

NC3Rs Maths Study Group - Applying mathematics to 3Rs problems

Mathematical Modelling of Chronic Drug Infusion for Toxicity Assessment

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Background to the problem

Adverse drug reactions are a major public health problem. Toxicity issues account for ~21% drug attrition during drug development and current safety testing strategies require considerable animal use.

A mechanistic understanding of the molecular and cellular events that culminate in whole organ toxicity underpins development of novel drug safety assessment strategies.

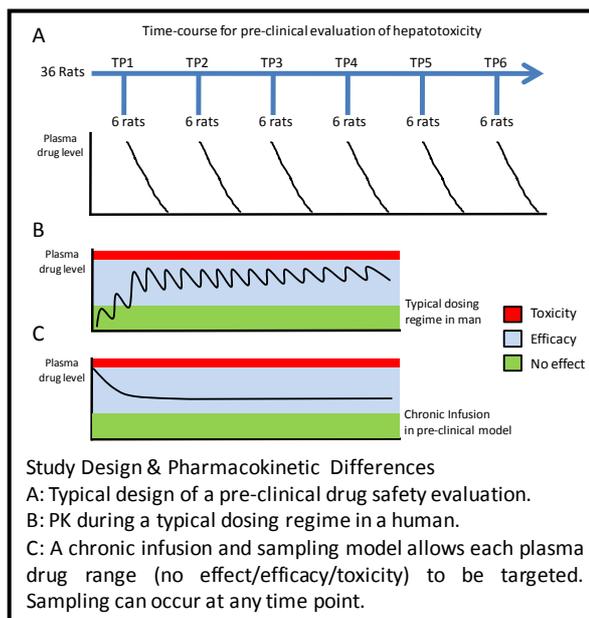
Current models for safety testing are limited by intrinsic differences between animal and man with respect to how drug levels in the blood are maintained. Specifically, the rapid in vivo elimination of drugs in rodents results in qualitative and quantitative differences in pharmaco-toxicological endpoints and confounds comparisons to the human setting.

Chronic longitudinal analysis allows the generation of *before-during-after* type of data sets and can give valuable information such as the

1. Steady state pharmacokinetics of the drug – reflecting the clinical situation
2. Side-step drug holiday issues in animal models on daily dosing regimes
3. appearance and time course of clinically relevant parameters
4. biomarker identification and validation
5. dynamic changes in combinations of biomarkers and association patterns
6. identification of transition points or switch between pathological states – eg apoptosis to necrosis
7. reduction of experimental variation and increase in experimental power

Details of the problem

We have found in a number of studies, that acute dosing of animals can lead to a compression of events of toxicological significance. For example, acute dosing of fed mice with hepatotoxic levels of paracetamol, led to a very short period (1-1.5 hours) where cell death via apoptosis was the initial toxicological consequence, prior to overt necrosis [1]. This needed to be verified extensively for the manuscript to be published, leading to further animal usage. The need for finer control over plasma drug levels (C_{max} , AUC, P_{ss} , etc) in animal models has become crucial, particularly as acute dosing regimes can compress or suppress events of toxicological, and possibly therapeutic, significance. Consequently, it was decided that chronic infusion and longitudinal sampling would help stratify the pharmacokinetics with biological endpoints, defining the toxicology as threshold-, exposure- or chronically-mediated.



A typical pre-clinical work plan for drug safety evaluation, is given in the figure (part A). However, we would like to achieve an 'experimentally regulatable' steady state plasma level (part C), which can inform upon the underlying biology causing toxicity, within a reasonable time frame.

Our preliminary studies into chronic infusion to rats have demonstrated that there appears to be quite a considerable adaptive response, which leads to a significant clearance of the parent drug. Essentially, chronic infusion of a drug at a set dose rate can lead to quite variable pharmacokinetics that may impact upon toxicological markers. Chronic infusion experiments are technically demanding and lengthy, consequently, maximizing experimental design is a priority, to ensure most efficient data generation and usage.

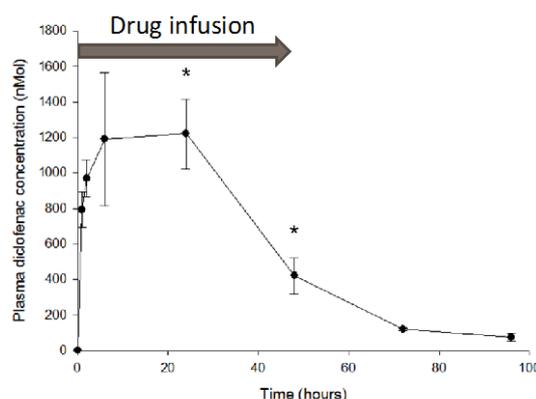
Definition

Acute dosing refers to the administration of a substance within a short period of time (<24 hours). The substance is generally administered as a bolus dose (or occasionally as multiple lower doses within 24 hours) via the most suitable route e.g. intraperitoneal, subcutaneous, intravenous or intramuscular injection, oral (gavage), dermal or inhalation administration.

What we mean by chronic dosing is the continuous slow administration of a substance over a period of days (2-14), usually via an indwelling catheter, with no cessation of treatment during the dosing period. Similar routes of exposure to acute dosing can be selected.

Available data for informing possible mathematical models

We have performed 3 chronic infusion studies in conjunction with AstraZeneca, two have looked at the infusion of paracetamol to rats between 2-3 days and one study infused diclofenac to rats over 2 days (see graph). Similar plasma profiles were obtained in each case. In the first paracetamol chronic infusion, toxicity was evident, even though the dose had been calculated to be sub-toxic, (based upon literature [2]) particularly within the rat, which is resistant to paracetamol hepatotoxicity. We have parent drug plasma levels in each case, along with various biomarkers of toxicity, and some end point toxicology. We have recently established chronic infusion of drugs to rats at Liverpool University, and can perform our own experiments in this area. If the workshop is able to address the below questions, we would be able to use this to inform future studies, but would make publication a primary focus, as this would help broaden the development of chronic infusion models in toxicity assessment, leading to a reduction in animal use.



Questions you would like to see answered

We would like to address the following questions:

1. Can a mathematical modelling framework be built that provides improved experimental design to link continual infusion pharmacokinetics and toxic or adaptive mechanisms, whilst giving insight into basic biology.
2. Can the framework help achieve an optimal infusion regime.
3. Can modelling help predict the most effective starting doses which result in mild toxicity and are sub-lethal.

The potential impact on animal use

Our initial assessment suggests that chronic infusion will lead to a reduction in the use of animals vs the acute dosing model, particularly, as each animal can also act as its own control.

| Dosing Model | Parameters measured | Degree of change required for biological significance | Variation | Power | Number of animals /condition |
|----------------|---------------------------|---|-----------|-------|------------------------------|
| Acute dosing | PK Toxicity biomarkers | 50% | 20% | 85% | 6 |
| Chronic dosing | PK Toxicity biomarkers | 50% | 2-4% | 85% | 2 |

Pre-clinical Safety testing

There were 64,722 rats used in safety testing in the UK. In 2011 and 10,854 used for ADME studies. The most basic 28 day pre-clinical safety study uses 40 rats (5 males, 5 females, at 4 doses including control). Better experimental methods linking the pharmacokinetics with safety endpoints would increase the amount of information gained on a per animal basis. Chronic infusion technology allows the dose of drug to be altered within a single animal, without this becoming a new procedure, hence spanning a wider exposure range. The ADME studies could be combined with the toxicology, hence reducing animal use.

References

Primary:

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Secondary:

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