Overview of reports on novel anticoagulants

Introduction

The group of novel anticoagulants consists of the oral anticoagulants apixaban, (Eliquis®) argatroban (Arganova®), dabigatran (Pradaxa®), rivaroxaban (Xarelto®) ximelagatran (Exanta®) and the non-oral anticoagulants bivalirudine (Angiox®) and fondaparinux (Arixtra®). The introduction of these drugs as a replacement for low molecular weight heparins (LMWH) and vitamin K antagonists (VKA) has raised questions regarding their safety [1,2]. Recently, Lareb published an overview of reports concerning novel anticoagulants in Quarterly Reports 2013-3, and since then, new reports have been received. On request of the Medicines Evaluation Board (MEB), Lareb provides a short update of the reports received on the novel anticoagulants for the current Quarterly Report.

For this overview, data from both the spontaneous reporting system and the Lareb Intensive Monitoring System (LIM) were used. Dabigatran, rivaroxaban and apixaban have been monitored with the LIM methodology since September 2012.

Reports

On October 21, 2013 the Netherlands Pharmacovigilance Centre Lareb had received 492 reports associated with the use of novel anticoagulants. Of these, 396 were received through the spontaneous reporting system and 96 through the LIM system. The reports contained a total of 709 possible adverse drug reactions. Of these 492 reports, 264 were reported as serious according to the CIOMS criteria. In 27 reports a fatal outcome was reported. Additional information is provided in table 1 and 2.

Table 1. Numbers of reports received by Lareb

	Quarterly report 2014-1
Number of reports	492
Spontaneous (%)	396 (80%)
LIM (%)	96 (20%)
Serious reports (%)	264 (54%)
Fatal reports (%)	27 (5.5%)

Table 2. Characteristics of reports received in association with novel anticoagulants

Active substance	**Number of reports**			**Reports with fatal outcome**
	Total	**Serious (%)**	**Non-serious (%)**	
Dabigatran	249	115 (46%)	134 (54%)	15
Rivaroxaban	161	81 (50%)	80 (50%)	6
Fondaparinux	67	55 (82%)	12 (18%)	0
Bivalirudine	11	11 (100%)	0 (0%)	6
Argatroban	1	0 (0%)	1 (100%)	0
Apixaban	2	0 (0%)	2 (100%	0
Ximelagatran*	1	1 (100%)	0 (0%)	0

* The application for a marketing authorization for ximelagatran was withdrawn by AstraZeneca prior to a recommendation by the CHMP

In order to provide more insight into the spectrum of ADRs reported to Lareb, the ADRs were grouped into MedDRA® System Organ Classes (SOCs). Grouping was

done on the basis of the pharmacokinetic profile. Since direct thrombin inhibitors (e.g. dabigatran) are mainly excreted unchanged by the kidney whereas factor Xa inhibitors (e.g. rivaroxaban) are metabolized by the liver, differences in ADR profiles could be observed. In order to determine if this is the case, the SOCs of the ADRs reported for each drug are displayed in table 3. Only dabigatran and rivaroxaban were selected since the other anticoagulants had an insufficient number of reports (argotraban, apixaban, ximelagatran) or belong to the non-oral anticoagulants (which can influence the results).

System Organ Class (SOC)	DABIGATRAN		RIVAROXABAN	
	N	%	N	%
Blood and lymphatic system disorders	7	1.9	7	2.7
Cardiac disorders	14	3.7	8	3.1
Congenital, familial and genetic disorders	1	0.3	0	0.0
Ear and labyrinth disorders	1	0.3	1	0.4
Eye disorders	5	1.3	2	0.8
Gastrointestinal disorders	92	24.6	39	15.0
General disorders and administration site conditions	37	9.9	30	11.5
Hepatobiliary disorders	2	0.5	0	0.0
Infections and infestations	5	1.3	1	0.4
Injury, poisoning and procedural complications	8	2.1	17	6.5
Investigations	5	1.3	6	2.3
Metabolism and nutrition disorders	10	2.7	2	0.8
Musculoskeletal and connective tissue disorders	5	1.3	10	3.8
Neoplasms benign. malignant and unspecified (incl cysts and polyps)	6	1.6	0	0.0
Nervous system disorders	49	13.1	36	13.8
Psychiatric disorders	10	2.7	9	3.5
Renal and urinary disorders	20	5.3	10	3.8
Reproductive system and breast disorders	5	1.3	6	2.3
Respiratory. thoracic and mediastinal disorders	21	5.6	20	7.7
Skin and subcutaneous tissue disorders	19	5.1	17	6.5
Surgical and medical procedures	6	1.6	1	0.4
Vascular disorders	46	12.3	38	14.6
TOTAL	**374**	**100**	**260**	**100**

Gastrointestinal ADRs

The results in table 3 show that the spectrum of ADRs is similar between dabigatran and rivaroxaban, except for gastrointestinal disorders, which were reported significantly more often in dabigatran users than in rivaroxaban users (24.6% vs. 15.0% respectively: $p<0.001$).

