bijwerkingen centrumlareb

Decreased international normalised ratio (INR) associated with substitution of acenocoumarol from the manufacturer Sandoz to acenocoumarol from the manufacturer Centrafarm

Introduction

Acenocoumarol is indicated for *prophylaxis and treatment of thromboembolic disorders* [1]. Since acenocoumarol has a narrow therapeutic range and dosing is affected by many factors, including genetic variation, drug interactions and diet, the effect is monitored by measuring the international normalized ratio (INR) [1,2]. In the Netherlands patients using a coumarin including acenocoumarol, are closely monitored by the thrombosis services, where INR values are monitored by specialised physicians [3].
Acenocoumarol was granted marketing authorization in the Netherlands in 1965 [1].

Reports

The Netherland Pharmacovigilance Centre Lareb received in a short period of time several reports of decreased INR after substitution of acenocoumarol from the manufacturer Sandoz to acenocoumarol from the manufacturer Centrafarm. Therefore all reports concerning changes in INR after this substitution received by Lareb, were evaluated and described in this report.

From 29 December 2015 until 25 July 2017 the Netherlands Pharmacovigilance Centre Lareb received ten reports concerning decreased INR after substitution of acenocoumarol from the manufacturer Sandoz to acenocoumarol from the manufacturer Centrafarm. Lareb also received two report where the INR was fluctuating (case A and L) and one report where the INR was increased (case C) [4]. The cases were reported by seven reporters: one consumer, three pharmacists and three specialist doctors. Cases E up to and including K were reported by the same reporter. In all the reports from health care professionals, other causes for the decreased INR values were excluded by the phycisians. In five reports (cases A, D, E, H, L) acenocoumarol from Centrafarm was withdrawn and acenocoumarol from Sandoz was restarted. In four reports (cases B, G, J, M) the patients recovered or were recovering after dose increase of acenocoumarol from Centrafarm. In case E, the patient also experienced a positive rechallenge.

The reports are summarized in table 1.

Table 1. Reports of INR changes after substitution of acenocoumarol from the manufacturer Sandoz to acenocoumarol from the manufacturer Centrafarm received by Netherland Pharmacovigilance Centre Lareb.

Patient Sex, age group, source	**Drug, indication**	**Concomitant medication**	**Suspected adverse drug reactions**	**Reported INR Sandoz (SDZ) Reported INR Centrafarm (CF)**	**Time to onset, action with drug, outcome**
A. 211747 M, 71 years and older Pharmacist	Acenocoumarol CF Unknown	Glimepiride Metformin Amlodipine Losartan Tamsulosine Sotalol	INR fluctuation	INR SDZ: unknown INR CF: 1.2-7.2	10 days Drug withdrawn Recovering
B. 235376, F, 61-70 years Physician	Acenocoumarol CF Atrial fibrillation		Lack of drug effect INR decreased	INR SDZ: unknown INR CF: unknown	Days Dose increased Recovering

C. 235848 F, 61-70 years Consumer	Acenocoumarol CF Thrombosis prophylaxis	Omeprazole Metoprolol Lisinopril Rosuvastatin Acetaminophen Nortriptyline	Nausea INR abnormal	INR SDZ: 2.3-2.8 INR: CF 4.3	1 day Dose reduced Recovering
D. 240994 M, 71 years and older Pharmacist	Acenocoumarol CF Coagulation disorder	Metformin Colecalciferole Hydrochloro-thiazide Bisoprolol Ramipril Simvastatin	INR decreased	INR SDZ: 2-3 INR CF: 1.8-1.9	7 days Drug withdrawn Recovered
E. 241654 M, 41-50 years Specialist doctor	Acenocoumarol CF Paroxysmal atrial fibrillation		INR decreased	INR SDZ: 2.1-3.2 INR CF: 1.5-1.8	Latency not exactly known Drug withdrawn Recovered
F. 241655 M, 61-70 years Specialist doctor	Acenocoumarol CF Atrial fibrillation		INR decreased	INR SDZ: 2.8-3.0 INR CF: 1.7-2.1	Latency not exactly known Dose increased Unknown
G. 241656 M, 41-50 years Specialist doctor	Acenocoumarol CF Atrial fibrillation		INR decreased	INR SDZ: 2.5-3.4 INR CF: 1.4-2.1	Latency not exactly known Dose increased Recovering
H. 241657 F, 71 years and older Specialist doctor	Acenocoumarol CF Paroxysmal atrial fibrillation		INR decreased	INR SDZ: 2.2-3.7 INR CF: 1.5-1.9	Latency not exactly known Drug withdrawn Recovered
I. 241658 F, 71 years and older Specialist doctor	Acenocoumarol CF Paroxysmal atrial fibrillation		INR decreased	INR SDZ: 2.2-2.8 INR CF: 1.5-1.8	Latency not exactly known Dose increased Not recovered
J. 241659 F, 71 years and older Specialist doctor	Acenocoumarol CF Atrial fibrillation		INR decreased	INR SDZ: 2.4-2.9 INR CF: 1.6-1.8	Latency not exactly known Dose increased Recovered
K. 241660 M, 71 years and older Specialist doctor	Acenocoumarol CF Paroxysmal atrial fibrillation		INR decreased	INR SDZ: 2.0-2.7 INR CF: 1.2-1.8	1 week Dose increased Not recovered
L. 242736 F, 71 years and older Pharmacist	Acenocoumarol CF Thrombosis		INR fluctuation	INR SDZ: 1.9-2.3 INR CF: 1.3-2.3	1 day Drug withdrawn Recovering
M. 243655 M, 71 years and older Physician	Acenocoumarol CF Atrial fibrillation	Simvastatin Bumetanide Digoxin Metoprolol Omeprazole Perindopril Isosorbide Mononitrate	INR decreased	INR SDZ: unknown INR CF: unknown	1 day Dose increased Recovered

Discussion

The Dutch branch organisation for Pharmacists, the KNMP, advises not to substitute drugs with a narrow therapeutic range, including acenocoumarol [6]. This is supported by two studies performed in the United States [7,8]. The first study was a historical cohort analysis using a commercial insurance claims database [7]. The conclusion of this analysis was “switching warfarin formulations exposed patients with atrial fibrillation to a higher risk of bleeding events compared to remaining on a single product. Maintaining patients on a product with consistent bioavailability may optimize the risk-benefit balance of anticoagulation therapy.” The other study was another analysis from a database [8] and concluded: “The use of both generic and branded formulations of warfarin interchangeably, or the use of generics from more than one manufacturer, was associated with increased use of all-cause health care resources and total costs in patients with atrial fibrillation.”
Lareb received ten reports concerning decreased INR, two reports of fluctuating INR and one report of increased INR after substitution of acenocoumarol from the manufacturer Sandoz to acenocoumarol from the manufacturer Centrafarm. The reports seem to indicate that substitution of acenocoumarol from the manufacturer Sandoz to the manufacturer Centrafarm may lead to a decrease of the INR, indicating a decreased drug effect. All cases except one, were reported in the period from 3 March 2017 until 25 July 2017. This is probably due to the acquired preference status of the acenocoumarol from the manufacturer Centrafarm since 2017 [5].

References

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8. Kwong WJ, Kamat S, Fang C. Resource use and cost implications of switching among warfarin formulations in atrial fibrillation patients. Ann Pharmacother. 2013;46(12):1609-16.

This signal has been raised on August 28, 2017. It is possible that in the meantime other information became available. For the latest information, including the official SmPC’s, please refer to website of the MEB www.cbg-meb.nl