Gastrointestinal bleedings during therapy with new oral anticoagulants are rarely reported

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ABSTRACT

INTRODUCTION: Post-marketing surveillance of drugs relies on spontaneous reporting of adverse drug events to the Health and Medicines Authority. A number of new oral anticoagulants (NOAC) have recently been marketed in Denmark. The purpose of this study was to evaluate the reporting of serious adverse drug events in patients treated with a NOAC and admitted for gastrointestinal bleeding.

MATERIAL AND METHODS: This study is based on an electronic free text search in patient records and a search in the electronic medication records of all patients admitted to the Department of Gastroenterology, Surgical Section, Hvidovre Hospital, during a one-year-period. Patients in treatment with NOAC and admitted for gastrointestinal bleeding were identified. Relevant patients were cross-checked for a reported adverse drug event in the Danish Health and Medicines Authority's database on adverse medical events.

RESULTS: A total of 20 patients were acutely admitted for gastrointestinal bleeding while in treatment with a NOAC, an adverse medical event was reported for one of these patients (5%; 95% confidence interval: 0-25%).

CONCLUSION: Serious adverse events in patients treated with NOAC are underreported which questions the current effectiveness of post-marketing surveillance of adverse drug effects.

FUNDING: not relevant.

TRIAL REGISTRATION: The study was registered with clinicaltrials.gov (NCT02107651).

Post-marketing surveillance in Denmark is primarily based on mandatory reporting of adverse drug events. Under Danish pharmaceutical legislation, all adverse effects of treatment with drugs are to be reported to the Danish Health and Medicines Authority if the drug is newly marketed (defined as occurring within two years of marketing) or if the event is serious (defined as fatal or causing hospital admission) regardless of time in relation to marketing.

Adverse effects of medical treatment are probably underreported. Underreporting of serious adverse effects in Denmark has not recently been evaluated systematically. Since 2007, several new oral anticoagulants (NOAC), including dabigatran etilexate (Pradaxa) and rivaroxaban (Xarelto), have been registered for use in Denmark.

The purpose of this study was to evaluate if the routine post-marketing surveillance system captures serious adverse drug events in patients treated with NOAC. Thus, we systematically registered reports of adverse drug effects recorded by the Danish Health and Medicines Authority in patients admitted for gastrointestinal bleeding while undergoing NOAC treatment.

METHODS AND MATERIAL

The study was a consecutive case series based on retrospective analysis of patient records.

Patients in treatment with NOAC at the time of admission were identified among all patients admitted to the Department of Gastroenterology, Surgical Section, Hvidovre Hospital, Denmark, during a one-year-period from 1 January 2012 to 31 December 312012, by a): a search algorithm in the free-text medical patient records for all occurrences of the text-strings: "dabigat", "pradax", "xarel", "rivarox" or b): use of NOAC documented in the electronic medication record. Acute admission for treatment of gastrointestinal bleeding (index admission) was identified by manual review of the files of the patients identified by the above described search strategy. Information regarding type of bleeding, morbidity and dosage of NOAC was extracted. Estimated glomerular filtration rate (eGFR) was calculated on the basis of the plasma creatinine level at the time of admission [1]. Patients in treatment with NOAC and admitted for gastrointestinal bleeding were cross-checked for occurrence of a reported adverse event in the Danish Health and Medicines Authority's database on adverse medical events more than a year after the date of the index admission. The surgical department (a non-private university clinic with unrestricted referral) receives all patients admitted for acute gastrointestinal bleeding within a catchment area counting 512,000. The department has 9,000 acute admissions per year of which approximately 30% are for evaluation of upper or lower gastrointestinal bleeding. The study was reported to the Danish Data Protection Agency (reference number 01675-HVH-2012-010). In pursuance of Danish research guidelines for retrospective studies and quality assur-

ORIGINAL ARTICLE

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TABLE 1

Details on gastrointestinal bleeding episode, co-morbidity and new oral anticoagulant medication. A total of 20 patients admitted for gastrointestinal bleeding and in new oral anticoagulant treatment at time of admission.

