

UCSF

UC San Francisco Previously Published Works

Title

Response to "CYP2C9 Polymorphism is Not a Major Determinant of Bosentan Exposure in Healthy Volunteers"

Permalink

<https://escholarship.org/uc/item/39p4m8wk>

Journal

Clinical Pharmacology & Therapeutics, 95(3)

ISSN

0009-9236

Authors

Markova, SM
Schwartz, JB
Kroetz, DL

Publication Date

2014-03-01

DOI

10.1038/clpt.2013.239

Peer reviewed

LETTERS TO THE EDITOR

Response to “CYP2C9 Polymorphism Is Not a Major Determinant of Bosentan Exposure in Healthy Volunteers”

SM Markova¹, JB Schwartz² and DL Kroetz¹

To the Editor: We appreciate the opportunity to respond to the letter by Markert *et al.*, “CYP2C9 Polymorphism Is Not a Major Determinant of Bosentan Exposure in Healthy Volunteers.”¹ In response to our study on genetic predictors of bosentan-induced liver injury in pulmonary arterial hypertension (PAH) patients, in which we demonstrated an association between the *CYP2C9*2* allele, encoding the cytochrome P450 complex subunit 2C9, and liver injury,² Markert *et al.* report steady-state bosentan pharmacokinetics in 36 healthy volunteers. They show that plasma bosentan levels were highly variable and not associated with CYP2C9 metabolizer phenotype. Consistent with a role for CYP2C9 in the formation of the major active metabolite hydroxy bosentan (RO48-5033), levels of RO48-5033 were 68.7% greater in extensive metabolizers than in poor metabolizers.

The pharmacokinetic data obtained by Markert *et al.* suggest that the genetic association that we reported is not easily explained by differences in bosentan plasma concentrations between CYP2C9 genotype groups. As Markert

et al. point out, CYP2C9-dependent intrahepatic bosentan concentrations may be more relevant and may not be directly related to bosentan plasma concentrations. Although hepatic transporter polymorphisms were not associated with bosentan hepatotoxicity in our study,² the possibility exists that transporter function is altered in PAH patients as a result of disease or drug treatment. Furthermore, as discussed in our paper, there is a possibility that *CYP2C9*2* is not a causative single-nucleotide polymorphism (SNP) but tags a regulatory SNP.² The difference in study populations may also have influenced the reported results. The pharmacokinetic study by Markert *et al.* was carried out in healthy volunteers, whereas our genetic association study was performed in PAH patients receiving steady-state bosentan for clinical indications. As also noted by Markert *et al.*, differences in pharmacokinetics between CYP2C9 metabolizer groups might be more apparent in PAH patients, especially because they may have a longer duration of exposure. Indeed, previously published bosentan pharmacokinetic data for PAH patients show that bosentan exposure is not proportional to dose and is approximately twofold higher than that in healthy subjects.³ In addition, because PAH affects expression of endothelin receptors,⁴ it may affect the tissue-to-plasma ratios of bosentan in these patients. Finally, the possibility that concurrent medications in PAH patients affect bosentan pharmacological and toxicological properties cannot be excluded.

Although studies in healthy volunteers provide important information about human pharmacokinetic characteristics, it is difficult to extrapolate this information to toxicity phenotypes in relevant and complex patient populations. We welcome further investigations to elucidate mechanisms of liver injury and the potential role of pharmacogenomics in patient groups that are candidates for bosentan therapy.

ACKNOWLEDGMENT

This work was funded by the National Institutes of Health through grant GM061390.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

© 2014 ASCPT

1. Markert, C., Burhenne, J., Weiss, J., Mikus, G. & Haefeli, W.E. CYP2C9 polymorphism is not a major determinant of bosentan exposure in healthy volunteers. *Clin. Pharmacol. Ther.* **95**, 250–251 (2014).
2. Markova, S.M. *et al.* Association of *CYP2C9*2* with bosentan-induced liver injury. *Clin. Pharmacol. Ther.* **94**, 678–686 (2013).
3. Dingemans, J. & van Giersbergen, P.L. Clinical pharmacology of bosentan, a dual endothelin receptor antagonist. *Clin. Pharmacokinet.* **43**, 1089–1115 (2004).
4. Bauer, M., Wilkens, H., Langer, F., Schneider, S.O., Lausberg, H. & Schäfers, H.J. Selective upregulation of endothelin B receptor gene expression in severe pulmonary hypertension. *Circulation* **105**, 1034–1036 (2002).

¹Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, San Francisco, California, USA; ²Department of Medicine, University of California, San Francisco, San Francisco, California, USA. Correspondence: DL Kroetz (deanna.kroetz@ucsf.edu)

Advance online publication 29 January 2014.
doi:10.1038/clpt.2013.239