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Bioequivalence in adults does not mean bioequivalence in children

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Introduction

For a new formulation of an existing drug, as well as for generics, one has only to demonstrate **pharmacokinetic (PK) bioequivalence** with the original formulation to obtain registration. This PK tests are performed in healthy young volunteers, taking for granted that PK follows **pharmacodynamics (PD).** However, this methodology hardly takes in account potential gender, size, age, maturation specific differences in bioequivalence. FDA and EMA-regulation on pediatric drug research have tried to find a compromise between minimal exposure of children to a pediatric research program, and acquiring minimal PK/PD and safety-data in children to reassure safe prescription of the drug, and therefore do not request bioequivalence studies in the pediatric age.

Aim

The aim of this overview was to question if bioequivalence between different solutions is similar over all populations.

Method

Desmopressin (dDAVP), a synthetic vasopressin analogue, is a level 1, grade A treatment of monosymptomatic enuresis nocturna (MNE). This oligopeptide was studied because of the low biodisponibility with large variation, and existing PK/PD data from previous studies[1].

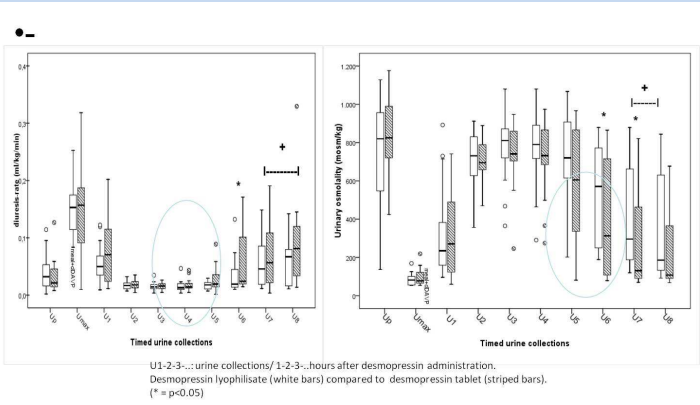
Results

Integrating the data of the different studies on different formulations, we observe

- A higher PD effect for dDAVP lyophilisate (MELT) to tablet, when adjusted with nutrition **(Fig.1 a-b-c (Ref.1))**
- A higher PK bioequivalent dose for lyophilisate (MELT) in children than in adults **(Fig.2 (Ref.2))**
- Compared with previous literature:

1. The relative bioavailability between the lyophilisate and tablet formulations is probably not the same in children as in adults
2. Poor correlation between circulating PK and PD-effect (hysteresis-effect)

Conclusion: This overview demonstrates that for an oligopeptide like dDAVP, with a narrow safety-profile, PK/PD bioequivalence of doses within the therapeutic range in children, cannot be extrapolated from adult data. This suggests that minor changes in formulation makes appropriate bioequivalence studies in children mandatory and collection of safety-data required.



U1-2-3-..: urine collections/ 1-2-3-..hours after desmopressin administration.
Desmopressin lyophilisate (white bars) compared to desmopressin tablet (striped bars).
(* = p<0.05)

Fig. 1a: Superiority of PD desmopressin melt 120 µg vs tablet 200µg

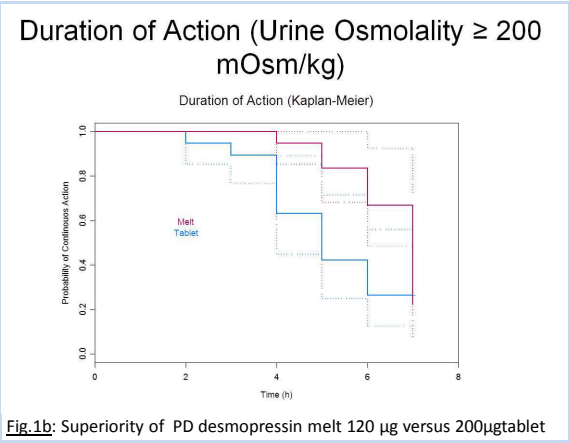


Fig.1b: Superiority of PD desmopressin melt 120 µg versus 200µgtablet

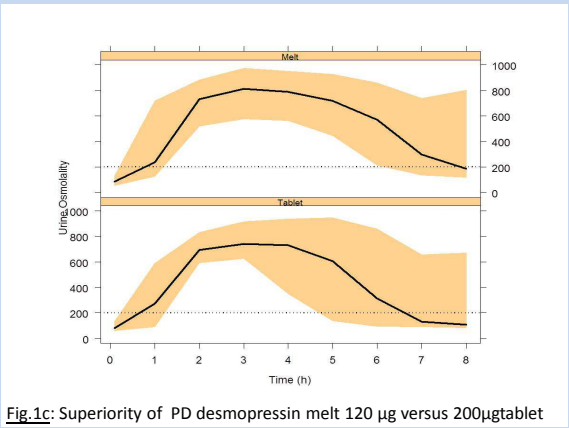


Fig.1c: Superiority of PD desmopressin melt 120 µg versus 200µgtablet

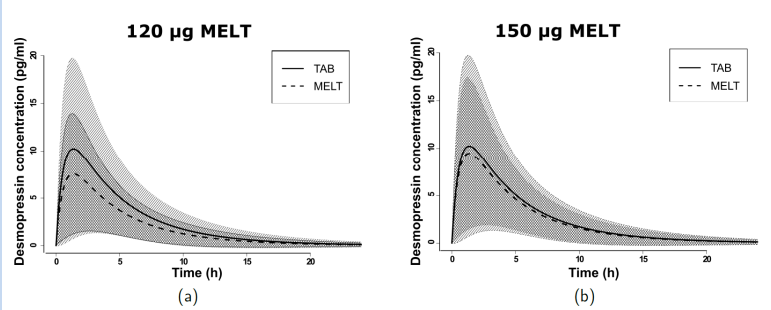


Fig.2: Simulated dDAVP plasma concentrations for four different scenarios (200µg tablet/150 µg lyophilisate (MELT) – fed/fast (food effect)) suggest that 150 µg instead of 120 µg is equivalent to 200µg tablet.

References

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