The Sweet Effect of Honey on Drug Metabolism

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The well-documented effects of grapefruit juice on the pharmacokinetics of many drugs have raised awareness that foods can have specific effects on cytochrome P-450 drug-metabolizing enzymes and drug transporters such as P-glycoprotein. Recently, reports have described the effect of honey on cytochrome P-450 isozymes in healthy patients and animals.

Effect of Honey on CYP450 Isozymes

In a recent study, 12 healthy patients were tested for activity of CYP2D6, CYP2C19, and CYP3A4 after 7 days of honey administration.[1]

Dextromethorphan was given to test for CYP2D6, proguanil to test for CYP2C19, and endogenous 6-beta-hydroxycortisol excretion as a marker for CYP3A4 activity. There were no changes in dextromethorphan or proguanil—suggesting that honey ingestion does not affect the activity of CYP2D6 or CYP2C19.

The excretion of endogenous 6-beta-hydroxycortisol was significantly increased, however—suggesting an increase in CYP3A4 activity. The substances in honey that might be responsible for the increased CYP3A4 activity are not known.

The evidence of increased CYP3A4 activity was consistent, occurring in 11 of the 12 patients. The study also found a marked difference in the magnitude of the effect, as is usually the case in drug-interaction studies; 1 participant had a doubling of the marker, and another had a 3-fold increase.

These results suggest that some people may have a marked increase in CYP3A4 activity, but actual drug–drug interaction studies will be needed to confirm this possibility. Of course, honey is not a standardized substance, and it is possible that different types of honey would have varying effects on drug metabolism.

Effect of Honey on CYP3A4 Substrates

Assuming that the CYP3A4 marker study described above reflects an increase in CYP3A4 activity, one would expect regular ingestion of honey to reduce the efficacy of drugs metabolized by CYP3A4, at least in some patients. Although animal studies have found reduced plasma concentrations of CYP3A4 substrates (diltiazem) with repeated doses of honey,[2] this finding does not necessarily apply to humans. Nonetheless, until more evidence is available, it would be prudent to consider regular honey ingestion as a possible cause for a reduced therapeutic effect of drugs metabolized by CYP3A4.

Effect of Honey on Carbamazepine

Based on the evidence of increased CYP3A4 activity described above, one would expect reduced plasma concentrations of drugs metabolized by CYP3A4, such as carbamazepine. This drug is itself a potent inducer of CYP3A4, however, and it can enhance its own metabolism over time. Thus, it is not clear that any CYP3A4 induction due to the ingestion of honey would add to the induction already occurring due to carbamazepine.

A study of 10 healthy patients found no effect from a single 30-mL dose of honey on carbamazepine pharmacokinetics,[3] but enzyme induction would not be expected after a single administration of an enzyme inducer.

Indeed, a study in rabbits found increased clearance of carbamazepine with 7 days of honey, but no effect with 1 day of honey.[4] Therefore, this negative single-dose study did not adequately assess the effect of honey on carbamazepine. Overall, at this time it does not appear necessary for patients taking carbamazepine to be warned about ingesting honey.

Summary

Preliminary evidence from human studies of honey on CYP450 activity suggests that honey may increase CYP3A4 activity but may not affect the activity of CYP2D6 or CYP2C19. It appears that increased CYP3A4 activity requires regular ingestion of honey for several days or more, and that occasional ingestion is unlikely to significantly affect drug plasma concentrations. Pending additional information, one should consider honey ingestion as a possible cause of altered response to drugs metabolized by CYP3A4. PT

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