatment and 7 received antidote all of which were for Warfarin. No patient after 2015 received an antidote. The advice given by NPIC staff after receiving a poisoning enquiry was to attend local emergency department in 42.3% (*n*=200), no treatment recommended in 18% (n=86), supportive management in 17% (n=80), seek GP advice in 15% (n=70) and antidote in 7.8% (*n*=37). 27 out of 37 in which antidote was recommended by NPIC for Warfarin had a PSS score of 0 or 1, 3 had a PSS of 2 (moderate), and 1 had PSS of 3 (severe). An antidote was recommended for Apixaban (n=1) in 2017 and Dabigatran (n=1) in 2018 but it was not given as both patients showed no signs of poisoning. 17 patients (<4%) were followed up by the NPIC, of which 8 patients had none to mild poisoning, 5 patients had moderate poisoning, and 4 had severe poisoning.

Data about type of overdose was available for 424 patients over the 11-year period. Therapeutic error was the most common type of oral anticoagulation overdose observed, *n*=232 (54.71%). Majority of therapeutic errors (71.6%) happened in elderly (>65-year) people, *n*=166 (112 warfarin & 54 DOAC overdoses). There were only 2 therapeutic errors in 5 to 17-year-old age group, 1 with DOAC and 1 with warfarin. There was no therapeutic error in the toddlers or infant group. There were 133 (31%) accidental oral anticoagulation overdoses recorded between 2010 to 2020. Toddlers were by far the commonest to overdose accidentally, *n*=105 (79%) out of which warfarin was the commonest agent *n*=92 (87.6%) compared to DOAC n=13 (12.38%). There were 7 accidental overdoses in infants (all with warfarin), 9 in 5-17-year-old (1 with DOAC, 8 with warfarin), 3 in 18-65-year-old (all with warfarin), and 9 in >65-year-old (5 warfarin, 4 DOAC). The number of intentional oral anticoagulation overdose enquiries in 18-65-year age group was of concern, 49 out of 59 (83%) total intentional overdoses. Majority of these were warfarin, *n*=42 compared to DOAC, *n*=7.

Discussion

Our study retrospectively analysed the trend of anticoagulant enquiries to the National Poisons Information Centre of Ireland over an 11-year period. A drug overdose is defined as a pathological level of drug toxicity and may be intentional or accidental or due to therapeutic error. We chose to analyse the trend in OACs due to their increasing popularity and a lack of local literature in this context. Our study shows a significant increase in DOACs (most commonly rivaroxaban) being the OAC implicated in the overdose in 2020, compared to 2010 where there was a 97.4% chance that the OAC in question would be Warfarin. This change is reflected in the availability of DOACs since 2013, and the prescribing trend seen both in the UK[12], Canada[13] and the United States [14] highlighting that DOACs are now the principal choice for stroke prophylaxis in the setting of atrial fibrillation. Anticoagulation is a cornerstone of preventative medicine, as evidenced by the recent introduction of the DOACs into the 21st WHO List of Essential Medicines[15]. Oral anticoagulants have long been used as prophylaxis against stroke in patients with non-valvular atrial fibrillation, the traditional choice being warfarin (a vitamin K antagonist), with the newer direct oral anticoagulants (DOACs) increasing in popularity over the past 10 years[16]. Warfarin exerts its effects via inhibition of the enzyme Vitamin K epoxide reductase, and although is long established, requires regular blood monitoring and dietary guidance, due to the risk of severe adverse events such as life-threatening haemorrhage. The DOACs have emerged in the past decade, primarily working by inhibiting Factor Xa or thrombin. Their convenience is underlined by the fact that regular invasive monitoring is not required, and they are less limited by dietary and medication interactions.

The risk of stroke is estimated to be increased 3-5-fold in patients with atrial fibrillation[17]. Stroke is one of the foremost causes of death and disability in Ireland, with significant financial impact estimated by the Stroke Alliance for Europe as approximately 1% of total expenditure in the health service[18]. Large, randomised, phase 3 trials have deemed the DOACs to be non- inferior to warfarin

prescription in stroke prevention in the setting of atrial fibrillation, with some studies suggesting superiority[19, 20, 21, 22].

Our study also reflected the trends in polypharmacy and its potential impact on our population. Polypharmacy is defined as prescription of >4 medications being taken by an individual at any one time and is generally accepted as a consequence of our ageing, multi morbid population. New medications are generally trialed through studies that exclude frail patients with multiple co-morbidities and as such the adverse effects of polypharmacy on the health of an elderly person are difficult to quantify. It is generally accepted that polypharmacy is associated with increased falls, increased risk of side effects and non-compliance with medication[24]. Polypharmacy overdoses were reported as constituting 2.5% of all drug overdoses in 2010, with this increasing to 13.7% in 2020. This reflects the prevalence of polypharmacy and its growth in Ireland, as well as the implication that the ageing population has on our prescribing as a nation. Our study showed a statistically significant (p value <0.043) increase in overdoses in elderly patients as opposed to other age cohorts. This brings to attention the need in future for extensive measures to avoid overdoses in older adult cohort. Other strategies to address polypharmacy going forward include regular medication reconciliation and rationalisation, and tools such as STOPP (screening tool of older persons' potentially inappropriate prescriptions) and START (screening tool to alert doctors to right treatment)[25].

Conclusion

This retrospective study of oral anticoagulation overdose provides insights into prescribing trends over an 11-year period. It highlights the importance of the growing need for DOAC reversal agents. Polypharmacy overdose, especially in elderly population, increases the susceptibility to major adverse events. Initiatives are required to address the issue of polypharmacy to reduce the risk of polypharmacy overdose such as rationalizing medications, pharmacist intervention and medication reconciliations. In our opinion, these issues are amenable to public health, quality improvement and community-based measures.

Declarations of Conflict of Interest:
None declared.

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