Letter to the Editor

Response to “Suspected Differential Interactions of Digoxin with Imidafenacin and Propantheline; Some Thoughts for Introspection”

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To the Editor:

We thank Dr. Srinivas for his thoughtful comments1) in response to our paper on the influence of imidafenacin on digoxin pharmacokinetics.2) These comments address possible causes of different effects on digoxin exerted by imidafenacin in our study and by propantheline in a previous report, with the assumption that the two anticholinergic drugs should have essentially the same effects on digoxin.3) We categorize the factors pointed out by Srinivas as 1) external factors that depend on the study design and 2) internal factors that depend on the compound. We would like to give our opinions on these issues and add some information on solifenacin, another anticholinergic agent, in discussing the different results from imidafenacin and propantheline studies.

1. External factors
a) Dosage form of digoxin: Digoxin tablets, more susceptible to interaction than digoxin capsules, were used in our study and there is no concern about the dosage form.

b) Dose of digoxin: the dose of digoxin in our study was less than that of propantheline. Half the clinical dose of digoxin was used to ensure the safety of the subjects.

c) Production batch of digoxin tablets: there is difference in batches between the imidafenacin and propantheline studies.

d) Measurement of digoxin: Generally, digoxin is measured by radioimmunoassay (RIA). However, the low sensitivity of RIA is a concern and thus we have established a digoxin assay using LC/MS/MS with higher sensitivity3) and generally higher specificity compared to RIA.

2. Internal factors
a) Contribution of P-gp: It is possible that propantheline is a substrate of P-gp,4,5) but there is no information to show that imidafenacin is a substrate or inhibitor of P-gp.

b) Metabolism in the small intestine: CYP3A4 metabolism in the small intestine does not seem to have much relevance to this issue; imidafenacin is not metabolized in human small intestinal microsomes.6)

f) Selectivity for muscarinic receptors: As we indicated in a previous paper, propantheline has no selectivity for the muscarinic receptor subtypes M1, M2 and M3,7) whereas imidafenacin is an M1 and M3 dual antagonist with low affinity for the M2 subtype.8)

However, the physiological roles of these receptor subtypes have not been completely elucidated.

We would like to add that solifenacin, an anticholinergic drug used for overactive bladder treatment, has almost no affect on digoxin bioavailability,9) as with imidafenacin. The digoxin dose in the solifenacin study was the same as in the imidafenacin study and the selectivity of solifenacin for muscarinic receptor subtypes is similar to that of imidafenacin.10) Too, solifenacin is a weak inhibitor of P-gp.11)

Based on our findings, differences in the digoxin dose and selectivity for muscarinic receptor subtypes remain factors that may account for the different effects on digoxin observed for imidafenacin (and solifenacin) compared to propantheline. However, other factors may complicate these effects and it is difficult to identify the exact causes. Nevertheless, the results from the imidafenacin study were similar to those with solifenacin and this should provide confidence to readers regarding the lack of effect of imidafenacin on digoxin bioavailability.

References
3) Hashimoto, Y., Shibakawa, K., Nakade, S. and Miyata, Y.: Vali-


