Letter to the Editors

Hydroxylation of lansoprazole in poor metabolizers of CYP2C19

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We read the recent paper by Saito *et al.* [1] with interest. The theme of their paper was quite similar to the one we published 6 years ago [2]. However, there was one curious point in the results. Individuals with the poor metabolizer (PM) genotype of CYP2C19 lack the CYP2C19 enzyme therefore hydroxylation of lansoprazole is assumed to be mediated by CYP3A4, as was explained briefly in the introduction section. Accordingly, hydroxylansoprazole concentrations should be decreased by clarithromycin in PMs because clarithromycin strongly inhibits the activity of CYP3A4, as we observed in our previous paper [2]. However, in the present paper, hydroxylansoprazole concentrations were increased by clarithromycin, just as observed in extensive metabolizers (EMs). The results of the present study by Saito *et al.* [1] indicated that the hydroxylation of lansoprazole in PMs was not mediated by CYP3A4, but by another enzyme which was not influenced by clarithromycin. We would like to know the candidate enzyme or an explanation for the discrepant results.

References

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Author's reply: Hydroxylation of lansoprazole in poor metabolizers of CYP2C19

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We appreciated the comments from Dr Furuta and colleagues regarding the hydroxylation of lansoprazole in poor metabolizers for CYP2C19. Dr Furuta and colleagues noted a discrepancy in the hydroxylation between omeprazole and lansoprazole, i.e. the AUC of hydroxyomeprazole decreased during clarithromycin co-administration in poor metabolizers (PMs) for CYP2C19 [1] while that of hydroxylansoprazole increased during clarithromycin co-administration in PMs for CYP2C19 [2].

As Dr Furuta and colleagues pointed out, it would be expected that the AUC of hydroxylansoprazole would decrease during co-administration of clarithromycin, a CYP3A4 inhibitor, in PMs for CYP2C19 if hydroxylation is mediated by CYP3A4 [3, 4].

Therefore the findings of increased hydroxylansoprazole might imply an alternative pathway of elimination. A recent *in vitro* study demonstrated that predicted CL_{int} (μl min⁻¹ nmol⁻¹ of P450) of hydroxylation of R- and S-lansoprazole in human liver

microsomes were 0.1 and 0.75 for CYP2C9, 1.32 and 1.65 for CYP2C19 and 0.46 and 0.35 for CYP3A4, respectively [5]. These results suggest that CYP2C9 is also an enzyme involved in the hydroxylation of lansoprazole in PMs for CYP2C19. In our study, the CYP2C9 genotype of the subjects were all *1/*1, which suggests normal activity of CYP2C9. In addition, the hydroxylation index (AUC ratio of hydroxylansoprazole : lansoprazole) did not differ [2].

Because sulfoxidation of lansoprazole is inhibited by clarithromycin through CYP3A4, plasma lansoprazole concentrations increased in our study [2]. It is reasonable that the increased substrate (lansoprazole) leads to the increased formation of metabolite (hydroxylansoprazole) proportionately. In addition, although further metabolism of 5-hydroxylansoprazole has not been proven, we assumed that formation of hydroxylansoprazole sulphone from hydroxylansoprazole would be catalyzed by CYP3A4 [6]. Therefore, the increase in AUC of hydroxylansoprazole may be partially attributed to inhibition of further metabolism during clarithromycin co-administration.

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