

Microdoses open new horizons for trials

In the 10th article in our series looking at developments in drug technologies, **Jenny Bryan** looks at a new clinical trial technique with huge potential

Human volunteers taking doses of experimental new drugs that are just one hundredth of those calculated to give a pharmacological effect could soon save pharmaceutical companies millions of pounds in wasted research. By outlining the kind of abbreviated preclinical toxicology and mutagenicity studies that will be needed before these so-called microdosing studies can be carried out, both European and US drug regulators have now given their seal of approval to what have been christened “phase 0 clinical trials”. As a result, a growing number of pharmaceutical companies are taking an interest in this new technique, which borrows high sensitivity carbon dating technology from archaeologists, to reduce dramatically the dose of a drug that is required to get key pharmacokinetic and bioavailability data.

Ian Wilding, special professor, School of Pharmacy, University of Nottingham, and co-founder and scientific adviser to research company Pharmaceutical Profiles, predicts that human microdosing could help to address the current crisis in drug development of rising costs and falling numbers of blockbuster drugs. “Seventy-five per cent of the \$900m it now costs to get a new drug to the market can be attributed to earlier failures, and 40 per cent of drugs that fail in phase I clinical trials do so because of inappropriate pharmacokinetics,” Professor Wilding explained to *The Journal*. He added that getting drugs into humans at an earlier — phase 0 — stage might not necessarily increase the hit rate of pharmaceutical research and development but it will help companies to “fail early, fail fast and fail cheaply”.

Colin Garner, chief executive officer of Xceleron, York-based specialists in the carbon dating technology required for microdosing, calculates that the technique will provide key pharmacokinetic data for a new compound in four to six months, at a cost of about \$0.35m per molecule. This compares with 12–18 months and a \$3–5m price tag for taking a compound through current phase I studies. “People always hope that their molecule will make it and there is great reluctance to kill it. But we have to be hard and dispassionate, and ensure that molecules that fail, fail early,” Professor Garner said.

Microdosing reduces costs because the microgram amounts of compounds that are required do not need to be expensively scaled up to manufacturing standards of production. Fewer animal studies are needed to support microdosing than phase I studies so there are ethical as well as cost advantages. And the information from microdosing studies can feed into better design of subsequent dose ranging and other phase I trials.

The microdosing technique in which there is currently most interest uses accelerator mass

spectroscopy (AMS) to count radioactive carbon atoms (usually ^{14}C) in blood, urine and/or faecal samples from volunteers who have taken radiolabelled doses of test compounds. The tiny amounts of radiation that are needed and the hypersensitivity of the technology are mind-boggling. Professor Garner explained that the dose of radioactivity used for AMS studies falls below the 1mSv level which requires approval by the Administration of Radioactive Substances Advisory Committee (ARSAC). He likens it to the radiation dose to which an individual would be exposed during a 10-minute walk in the street.

The level of radioactivity needed for microdosing is so small because AMS can measure ^{14}C levels in human samples in attograms (10^{-18}g) and zeptograms (10^{-21}g). Weeks after a volunteer is dosed with a ^{14}C -labelled compound, AMS can detect levels of the parent drug and its metabolites in blood or other samples, making it an ideal tool for testing the pharmacokinetics of drugs with long half-lives or poor bioavailability.

New possibilities

Professor Garner predicts that with such small amounts of drug being administered microdosing opens up the possibility of including women of child-bearing age in pharmacokinetic studies as well as patients with diseases likely to affect drug metabolism — not just healthy volunteers. However, the big question hanging over microdosing, has been how well the pharmacokinetic data that are collected correlate with data gathered from conventional phase I studies using pharmacological doses of drugs. To this end, the consortium for resourcing and evaluating AMS microdosing (CREAM) trial was set up to show whether microdosing could predict the pharmacokinetic properties at therapeutic doses of five drugs with different properties. These were warfarin, ZK 253 (an anti-oestrogen compound), diazepam, midazolam and erythromycin.

Presenting the results at a conference in London in June, Malcolm Rowland, research professor of pharmacy, Centre for Applied Pharmacokinetics Research, University of Manchester, explained that each drug was chosen to address a different question. For example, midazolam was chosen as a drug that undergoes extensive first pass intestinal wall metabolism and hepatic CYP3A4 metabolism, and ZK253 for its low oral bioavailability. The companies sponsoring the study (eg, Eli Lilly, Roche, Servier and Schering) did not want to be accused of choosing easy drugs that lent themselves to microdosing.

Professor Rowland reported that, overall, the results were promising. The kinetics of diazepam and midazolam were not affected by the therapeutic dose, and the microdosing

results were comparable to population kinetic data for the two drugs. For ZK253, microdosing confirmed the low oral bioavailability seen in conventional pharmacokinetic studies that had led Schering to halt development of the drug.

For warfarin, which is known to have low clearance, the oral microdose data were within the published range, but there was a difference in the disposition kinetics compared with the therapeutic dose, suggesting saturation of a high affinity, low capacity binding site. The results for erythromycin were inconclusive owing to instability of the oral microdose solution in the gastrointestinal tract.

Professor Rowland concluded that the data were encouraging and suggested that when used appropriately microdosing, coupled with AMS, offers a promising tool for candidate selection at an early stage of drug development. However, more data on a wider range of compounds will be needed to clarify the uses and limitations of the approach. Whether or not the pharmaceutical industry will be quite so easily convinced remains to be seen. However, GlaxoSmithKline, having experimented with AMS with Xceleron over the past eight years, has now invested in two state-of-the-art AMS machines of its own, one in the UK.

Professor Wilding explains that, to date, it has been the biotechnology companies, which can least afford to waste valuable R&D resources, rather than big pharmaceutical companies, that have embraced microdosing. “The bigger companies are good at doing what they have always done and tend to be slow to change. They also tend to have more leads than the smaller companies and can afford to speculate. But even they realise that the numbers of new drugs that are emerging do not add up against the increasing costs of R&D,” he pointed out. Professor Wilding believes that the recent decision of the US Food and Drug Administration to follow the European lead in issuing guidance on the preclinical requirements needed to support phase 0 studies could be the turning point for microdosing.

Other high-sensitivity techniques are also in development to rival AMS as the technology of choice to accompany microdosing. There is also talk of cassette microdosing (administering microdoses of cocktails of drugs) to provide an early insight into how drugs might work together and what interactions might emerge.

As Professor Rowland pointed out at the conference, microdosing is not a panacea for all the pharmaceutical industry’s R&D woes but it could aid some of the “stop or go” decisions that all companies must make during the early stages of drug development, which can prove so expensive if the decision is wrong.

Correction

The dose of radioactivity above which Administration of Radioactive Substances Advisory Committee approval is required 0.1mSv, not 1mSv.