Patient no.	Gender/age, yrs	Type of bleeding	Haemoglobin at time of admission, mmol/l	Plasma-creatininine concentration at time of admission, µmol/l	Endoscopy/finding at endoscopy	Co-morbidity	NOAC medication
1	M/66	Haematochezsia	5.8	52	Gastroscopy/no specific pathology found	AF, type 2 DM	Pra 110 mg × 2
2	M/69	Haematemesis and melena	2.7	184	Gastroscopy/no specific pathology found	COPD, AF, CHF, type 2 DM, lung cancer	Pra 150 mg × 2
3	M/83	Haematochesia	7.9	88	Sigmoideoscopy/ no specific pathology found	Asthma, AF, depression	Pra 110 mg × 2
4a	M/76	Severe anaemia	4.3	168	Colonoscopy/ angiodysplasia	AF, CHF	Pra 150 mg × 2
5	F/87	Melena	4.4	123	No/n.a.	AF, AH, previous admissions for nosebleeds	Pra 75 mg × 2
6	F/80	Severe anaemia	4.2	134	Gastroscopy/gastric ulcer, non-bleeding	AF, type 2 DM	Pra 110 mg × 2
7	F/88	Haematochesia	6.7	65	Sigmoideoscopy + gastroscopy/no specific pathology found	AF, CHF, hypothyreosis	Pra 110 mg × 2
8	M/76	Haematochesia	8.8	121	Sigmoideoscopy/ bleeding haemorrhoids	AF, sinus node dysfunction	Pra 110 mg × 2
9	M/70	Haematochesia	5.9	101	Gastroscopy/ oesophagitis	AH, type 2 DM	Pra (dosage unknown)
10	M/70	Haematochesia and melena	6.6	92	Gastroscopy/bleeding prepyloric ulcer	AF, previous gastro-duodenal ulcer	Pra 150 mg × 2
11	K/90	Haematochesia	7.3	109	No/n.a.	AF, anal prolapse, INR 1.3	Pra 110 mg × 2 (for 2 days VKA discontinued 2 days pre admission)
12	M/67	Haematemesis and melena	4.1	143	Gastroscopy/gastric ulcer, non-bleeding	AF, AH, microscopic haematuria	Pra 150 × 2
13	K/72	Haematochesia	6.9	506	Gastroscopy/no specific pathology found	AH, type 2 DM, sequelae from previous cerebral apoplexy	Pra 150 mg × 2,
14	K/83	Haematochesia	7.4	42	No/n.a	AF, AH, rectal cancer, sequelae from previous cerebral apoplexy	Pra 110 mg × 2
15	K/91	Haematochesia	8.2	113	No/n.a.	AF, AH, chronic leg ulcers	Pra 75 mg × 2
16	K/82	Melena	3.8	185	Gastroscopy/gastritis	AF, type 2 DM, sequelae from previous cerebral apoplexy , 3rd-degree AV block	Pra 110 mg × 2
17	M/75	Haematochesia	8.7	124	No/n.a	Lung cancer, haemorrhoids	Pra 110 mg × 1
18	M/83	Haematemesis	5.8	164	Gastroscopy/ oesophagitis	AF, AH, aortic stenosis, COPD, CHF	Pra 110 mg × 2
19	K/89	Haematochesia	6.5	80	Gastroscopy/no specific pathology found	Sequelae from previous cerebral apoplexy, previous episode of deep vein thrombosis and pulmonary embolus, INR 1.3	Xar 20 mg × 1 (for 3 days - VKA discontinued 3 days pre admission)
20	M/81	Haematemesis	5.6	197	Gastroscopy/gastric ulcer, bleeding	AH, bleeding episode post-operatively after knee alloplasty	Xar 20 mg × 1

AF = atrial fibrillation; AH = arterial hypertension; AV = atrioventricular; CHF = chronic heart failure; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; F = female; INR = international normalized ratio; M = male; n.a. = not available; NOAC = new oral anticoagulant; Pra = Pradaxa (dabigatran etilexate); VKA = vitamin K-antagonist; Xar = Xarelto (rivaroxaban).

a) Patient with occurrence of a reported adverse event in the Danish Health and Medicines Authority's database.

ance, approval from an ethics committee was not required.

Descriptive statistics are presented using frequencies, percentages, and 95% confidence intervals (CIs) when appropriate.

Trial registration: The study was registered with clinicaltrials.gov (NCT02107651).

