Poster

[P27-9] P27-9: Pharmacokinetics and PK/PD

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[P27-9-8] Benchmark dose analysis for safety assessment in pharmaceutical development

Antero Vieira Silva[1], Antero Silva[2], Oberg Mattias[3] (1.Karolinska University Laboratory, 2.Karolinska Institutet, Institute of Environmental Medicine, Unit of Work Environment Toxicology, Stockholm, Sweden &Swedish Toxicology Sciences Research Center (SWETOX), 3.Karolinska Institutet, Institute of Environmental Medicine, Unit of Work Environment Toxicology, Stockholm, Sweden &Swedish Toxicology Sciences Research Center (SWETOX))

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Background

Generally, risk assessment of chemicals has been performed using the no-adverse-effect-level (NOAEL) approach or the more advanced benchmark dose (BMD) approach. The benchmark dose approach is an alternative approach method where a mathematical model is fitted to the toxicological data and the benchmark dose is then defined as the dose that most likely gives rise to a small predefined change in response. The derived dose, or the limit of a confidence interval for that dose, will then be used as a point of departure for risk and safety analysis. BMD modelling is a tool of growing importance for risk assessment in regulatory matters, recommended by WHO (2009), EFSA (2009), US EPA (1995) but is not yet accepted for safety assessment in pharmaceutical development. Thereby, it was hypothesized if BMD could be used in pharmaceutical development, by contributing to the dose-setting process, it could potentially improve the quality of the results obtained.

Methods

BMD analysis was performed on data from three sequential *in vivo* rat studies, to assess the toxicity of a candidate drug. These studies were 7, 14 and 28 days repeated toxicity testing studies. 66 endpoints were modelled, including organ weights, histopathology, clinical chemistry, hematology and immunophenotyping. Using the same endpoints, NOAEL analysis (group-wise comparisons) were performed and the results compared to those obtained using BMD approach.

Results

Some benchmark doses were lower than the study’s NOAEL. Moreover, it was possible to estimate BMDs when there were no NOAELs in the study. Critical effect doses were derived, with less uncertainty when compared to results obtained using NOAEL approach.

Conclusions

Benchmark dose modelling is a viable alternative to the NOAEL approach in *in vivo* studies for safety assessment in pharmaceutical development. As it has been shown that the BMD method is more scientifically sound it is recommended to complement or replace NOAEL approach with the BMD method, with the purpose of performing a more powerful dose-response analysis.

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