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A global pharmaceutical company initiative: An evidence-based approach to define the upper limit of body weight loss in short term toxicity studies ☆

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ABSTRACT

Short term toxicity studies are conducted in animals to provide information on major adverse effects typically at the maximum tolerated dose (MTD). Such studies are important from a scientific and ethical perspective as they are used to make decisions on progression of potential candidate drugs, and to set dose levels for subsequent regulatory studies. The MTD is usually determined by parameters such as clinical signs, reductions in body weight and food consumption. However, these assessments are often subjective and there are no published criteria to guide the selection of an appropriate MTD. Even where an objective measurement exists, such as body weight loss (BWL), there is no agreement on what level constitutes an MTD. A global initiative including 15 companies, led by the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs), has shared data on BWL in toxicity studies to assess the impact on the animal and the study outcome. Information on 151 studies has been used to develop an alert/warning system for BWL in short term toxicity studies. The data analysis supports BWL limits for short term dosing (up to 7 days) of 10% for rat and dog and 6% for non-human primates (NHPs).

1. Introduction

1.1. Background

The pharmaceutical industry recognises the need to re-assess the design and conduct of toxicity studies in animals as new scientific practises and knowledge develop. The assessment includes the consideration of the '3Rs', the replacement, refinement and reduction of animals in research (Russell and Burch, 1959),

Abbreviations: 3Rs, replacement, reduction, refinement; NC3Rs, National centre for the replacement, refinement and reduction of animals in research; BWL, body weight loss; MTD, maximum tolerated dose; NHPs, non-human primates.

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so that the conduct of animal studies are continuously challenged, are performed to the most up to date scientific knowledge and that opportunities for the 3Rs are identified.

Historically, the first toxicity test performed in pharmaceutical development was the acute toxicity study (Casarett and Doull's Toxicology, 1999). The main objective of this study was to identify a single dose causing major adverse effects/life threatening toxicity, which often involved an estimation of the minimum dose causing lethality. Since 2009, conventional acute toxicity studies are no longer required to support clinical trials of pharmaceuticals in man (ICH, 2009). This is a direct result of a collaboration of 18 companies led by the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) and AstraZeneca. Data were analysed from 70 compounds in a wide range of therapeutic areas and it was demonstrated that acute toxicity studies had little value in assessing risk to humans (Robinson et al., 2008). Additionally, acute toxicity studies are no longer used for managing overdose of pharmaceuticals and have been found to be of little value in treating human poisoning from chemicals. This consensus was reached at a workshop held by the NC3Rs which brought together clinicians, toxicologists, regulators and directors of Poison Centres (Chapman et al., 2010; Robinson and Chapman, 2009). In the absence of acute toxicity data, the necessary information can instead be obtained from short term studies (up to 7 days daily dosing) that are already an existing part of the drug development process. Such studies provide information on major adverse effects that are observed at the maximum tolerated dose (MTD). This dose is referred to as the MTD because the animal receiving the test item would not tolerate adverse effects that may occur at higher doses. The MTD is defined as the highest dose that will be tolerated within a given study for the study duration.

Defining the MTD in the studies of shortest duration (up to 7 days) informs dose setting in subsequent toxicity studies and is crucially important in the application of the 3Rs, since this reduces the chances of larger numbers of animals that are used in regulatory studies being exposed to unanticipated suffering (NC3Rs/LASA, 2009). The MTD is usually determined by parameters such as clinical signs and reductions in body weight and food consumption. However, there are no published criteria on the intensity and duration of clinical signs that would optimise the selection of an MTD, especially in studies of short duration. Body weight loss (BWL) is an objective measurement and is often used as a primary endpoint in these studies but there is no agreement on what level of BWL constitutes an MTD, although cross company experience indicates typical upper limits of between 15% and 25% loss. Therefore, despite the crucial importance of defining a short term MTD from a scientific, regulatory and ethical perspective, variation exists across the industry and regulators on the interpretation of clinical signs and BWL indicative of the MTD.

