Monitoring direct oral anticoagulant plasma concentrations – experience from the Princess Royal University Hospital

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Introduction

The prescribing of direct oral anticoagulants, DOACs, has increased exponentially in the past decade. Fixed dosing, combined with the more predictable pharmacokinetic profiles compared to traditional oral anticoagulants, has led to the general consensus that the routine therapeutic monitoring of DOAC therapy is unnecessary.[1-5]

Despite this, there is much evidence to suggest that the monitoring of therapy in specific patient groups would be beneficial, e.g in patients with renal impairment, at extremes of body weight, with potential altered GI absorption, on concomitant interacting drug therapy and those who have previously been subject to adverse events, would likely benefit from a check in the plasma concentration.[6] This study aimed to explore the reasons behind DOAC assay requests at the Princess Royal University Hospital (PRUH) and establish whether there was any relationship between DOAC plasma concentration and patient outcomes, in those where an assay was requested.

Methods and Analysis

Between 1 June 2017 and 30 June 2019, all DOAC assays requested by clinicians at the PRUH were retrospectively collated from DAWN and Electronic Prescribing Records and reviewed. These assays were typically requested in patients where there was concern that exposure to the DOAC could significantly be altered, potentially impacting on outcomes. Information, including patient demographics, comorbidities and indication for assay, was recorded onto Excel and analysed. Patient outcomes (bleeding as defined by ISTH or thromboembolism) in the 90 days following the assay draw was also recorded.

Assay results were categorised as peak, trough or other, based on time of last dose, using summary of product characteristics. Peak and trough values were considered in range using data published by Gosselin et al (2018).[7]
For assays considered 'other', it was deduced whether the result was in range using data published by Krekels et al (2016)[8] and Mueck et al (2013)[9]. The severity of any bleeding events were assessed and categorized according to ISTH definitions.

Key Findings

Over the 2-year study period a total of 588 assays were requested, 500 of which had sufficient information to be included for review. These 500 assays were from 446 patients (median age 77 [IQR 64– 86 years], 50% male).The assay requests were comprised of 218 (43.6%) apixaban, 186 (37.2%) rivaroxaban, 80 (16.0%) edoxaban and 16 (3.2%) dabigatran. These assays were most commonly requested for patients with renal impairment and patients at the extremes of body weight (Table 1).

There was no link between the result of the assay and the patient outcome in the frequency of bleeding observed in patients that had DOAC concentrations within the expected range, which was very similar to the frequency of bleeding seen in those who had a concentration that was out of range (Table 2).

In total 67 bleeding events were reported, two of which could be considered major bleeds; one fatal intracerebral haemorrhage on edoxaban and one episode of melena on rivaroxaban. Both major bleeds had a previously measured DOAC plasma concentration result that was considered in range (as defined by Gosselin et al 2018). There were also two thromboembolic events: an ischaemic stroke on apixaban and a DVT on rivaroxaban. The assay result for the patient who suffered a stroke showed an apixaban concentration that was in range and the rivaroxaban assay was below range.

There appeared to be no link between the DOAC plasma concentration and the patient outcome in the frequency of bleeding observed in patients that had DOAC concentrations within the expected range and those who had a concentration above or below the range.

Table 1: Indications for measuring assay

Indication	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
	(n = 218, 43.6%)	(n = 16, 3.2%)	(n = 80, 16.0%)	(n = 186, 37.2%)
Renal Function - n (%)	108 (49.5)	2 (12.5)	17 (21.3)	48 (25.8)
Extremes of weight - n (%)				
High body weight	40 (18.3)	3 (18.8)	24 (30.0)	64 (34.4)
Low body weight	44 (20.2)	2 (12.5)	19 (23.8)	13 (7.0)
Interacting medication - n (%)	44 (20.2)	10 (62.5)	15 (18.8)	24 (12.9)
Absorption concerns - n (%)	16 (7.3)	0 (0.0)	6 (7.5)	15 (8.1)
Other - n (%)	5 (2.3)	4 (25.0)	8 (10.0)	2 (1.1)
Routine - n (%)	4 (1.8)	0 (0.0)	5 (6.3)	34 (18.3)
Adverse effects - n (%)	7 (3.2)	0 (0.0)	1 (1.3)	3 (1.6)

