Hammersmith Medicines Research

Drug-drug interactions…

…can cause serious injury, and led to the withdrawal from the market of blockbusters such as terfenadine, astemizole and cisapride. So, all new drugs must be tested in humans for their drug-interaction potential.

We have extensive experience of interaction trials in healthy volunteers to assess:

- drugs with a narrow therapeutic window, such as digoxin, warfarin and aminophylline;
- oral contraceptives;
- anticonvulsants, such as valproate, carbamazepine, phenytoin;
- inhibitors of CYP3A4 – the most important hepatic metabolic enzyme – such as itraconazole, erythromycin, and grapefruit juice;
- inducers of hepatic metabolic enzymes – such as rifampicin; and
- cocktails of 'probe' drugs to test effects on panels of hepatic metabolic enzymes.

For more information, please contact:

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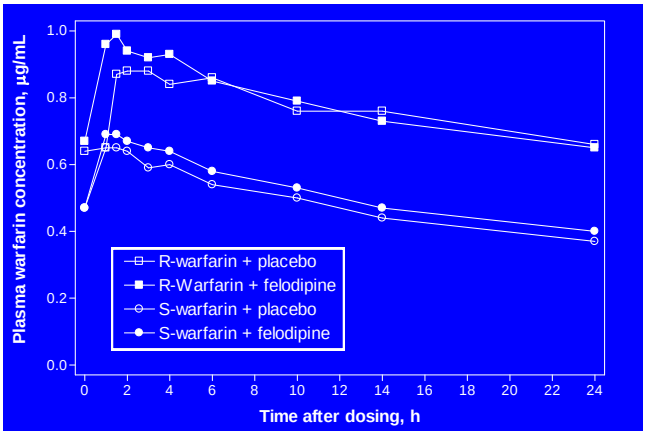
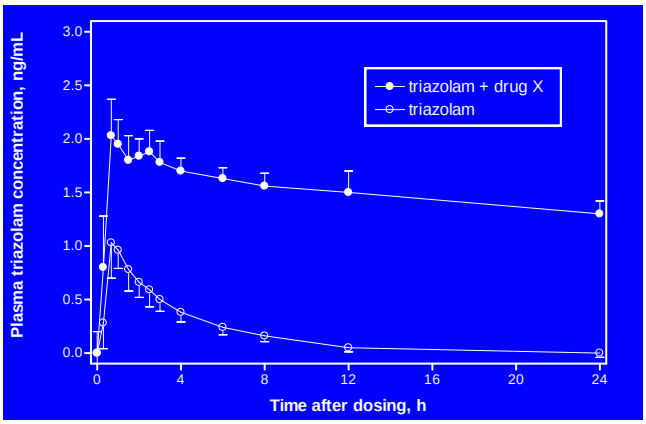
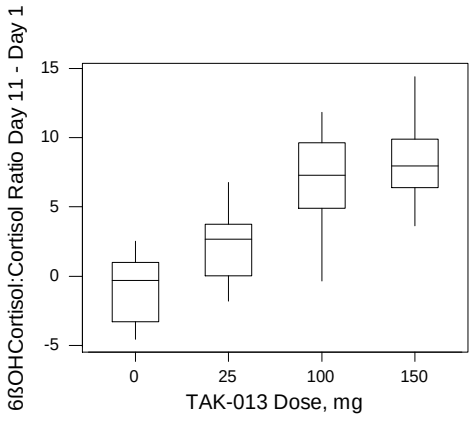


No effect of felodipine for 14 days on steady state S- and R-warfarin (n = 18).
Warfarin dose adjusted to maintain INR 1.4–1.6
Clin Pharmacol Ther 1993; 54: 381–387



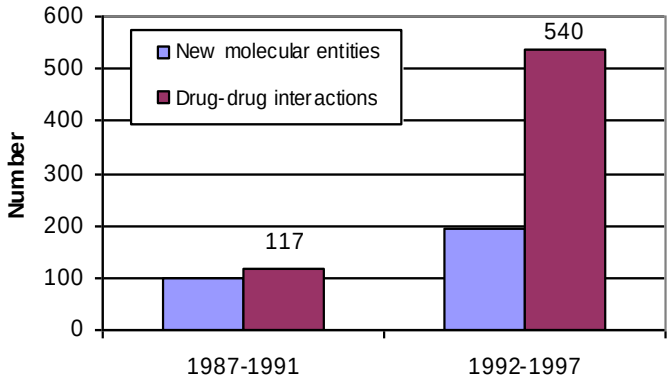
Large increase in plasma triazolam after a single 0.125 mg dose, alone and after 6 days' pretreatment with a new antimicrobial (n = 10)



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

We offer a full service – design, subject selection by phenotyping or genotyping, exclusion diets, drug assays, pharmacokinetic and statistical analysis, and report – for the well-designed interaction studies that regulatory authorities expect.

Increase in drug-drug interaction studies in man for all new molecules approved by FDA 1987–1997

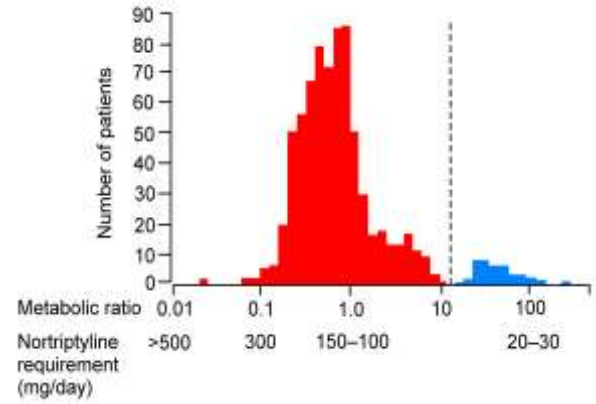


Clin Pharmacol Ther 2000; 68: 280–285

Drug-subject interactions

6–8% of European subjects are poor metabolisers via CYP2D6, because of genetic polymorphism. That can make a big difference to the dose that they need, and we can investigate that in panels of genotype or phenotyped subjects.

Dose requirement for nortriptyline in patients with different CYP2D6 phenotypes



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

References

1. Grind M, Murphy M, Warrington S, Åberg J. Method for studying drug-warfarin interactions. Clin Pharmacol Ther 1993; 54: 381–387.
2. 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.
3. 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.
4. Frye *et al*. Pittsburgh cocktail. Clin Pharmacol Ther 1997; 62: 365–376.