There are various publications that relate to animal study endpoints (FELASA, 1994; Morton, 2000; Morton and Griffiths, 1985; Workman et al., 2010). In general, these publications recommend a maximum upper BWL limit of 20%. However, these recommendations are not based on data sharing and do not address BWL in short term toxicity studies specifically. For example, the Organisation for Economic Co-operation and Development (OECD) guidance describes endpoints in toxicity studies, such as clinical signs, BWL, and decreases in food consumption, that are indicators of severe pain, distress, suffering, or impending death and therefore addresses findings characterised as being above the limit of suffering that is considered within the MTD range (OECD, 2000). Similarly, Morton (2000) discusses the use of a clinical scoring system to indicate the overall well-being of the animal and to establish humane endpoints. However, this publication is more general, and recommends a technique that should be developed and tailored to the needs of the individual study, and does not provide specific evidence-based guidelines. Nevertheless, the examples presented by Morton (2000) imposed an upper BWL limit of 20%, and suggest that BWL may be an early indicator of adverse effects, often occurring before the appearance of additional clinical signs. Correspondingly, the Federation of European Laboratory Animal Science Associations (FELASA) working group report on pain and distress in animals contains examples of clinical signs and BWL that address the range of mild, moderate and substantial severity animals may experience during toxicity studies (FELASA, 1994). Further to this, and in collaboration with the Laboratory Animal Science Association (LASA), the NC3Rs has worked with an expert group of toxicologists to develop guidance on dose level selection in regulatory general toxicology, stating that it is possible to define an MTD in animal studies using clinical signs of moderate severity (NC3Rs/LASA, 2009). The FELASA report suggests that up to 20% BWL is acceptable under a moderate severity categorisation. However, this reduction in BWL is not evidence-based and there is no definition of study duration or differentiation between rapid BWL (as might occur in a short term toxicity study) and slower BWL, more likely to be experienced during sub-chronic and chronic toxicity studies. The ICH Guideline S1C(R2) for dose selection for carcinogenicity studies of pharmaceutical states 'no more than 10% decrease in body weight gain relative to controls' as one of the factors included in the definition of MTD (ICH, 2008). However, this is a specific guideline for carcinogenicity studies and refers to weight gain, rather than weight loss.

1.2. Working group objectives

The NC3Rs industry working group was initially established in 2003 to challenge the requirement for acute toxicity studies in the development of new medicines. In 2008, the group successfully completed an objective of collecting an evidence base to demonstrate that conventional acute toxicity studies did not add value in the development of medicines.

For the past 4 years, the NC3Rs working group has continued with further objectives of refining endpoints within short term toxicity studies (up to 1 week in duration). Among a number of potential endpoints considered (including pain, clinical signs and seizures), BWL was chosen as the most objective and quantifiable endpoint and thus amenable to collecting data ontodevelop evidence-based limits. The group currently represents 10 global pharmaceutical companies and 5 contract research organisations (see author affiliations) and is facilitated by the NC3Rs.

BWL is one of the few objective measures assessed in short term toxicity studies, and is often the primary endpoint used in safety assessment. Therefore, the main objective of this work was to share data on BWL in toxicity studies following dosing of up to 7 days in duration, in rat, dog and non-human primates (NHPs). The aims were to assess the treatment impact on the animals both within studies of short duration and for dose setting in follow up studies (typically with longer treatment duration), to review whether limits for BWL could be refined to improve animal welfare. We set out to build an evidence-based upper limit for BWL in 3 primary species used for safety assessment that could be used in short term studies as part of the criteria for defining the MTD.

To do this we asked the following questions:

(1) How does BWL relate to the MTD in short term studies?
(2) What happens in the study at BWL above certain thresholds e.g. is the dosing stopped and/or do animals die prematurely or require euthanasia?
(3) What impact does significant BWL have on dose-selection for follow up studies?
(4) Does BWL at MTD differ for different species, different study durations, or for specific pharmacological subclasses?