Table 2: Assay result and subsequent outcomes of therapy

Outcome	Apixaban (n=218, 43.6%)	Dabigatran (n=16, 3.2%)	Edoxaban (n=80, 16.0%)	Rivaroxaban (n=186, 37.2%)	Total (n=500, 100.0%)
In range - n (%)	165 (75.7)	6 (37.5)	48 (60.0)	147 (79.0)	366 (73.2)
No event - n (%)[a]	140 (84.8)	5 (83.3)	38 (79.2)	130 (88.4)	313 (85.5)
Bleed - n (%)[a]	24 (14.5)	1 (16.7)	10 (20.8)	17 (11.6)	52 (14.2)
Thromboembolic event - n (%)[a]	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Above range - n (%)	11 (5.0)	3 (18.8)	3 (3.8)	19 (10.2)	36 (7.2)
No event - n (%)[b]	8 (72.7)	3 (100.0)	2 (66.7)	17 (89.5)	30 (83.3)
Bleed - n (%)[b]	3 (27.3)	0 (0.0)	1 (33.3)	2 (10.5)	6 (16.7)
Thromboembolic event - n (%)[b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Below range - n (%)	42 (19.3)	7 (43.8)	29 (36.3)	20 (10.8)	98 (19.6)
No event - n (%)[c]	35 (83.3)	7 (100.0)	28 (96.6)	18 (90.0)	88 (89.8)
Bleed - n (%)[c]	7 (16.7)	0 (0.0)	1 (3.4)	1 (5.0)	9 (9.2)
Thromboembolic event - n (%)[c]	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	1 (1.0)

[a] percentage value is calculated based on total number in range [b] percentage value is calculated based on total number above range [c] percentage value is calculated based on total number below range

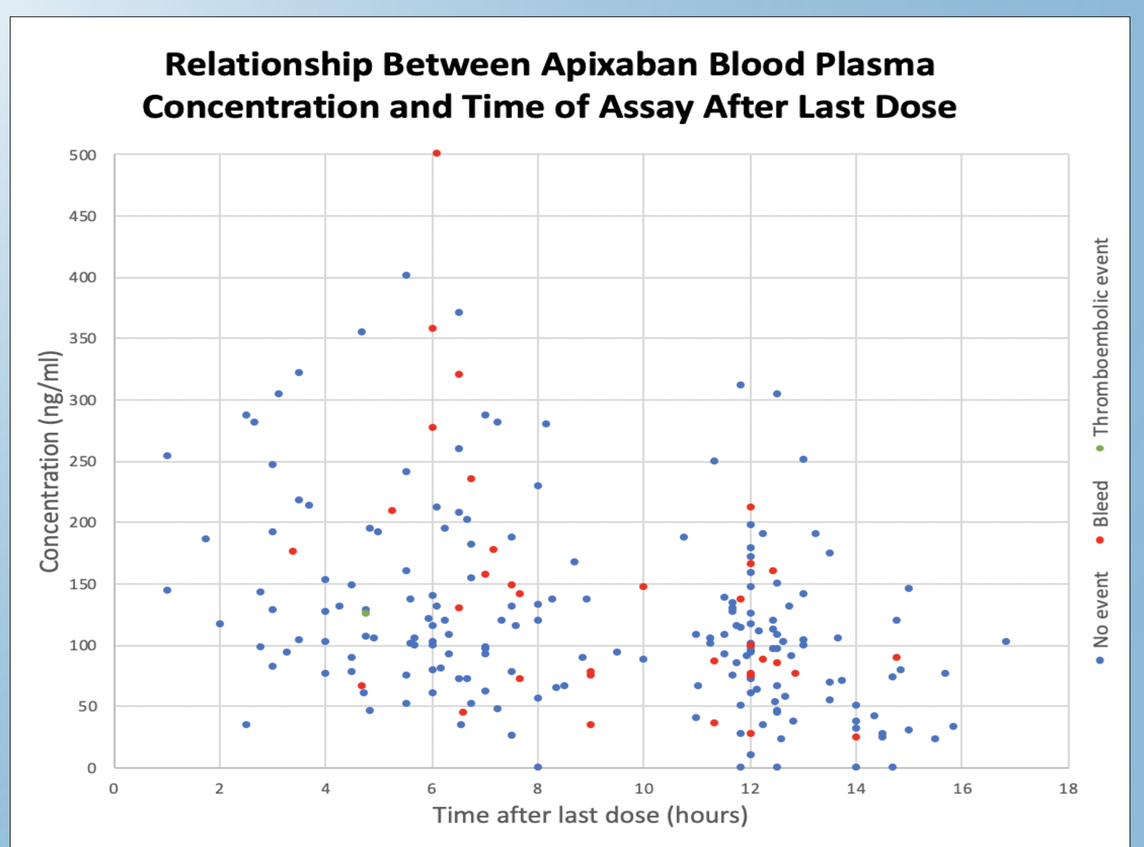

Figure 1: Apixaban concentration values plotted against the time after the last dose

Conclusions

Overall, there appeared to be no link between the DOAC plasma concentration and the patient outcome in the frequency of bleeding observed in patients that had DOAC concentrations within the expected range and those who had a concentration above or below the range. Our findings suggest there is no need for routine plasma concentration monitoring of direct oral anticoagulants. However, in situations of uncertainty, for example morbidly obese patients, they do provide reassurance to clinicians.

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