LETTER TO THE EDITOR

Authors’ reply to Dr. Bailey’s commentary: Predicting clinical relevance of grapefruit-drug interactions: A complicated process

We read with great interest Dr. Bailey’s commentary to our previous article. He argued that our approach to the prediction of clinically relevant drug interactions with grapefruit juice (GFJ) was potentially misleading. The reasons given were as follows: (i) we arbitrarily considered a 2.0-fold or greater increase in ratio of AUC for a drug coadministered with GFJ (AUC_{GFJ}) relative to that for the drug administered alone (AUC_{control}) to be clinically significant and (ii) we evaluated the clinical implication of AUC_{GFJ} solely by changes in mean or median values. Meanwhile, he proposed a diagram that would be more stringent than our approach in providing guidance on avoidance of GFJ consumption. He recommended that GFJ consumption should be avoided when patients take orally administered drugs with known serious overdose toxicity, low bioavailability, cautionary statement about GFJ in their labelling information, reports of increased bioavailability with other CYP3A4 inhibitors and indication for use in the elderly. According to these criteria, GFJ would be prohibited in a real sense for almost all patients. Although we totally agree with his recommendation of categorically avoiding GFJ consumption in frail patients or patients taking drugs with narrow therapeutic windows, we consider that probabilistic information about change in AUC_{GFJ} is useful for prescribers when they counsel uncomplicated patients receiving drugs with moderate to wide therapeutic windows. Here, we report such information by reanalysing our database, taking into account variability of changes in AUC_{GFJ} reported in the literature.

We aimed to estimate the highest AUC_{GFJ} that may be encountered in clinical practice. In reports of drug-GFJ interaction, changes in AUC_{GFJ} are expressed either as median with range or as mean with standard deviation (SD). When the interpatient variability of AUC_{GFJ} for a drug was reported by a range in the literature, the highest value of the range was considered the quasi-maximum value. When the interpatient variability of AUC_{GFJ} for a drug was given by a mean and SD, the quasi-maximum value was estimated to be mean plus 2.32 SD, corresponding to a probability of 0.01 in the upper tail of normal distribution (one-sided). In other words, there will be only one or fewer subject of 100 who consume GFJ with the drug showing AUC_{GFJ} greater than 2. Assuming that AUC_{GFJ} and AUC_{control} of a drug are independent of each other, the square of the coefficient of variation (CV) of AUC_{GFJ}, defined as \( \sigma_{AUC_{GFJ}} \) divided by mean AUC_{GFJ}, would be equal to the sum of the squares of CVs for AUC_{GFJ} and AUC_{control} as follows:

\[
\left( \frac{\sigma_{AUC_{GFJ}}}{AUC_{GFJ}} \right)^2 = \left( \frac{\sigma_{AUC_{GFJ}}}{AUC_{GFJ}} \right)^2 + \left( \frac{\sigma_{AUC_{control}}}{AUC_{control}} \right)^2,
\]

where \( \sigma_{AUC_{GFJ}} \) and \( \sigma_{AUC_{control}} \) are the SD of AUC_{GFJ} and AUC_{control} respectively.

We compared the quasi-maximum AUC_{GFJ} estimated above with the arbitrary cut-off value corresponding to equal to or greater than 2.0-fold AUC_{control} for 194 drugs in our database, and found that the quasi-maximum values of AUC_{GFJ} were less than the cut-off values in 27% of the drugs. For instance, whereas the quasi-maximum values of AUC_{GFJ} for felodipine and lovastatin were 11.8 and 34.6, respectively, that for amlodipine was 1.6. These data would agree with prescribers’ anecdotes that the former drugs should not be administered with GFJ but the latter drug may be.

Dr. Bailey referred to eight patients who developed severe adverse drug events upon consuming GFJ. Scrutinizing the clinical data of these cases, all patients consumed a large volume of GFJ (typically more than 1 L/d), a whole fruit per day or 1.5 kg of marmalade during the preceding one week. A previous study reported that consumption of more than 1 L/d of GFJ may be associated with CYP3A4 inhibition not only in the intestinal wall but also in the liver.

Collectively, we agree with Dr. Bailey’s opinion that consumption of a large volume of GFJ should always be avoided when patients are frail (eg elderly) or are taking drugs with high risk of interaction. However, we consider that the judgement of avoiding or accepting GFJ consumption with other drugs in otherwise uncomplicated patients should be made taking into consideration the highest AUC_{GFJ} predictable from previous data as well as toxicological properties of the drugs. GFJ is a popular beverage and the worldwide consumption of grapefruit increased from 4.5 million tons in 2008 to 5.8 million tons in 2014. According to the consumer report issued by US Food and Drug Administration in 2014, they stated that GFJ does not affect all drugs and recommended counselling with pharmacists or physicians to find out whether a specific drug prescribed to him or her is affected or not. In aid of pharmacists and other medical professionals counselling patients about the risk of taking GFJ with drugs, we are compiling data of the probabilistically highest AUC_{GFJ} values for drugs using our database.

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REFERENCES
