Hammersmith Medicines Research

Drug-drug interactions

All new drugs must be assessed in man *in vitro* and *in vivo* for their potential to interact with established drugs. In recent years, regulatory authorities have withdrawn several drugs – such as terfenadine, astemizole and cisapride – from the market, mainly because of the risk of interaction with other drugs.

We have done many studies in healthy subjects to assess the potential of new and established drugs to interact with:

- drugs with a narrow therapeutic window, such as digoxin, warfarin and aminophylline;
- oral contraceptives;
- anticonvulsants, such as phenytoin and carbamazepine;
- inhibitors of the most important P450 enzyme – CYP3A4 – such as ketoconazole, erythromycin, and grapefruit juice; and
- a 'cocktail' of drugs to test for effects on cytochrome P450 enzymes, selected from 1A2, 3A4, 2C9, 2C19, 2D6 and 2E1, and acetylation.

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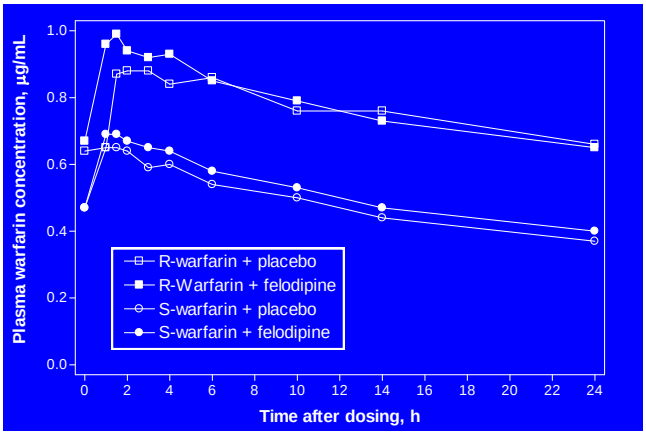
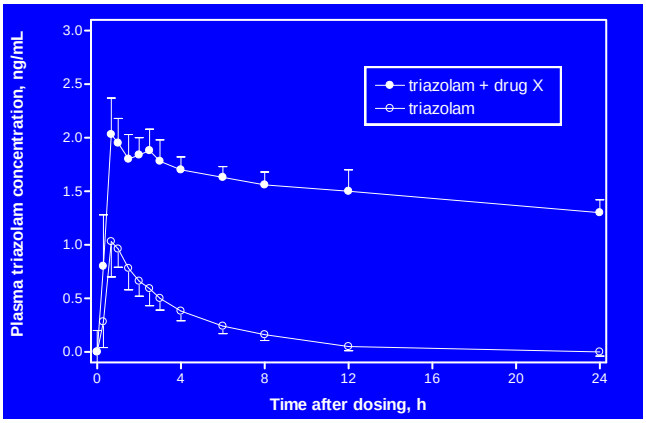
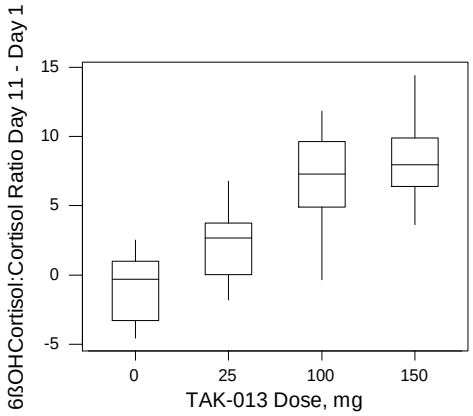
Examples of our studies



No effect of felodipine for 14 days on mean steady state plasma S- and R-warfarin in 18 healthy men. Warfarin dose adjusted to maintain INR 1.4–1.6 (Clin Pharmacol Ther 1993; 54:381–387)



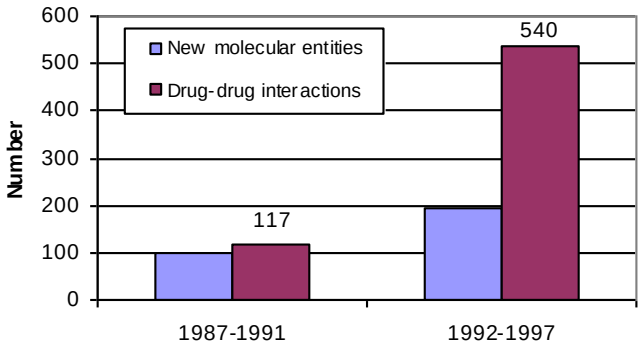
Large increase in plasma triazolam after a single 0.125 mg dose, alone or after pre-treatment with drug X (a new antimicrobial) daily for 6 days, in 10 healthy men (unpublished)



Dose-dependent increase in urinary 6-ß-OH cortisol:cortisol ratio after 11 days' dosing with TAK-013 in healthy women (n=9 per dose) consistent with CYP3A4 induction (Fertility and Sterility 2002;78: S281)

We can provide a full service – design, subject selection by phenotyping or genotyping, exclusion diets, drug assays, pharmacokinetics, statistical analysis, and report – for the well-designed interaction studies that regulatory authorities expect when they are considering an application to market a new drug.

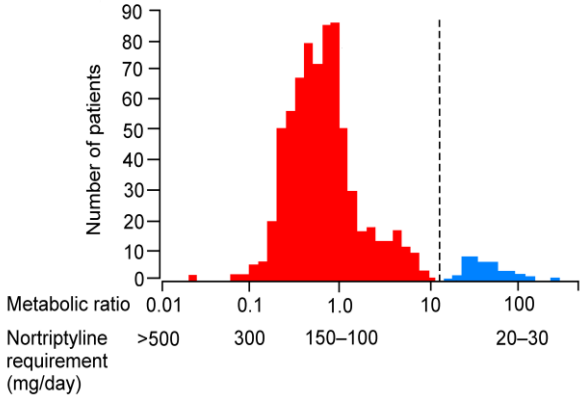
A survey showing the big increase in drug-drug interaction studies in man for all new molecules approved by the FDA from 1987 to 1997 (Clin Pharmacol Ther 2000; 68: 280–285)



Interaction between drug and subject

6–8% of our European subjects are poor metabolisers of debrisoquine because of genetic polymorphism for CYP2D6. That can make a big difference to the dose that they need.

Dose requirement for nortriptyline in patients with different CYP2D6 phenotypes



Poor metabolisers = debrisoquine urinary metabolic ratio of >12.6 (dashed line). Meyer. Lancet 2000; 356: 1667–1671

References

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4. Grind M, Murphy M, **Warrington S**, Åberg J. Method for studying drug-warfarin interactions. Clin Pharmacol and Ther 1993; 54: 381–387.
5. Johnston A, Holt D, Lee T, **Clark E, Dunn K, Boyce M**. Urinary 6β-OH cortisol / cortisol ratio as a marker of CYP3A4 activity. Br J Clin Pharmacol 2003; 55: 440.
6. **Boyce M**, Clark E, Johnston A et al. TAK-013, a new non-peptide gonadotropin-releasing hormone antagonist, in healthy women. Fertility and Sterility 2002; 78: S281–S282.
7. Frye et al. Pittsburgh cocktail. Clin Pharmacol Ther 1997; 62: 365–376.