Analysis of these data reveals that the main difference in ADR pattern within the gastrointestinal subset of ADRs relates to a difference hemorrhagic events versus non-hemorrhagic events. The percentages of hemorrhagic events were 23% for dabigatran and 41% for rivaroxaban (see also table 4).

Table 4. Numbers of hemorrhagic versus non-hemorrhagic gastrointestinal ADRs

	Dabigatran	Rivaroxaban
Hemorrhagic*	21 (23%)	16 (41%)
Non-hemorrhagic#	71 (73%)	23 (59%)
TOTAL	**92 (100%)**	**39 (100%)**

* Hemorrhagic ADRs were gastrointestinal bleedings including hematemesis, hematochezia and melaena
# The most frequently reported non-hemorrhagic ADRs were gastrointestinal pain / discomfort, diarrhoea, nausea

Renal ADRs

Although the percentage of reported renal ADRs seems similar between dabigatran and rivaroxaban (5.3% and 3.8% respectively), the types of ADRs that were reported within this SOC were different for dabigatran and rivaroxaban. Although the numbers are small, bleedings (including hematuria) seem to occur more in rivaroxaban users whereas renal impairment and renal failure occur more in dabigatran users (see also table 5). Further analysis showed a difference in prescription indication between dabigatran users (mainly atrial fibrillation) and rivaroxaban users (mainly thromboprophylaxis). Based on this, a difference in mean age between dabigatran and rivaroxaban users could be expected. However, the small difference that was found does not seem relevant (dabigatran 74.5 years; rivaroxaban 72 years).

Table 5. Numbers of renal ADRs

	Dabigatran	Rivaroxaban
Hemorrhagic (including hematuria)	3 (15%)	6 (60%)
Renal impairment (including failure)	6 (30%)	2 (20%)
Other	11 (55%)	2 (20%)
TOTAL	**20 (100%)**	**10 (100%)**

Other sources of information

Prescription data

The number of patients using novel anticoagulants in the Netherlands [3] is shown in table 6.

Table 6. Number of patients using novel anticoagulants in the Netherlands between 2007 and 2012 [3].

Drug	2007	2008	2009	2010	2011	2012
Dabigatran	-	29	1,026	1,048	2,064	4,648
Rivaroxaban	-	-	1,960	6,244	7,037	9,843
Fondaparinux	5,837	6,966	8,592	6,864	5,842	5,441

Prescription data were not available for bivalirudine, argatroban and apixaban

Discussion and conclusion

Recently, Lareb published an overview of the novel anticoagulants in their quarterly report (2013-3). The aim of this report was to give an update on the number of the ADRs associated with the use of novel anticoagulants. Additionally, possible differences in ADR pattern due to pharmacokinetic differences between direct thrombin inhibitors and factor Xa inhibitors were investigated.
Since the previous quarterly report, the number of reports sent to Lareb regarding novel anticoagulants has increased with 53%. Although the percentage of serious reports has decreased (from 61% to 54%) a small increase in the number of

reports with a fatal outcome was observed (from 4.7% to 5.5%). It should be noted however, the latter is based on a small number of reports. In general, the distribution of ADRs over the different SOCs is rather similar between both groups, with the exception of gastrointestinal ADRs, which seem to occur more frequently in patients using dabigatran. Further analysis revealed that the ratio of reported hemorrhagic versus non-hemorrhagic ADRs was higher in rivaroxaban users than in dabigatran users for gastrointestinal ADRs. The same was observed for renal ADRs, although it should be mentioned that this applies to a small number of reports and the difference was not tested for statistical significance.
The current overview did not give rise to a new signal of adverse drug reactions related to the use of novel anticoagulants.

References

1. Bijl D. Publiciteit nieuwe orale antistollingsmiddelen. Geneesmiddelenbulletin 2013;47(3):37-8.
2. Bijl D. Nieuwe orale anticoagulantia: niet vergoed. wel voorgeschreven. Geneesmiddelenbulletin 2012;46(5):58-60.
3. College voor Zorgverzekeringen. GIP Databank. College voor Zorgverzekeringen. GIP Databank. (version date: 22-3-2011. access date: http://www.gipdatabank.nl/).

This signal has been raised on February 2014. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).