Lareb
Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

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Bosentan and coagulation disorders

Introduction

Bosentan (Tracleer®) is an endothelin receptor antagonist (ERA) with affinity for both endothelin A and B receptors (ET_A and ET_B). Bosentan decreases both pulmonary and systemic vascular resistance resulting in increased cardiac output without increasing heart rate [1]. In Europe the drug was approved in May 2002 for *treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with grade III functional status*.
Until the introduction of bosentan, the oral treatment options included long-term anticoagulant therapy and therapy with calcium channel antagonists, diuretics, digoxin and oxygen [2].

Since the introduction of bosentan the Netherlands Pharmacovigilance Centre Lareb received two reports of a decreased International Normalized Ratio (INR) in association with bosentan after addition to the therapy with coumarinderivates phenprocoumon and acenocoumarol. The SPC of bosentan states that *no dose adjustment is needed for warfarin and similar oral anticoagulant agents when bosentan is initiated but intensified monitoring of INR is recommended, especially during bosentan initiation and the up-titration period* [1].

These reports raised a concern on this interaction.

The coumarinderivates warfarin, acenocoumarol and phenprocoumon are vitamin-K-antagonists [3]. They are antagonists of vitamin K synthesis and block the synthesis of the coagulation factors II, VII, IX and X in the liver and inhibit indirectly the coagulation process. They act in a similar way and are similarly metabolized. The effect of phenprocoumon is of longer duration than the effect of warfarin and acenocoumarol.
Acenocoumarol and phenprocoumon are internationally approved, but are mainly prescribed in Europe. Warfarin is not approved in the Netherlands.

Reports

Up to 28th February 2005, Lareb received two reports from the Federation of Dutch Thrombosis Services of a decreased INR on the combination of bosentan and phenprocoumon and acenocoumarol, respectively. In both patients neither daily doses for anticoagulants nor exact INR were reported.

Other sources of information

Literature

Four publications describe an interaction between bosentan and coumarinderivates.
In a study on bosentan including 20 patients, INR decreased in 17 patients, requiring increased doses of phenprocoumon in all of these patients [4].
In a study of Weber *et al*. bosentan has shown to cause a significant increase in the elimination of *R*- and *S*-warfarin and a subsequent decrease in the anticoagulant properties of warfarin compared to placebo [5]. Bosentan treatment in addition to warfarin led to a reduction of the maximal prothrombin time (PT_{max}) by 23% compared to placebo [5].
Dingemanse and Van Giersbergen (employees of Actelion Pharmaceuticals) analyzed the data from the BREATHE-1 study, in which 99 patients (63 on bosentan, 36 on placebo) participated, who were stable on warfarin therapy before start of bosentan treatment. The analysis focused on the frequency of

warfarin dosage modifications due to either a laboratory abnormality (change in INR) or an adverse event (e.g. bleeding). The proportion of patients with changes in the warfarin dosage was 44.4% in both treatment groups [2].
In the interaction database of WINAp an interaction between bosentan and coumarinderivates is not reported [7].

Databases

On 17th March 2005 the database of the Uppsala Monitoring Centre of the WHO contained 52 associations of bosentan and coagulation disorders. Increased coagulation as well as decreased coagulation was reported (see table 1). Disproportionality was seen in coagulation disorder (ROR 3.89, 95% CI 1.62-9.38), coagulation time increased (ROR 22.94, 95% CI 8.55-61.55), hemorrhage NOS (ROR 1.97, 95% CI 1.02-3.80) and prothrombin increased/INR decreased (ROR 6.34, 95% CI 2.63-15.28).

Table 1. reports in the WHO database on 17th March 2005 of coagulation disorders associated with the use of bosentan

coagulation disorder	ADR	total	warfarin as concomitant medication*	no warfarin*	no concomitant medication reported
not specified	coagulation disorder#	**6**	3	2	1
increased coagulation	coagulation time decreased	**1**	1		
	INR decreased	**6**	5	1	
	prothrombin increased#	**2**		2	
	pulmonary embolism	**5**	3	1	1
	thromboembolism	**1**		1	
	pulmonary thrombosis	**2**			2
decreased coagulation	coagulation time increased#	**4**	3		1
	INR increased	**15**	7	5	3
	prothrombin decreased	**2**	2		
	haematoma	**2**	1	1	
	haemorrhage NOS#	**6**	3		3

* no phenprocoumon or acenocoumarol was used in these patients
# disproportional

Mechanism

The effect of bosentan on the coagulation seems to be divers. Increased as well as decreased coagulation may occur in bosentan monotherapy. The combination with coumarinderivates also can cause divers coagulation disorders. Pulmonary arterial hypertension in itself tends to cause hepatic congestion, which can be complicated by an increased coagulation.
One possible explanation for the decreased INR in combination with coumarinderivates is a pharmacokinetic effect of bosentan on the metabolism of coumarinderivates. Murphey and Hood highlight bosentan as a known inducer of the CYP2C9, CYP3A4 and possibly the CYP2C19 isoenzyme systems. Warfarin is comprised of the *R*- and *S*-isomers, with the *S*-isomer being 3-5 times more potent than the *R*-isomer. The *S*-isomer of warfarin is primarily metabolized by CYP2C9 and the *R*-isomer by CYP3A4 and CYP1A2 [6].

The reduction of the maximal prothrombin time (PT_{max}) could be explained by an increase in the elimination of warfarin, according to the findings in the article of Weber *et al.* [5].
Another possibility is a reduction in hepatic congestion related to the reduction in pulmonary resistance, and right atrial and pulmonary arterial pressure with bosentan [8]. Hepatic functioning improves and consequently the coagulation factors will act more effectively.
Not all reported ADRs can be explained. A definite mechanism has not yet been described.

Conclusion

The case reports received by the Netherlands Pharmacovigilance Centre Lareb raised the concern that bosentan prolongs the INR induced by coumarinderivates. Literature and the WHO database however, support that the combination of bosentan with a coumarinderivative may have various effects on the level of coagulation. It remains unclear what mechanisms could cause these effects. The concern raised by the two reports that led to this analysis was not confirmed as the SPC includes guidance for monitoring of INR.

References

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