Development of a database containing clinical data on bioequivalence and relative bioavailability studies conducted in pediatric populations

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Introduction and Aim

Generally, bioequivalence (BE) studies of drug products for pediatric patients are conducted in adults due to ethical reasons. Given the lack of direct BE assessment in pediatric populations, development of a database with BE and relative bioavailability studies in pediatric populations will enable the identification of risk factors associated with certain drug substances or products that may show discrepancy in BE between adults and pediatrics. However, there is no such database containing pharmacokinetic (PK) BE studies conducted in pediatric populations; particularly those where BE acceptance criteria are not met.

The aim of this work is to develop a database containing clinical data on BE and relative BA studies conducted in pediatric populations.

Methods

A literature search from 1965 to 2020 was conducted using PubMed[1], Cochrane library[2] and Google Scholar[3] to identify BE and relative BA studies conducted in pediatric populations (Figure 1). The following keywords were used to identify all relevant clinical studies for oral products in pediatrics: “BE”, “relative BA”, “non-bioequivalent”, “failed BE”, “lack of BE” and “bioinequivalent”. Clinical studies were collected according to predefined inclusion and exclusion criteria. Data (study details, study population, test and reference drugs, administration details, study results, risk factors for bioinequivalence, and clinical impact of bioinequivalence) were then extracted and summarized.

Inclusion criteria include:

- Studies conducted on U.S. FDA or European Medicines Agency (EMA) approved drugs for oral administration
- Studies that include data from pediatric populations
- BE studies that report the statistical analysis containing the 90% confidence intervals (CIs) (80-125%)[4,5] or geometric mean ratios (0.8-1.25) for both test and reference products for PK parameters, e.g., AUC and Cmax
- In case of relative BA studies that report the PK profiles of both test and reference products, PK parameters such as AUC, Cmax data are collected.

Exclusion criteria include:

- Studies on drugs not administered orally
- Studies reporting bioinequivalence due to the presence of food or drinks or herb-drug interactions or drug-drug interactions.

Further analysis was conducted to identify 1) BE studies where BE criteria were not met (bioinequivalent studies where 90% CI of geometric mean ratio of AUC or Cmax between test and reference products are outside of 80-125%); and 2) relative BA studies conducted in pediatric populations where significant differences in PK parameters including AUC and Cmax were reported between test and reference products (e.g., geometric mean ratio of AUC or Cmax is outside of 0.8-1.25). The risk factors for bioinequivalence were extracted from the study data set based on the original authors’ comments, this could also include links to secondary references where authors’ interpreted their data in the context of wider literature.

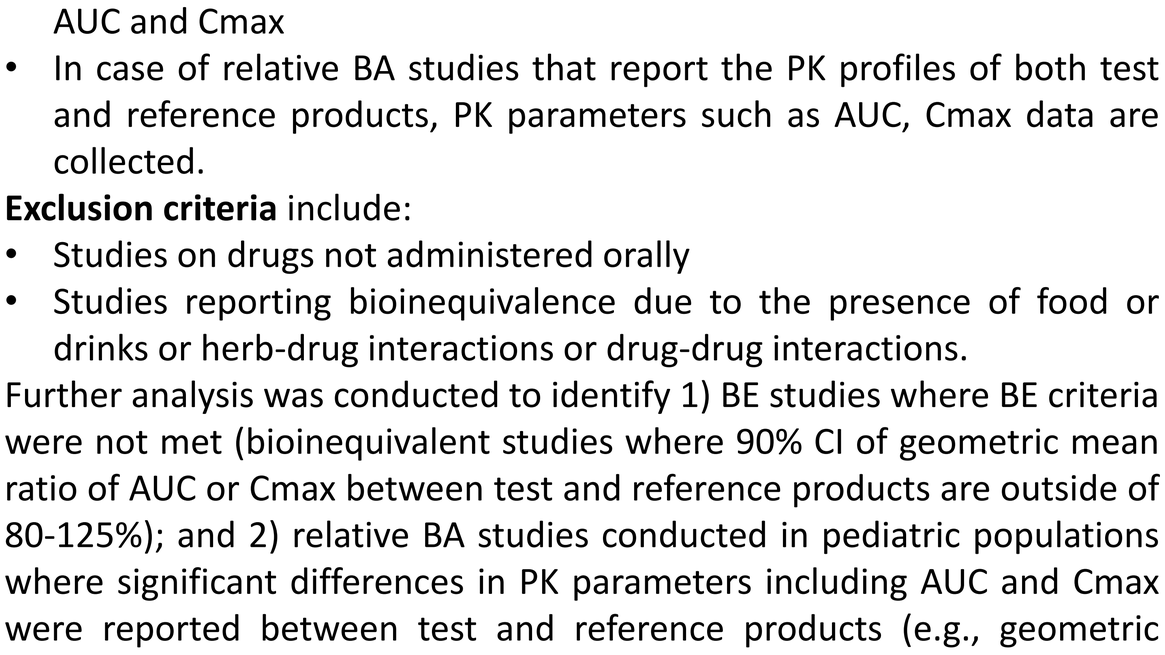

Figure 1. Search strategy and steps involved in the development of pediatric BE database; API: active pharmaceutical ingredients.

Results

Overall 78 studies covering 37 active pharmaceutical ingredients (APIs) were included in the database: 14 clinical studies with data that passed BE evaluations; 9 studies showed bioinequivalence results; 24 relative BA studies showing comparable PK parameters and 31 relative BA studies showing significant differences in PK parameters between test and reference products. Based on the above identified studies, Table 1 presents putative risk factors associated with bioinequivalence or significant differences in PK parameters in BE or relative BA studies in pediatrics.

	Putative risk factors	Number of studies
Physiological factors	Age-related absorption effects (e.g., Gastrointestinal (GI) motility, GI fluid volume or composition, GI transit time)	**27**
	Age-related distribution effects (e.g., protein binding)	**3**
	Age-related clearance including metabolism effects	**15**
Population characteristics	High inter- and/or intra-individual variabilities associated with pediatrics	**17**
Drug substance or formulation effects	Drug substance effect (e.g., alternative salt or polymorphic form of drug substance)	**5**
	Drug product/formulation effects	**9**
Disease	Age-related disease progression	**4**
Study design	Non-equivalent dose	**2**
	Accuracy of administered dose	**3**
	Poor study design including small sample size	**14**

Table 1. Putative risk factors reported to be associated with bioinequivalence or significant differences in PK parameters in relative BA studies in paediatrics. Note that multiple risk factors may have been extracted from one study.

Conclusions

A database containing 78 clinical studies on BE or relative BA in paediatrics has been developed. Common risk factors reported to be associated with bioinequivalence or significant differences in PK parameters in relative BA studies in pediatrics, include: age-related absorption effects, high inter- or intra- individual variability associated with pediatric populations and poor study design (Table 1). These risk factors could be the reasons for causing discrepancy in bioequivalence/bioavailability results between adults and pediatrics.

The collated risk factors resulting in bioinequivalence will need to be further evaluated but could potentially serve as checkpoints during innovative pediatric formulation development and the extrapolation of BE results based on the clinical studies in adults.

References

1) PubMed [Available from: https://www.ncbi.nlm.nih.gov/pubmed/.
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