RESULTS

Only one patient (5%; 95% CI: 0-24%) was recorded by the Danish Health and Medicines Authority as having an adverse drug event associated with NOAC treatment.

During the one-year study period, 65 patients in NOAC treatment were admitted to the surgical department. Among these patients, 20 were admitted for acute gastrointestinal bleeding. Details on gastrointestinal bleeding episode, co-morbidity and NOAC medication are shown in **Table 1**. The median haemoglobin level at the time of admission was 6.1 mg/l (interquartile range: 5.2-7.4 mg/l), 12 patients (60%; 95% CI: 36-81%) received one or more SAG-M transfusions and 12 patients (60%; 95% CI: 36-81%) underwent emergency endoscopy, of which only one was therapeutic and ten were diagnostic. The median age was 80.5 years, the median eGFR was 30 ml/min (interquartile range: 40-20 ml/min), 55% were males, the median length of stay was four days (interquartile range: 1-11 days), and no patients died during admission. Most patients (n = 11) were admitted for lower gastrointestinal bleeding, whereas seven patients were admitted for upper gastrointestinal bleeding and two patients were admitted with severe anaemia (haemoglobin level < 4.5 mmol/l) and clinical suspicion of gastrointestinal bleeding.

DISCUSSION

We found a low reporting rate for serious adverse drug effects in patients treated with NOAC.

The adverse effect profile for NOAC therapies includes risk of bleeding episodes comparable to the profile for conventional vitamin K antagonists (VKAs). Although reported to have an overall lower risk of bleeding than VKAs, a higher risk of specific gastrointestinal bleeding is found in patients treated with NOAC [2]. Furthermore, the patients in this material are old and a high proportion have renal impairment, factors associated with an increased risk of adverse effects in patients treated with NOAC [3]. A causal relation between concurrent NOAC treatment and admission for a bleeding episode is thus likely. By statutory provision, the reporting of such adverse drug events is mandatory. Our finding that most (95%) of the serious adverse drug effects in patients treated with NOAC go unreported questions the efficiency of the current post-marketing surveillance

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in Denmark. This potentially has implications for the regulatory agencies' ability to improve patient safety.

Identification of potential patients by use of text mining is conceptually simple when based on a combination of highly selective text terms and manual review of cases and can be used for many purposes. In contrast, using text mining to exclude irrelevant cases is a complex process, as exclusion has to be based on context and semantics, although comprehensive algorithms to automatically detect and classify possible adverse drug events have previously been described [4].

The reason for the observed underreporting of serious adverse drug events remains unknown. It is probably related to the large number of physicians involved in the treatment of acutely admitted patients, all with a focus on diagnosis and treatment, and without a clear responsibility for the reporting of a specific adverse drug effect. In this context, a newly organised system for reporting adverse drug effects introduced in the Copenhagen Region (the "Adverse Drug Effect Manager") facilitates the reporting process with the aim of lowering the threshold for and the workload involved in the reporting. This increases the spontaneous reporting of adverse drug effects [5].

In the US, a perceived high frequency of serious and fatal episodes of bleeding in patients treated with dabigatran etilexate has led to specific analysis of available data in administrative and insurance claims data bases. Based on this analysis, it was concluded that the high number of reported bleeding episodes were due to non-pharmacological issues, including the increased focus on a new drug, known as the Weber-effect or "stimulated reporting" [6]. Using readily available information in clinical information systems could be an efficient way to systematically monitor post-marketing safety for newly introduced drugs in Denmark, and it would supplement an apparently flawed system of unsystematic reporting of adverse drug effects. However, the complexity needed to establish such a central monitoring system could be significant.

The present study does not quantify the risk of gastrointestinal bleeding in relation to NOAC treatment as

the number of patients in the catchment area who undergo NOAC treatment is unknown. The study is limited by only focusing on reporting of adverse drug effects related to treatment with NOAC in patients admitted to a single department. However, it is very likely that similar results would be found in relation to other types of anticoagulants, including VKAs, in relation to other types of substances and in other settings.

CONCLUSION

By systematic use of electronic medical record data, we found that severe adverse drug effects in patients treated with NOAC are underreported. This indicates that there may be a need for a more systematic approach to post-marketing surveillance of adverse drug effects.

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