This paper describes how the size of the first dose of a medicine is determined and also discusses the safety measures employed in the dose escalation using the case of a potential new anti-hypertensive drug (AHD).

The next step following the estimation of the NOAEL or MABEL will be the calculation of the Human Equivalent Dose (HED) [4]. In this step, the animal dose is extrapolated to an equivalent dose in human based on the body surface area. The HED can either be expressed in mg/m² or mg/kg depending on the conditions the new AHD will satisfy as indicated by FDA guidelines. Having determined the HED for all available non-clinical studies, the HED corresponding to the most appropriate species will be selected for the Maximum Recommended Starting Dose (MRSD) [4]. Nonetheless, in the absence of relevant data on the most appropriate species, decision will be made in accordance with further directions by FDA by selecting by default the species corresponding to the species with lowest determined HED among other recommendations.

Once the HED is determined from the most appropriate species or other relevant recommendations, a safety factor will be applied to the HED in order to create a safety margin to safeguard the safety of introducing the potential new AHD to healthy volunteers who will not derive any therapeutic benefit and thus minimise their exposure to any risks [4]. The FDA [4] suggests the conventional safety factor of 10 which can further be increased or decreased with justifiable reasons some of which have been outlined in the guidelines. The application of the chosen safety factor to the HED will be by means of dividing the HED by the safety factor which will finally yield the MRSD. The MRSD obtained from the above steps will be the size of the first dose to be administered in humans.

However, in some cases, the pharmacologically active dose (PAD) is preferably compared with the MRSD because of its increased sensitivity to potential toxicity compared with NOEL [4]. In that case, an appropriate pharmacodynamic model will be utilised to determine the PAD. For a model which utilises in vivo studies, the PAD will be converted to the corresponding HED using the body surface area conversion factor (BSA-CF). If the corresponding HED is lower than the MSRD derived from the nonclinical studies, FDA [4] advice a reduction in the MRSD which represents the first human dose to reflect practical scientific reasons. Once the starting dose has been established, a dose escalation scheme follows to explore the dose-response relationship, maximum tolerated dose (MTD), a dose range which will be void of potential toxicity and the dose range within which the therapeutic dose for the potential new AHD can be explored in later phase [3]. It is therefore necessary to ensure utmost safety in increasing the size of the first dose and thus highlight on some safety measures in the dose escalation scheme are elaborated under three themes namely; study design considerations, dose escalation rules and the process management.

The study designs employed in phase 1 for the dose escalating scheme are usually titration designs; single ascending dose (SAD) or multiple ascending dose (MAD) [5]. In SAD, a new cohort is used at each dose increment which is contrary to MAD where the same cohort receives all the escalated doses at regular time intervals to allow washout period [3]. These titration designs can also be performed as parallel group (PG) or crossover (CO) designs depending on a number of factors [6]. For the potential new AHD under consideration, the choice between SAD or MAD designs coupled with either PG or CO will depend on factors such as the anticipated risks associated with the active compound, potential dropouts relating to multiple dosing or increased trial duration and flexibility to adjust as clinical data develops [6]. Additional considerations by Chin and Lee [3] include half-life of the active compound, intended dosing schedule in clinical practice, potential adverse effects and long term toxicity. The study design will also take into account a justifiable time interval allowed between the first administered dose and the next. This will allow time to observe the first in human response of the new AHD before deciding the appropriateness to carry on to the next and subsequent volunteers [6].

Having decided on the study design, the next line of action will be to set reasonable dose escalation rules (DER) which involve an appropriate dose escalation method and time to stop the escalation. The various dose escalation methods include modified Fionacci, double spacing, equal spacing and the log scale. Other methods are continual re-assessment method (CRM) or modified CRM, accelerated titration design and pharmacologically guided dose escalation [3]. As a potential new AHD, the potential toxicity being guarded against is the state of hypotension crisis. Hence in addition to the method of escalation employed, extra efforts will also be made towards safety. This will involve the application of the 3 + 3 rule to determine the maximum tolerated dose (MTD) and decide when to stop the dose escalation [3]. According to TER (Traditional Escalation Rule) and STER (Strict Traditional Escalation Rule), 33% or more incidence of toxicity is the threshold to stop dose escalation [3]. However this threshold is more inclined to studies in areas such as oncology where relatively high levels of toxicity are acceptable. As a guide, the toxicity threshold of TER or STER will be lowered to minimise exposure to potential toxicity, since the new AHD is being investigated in healthy volunteers with no life threatening conditions. The dose level prior to the dose at which the escalation is stopped will define the MTD. In case no toxicity is observed at high doses, two strategies proposed by Chin and Lee [3] will be applied. Firstly, the dose will be stopped 2 logs exceeding the postulated target dose and secondly, before attaining a dose that is 1/5th to 1/25th of the dose that does not cause toxicity in animal trials.

The final and yet crucial means of ensuring safe dose escalation is the establishment of an efficient process management which will be discussed according to recommendations by Williams et al. [6]. Firstly, for process management to be effective in contributing to safe dose escalation, the research site has to be fully equipped in both infrastructure and personnel. Inspection of the research unit will
focus on the experience in FIH trials, experience and expertise in the conduct and decisions regarding dose escalations, qualified expertise for stabilising volunteers in acute emergency situations, the site’s facilities to carry out resuscitation and proximity to a hospital’s intensive care unit facilities. Secondly, the study protocol should be written flexibly with respect to the doses to give room for dose adjustments within predetermined range without requiring the amendment of the trial protocol [6]. This is a key determinant to ensure smooth dose adjustments when necessary as part of safety and tolerability monitoring.

Also, pharmacokinetic (PK), safety and tolerability data of each dose administered will be assessed and made available, where possible, prior to subsequent dose level. This will serve as an additional basis for justifying the size of subsequent doses. In addition, a predefined threshold of safety and tolerability data will encompass areas such as adverse effects, blood pressure, cardiac monitoring and laboratory parameters before and after each dosing session. Such data will be reviewed by the principal investigator and research site staff as the trial is on-going. Dose escalation meetings will be conducted after completion of a dose level and prior to escalating to another dose level. For any decision to be effective, a minimum number of representatives from both the sponsor and the research site as indicated in the protocol will be present to form a quorum. However, provisions will be made such as having a fully available correspondent to the principal investigator in urgent situations where a formal meeting cannot be scheduled on short notice. Any review or decision will be documented by the principal investigator and presented as part of the progress report.

In conclusion, the efficient running of the process management will go a long way to ensure that safety measures put in place for determining the starting dose and conduct of dose escalation trials are followed through the appropriate channel of communication.

References


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