How to substitute efficacy/safety studies by PD analysis in locally applied/locally acting drugs?

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BIO '89: discussion on topical drugs

Issues ...

- oral administration
  - site of action (stomach, small intestine, colon)?
  - localisation of drug delivery ("targeting")?
- inhalation, nasal/ocular administration
  - systemic site effects (swallowing, GI absorption)?
- dermal application
  - local or systemic development of efficacy (e.g. diclofenac)?
  - measurement of uptake into the skin (BA at site of action) possible?

... solutions?

- C.C. Peck: "steepest learning curve ..."
- however, no conclusive and generally acceptable concept presented ...

Regulatory consequences

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Cornerstones

- in case of non-systemic drugs excipients are of particular importance as they may affect absorption/skin penetration
- differences between preparations (excipients!) or variations, post approval changes may influence efficacy and/or safety

European requirements

European Medicines Agency

London, 26 July 2001
CPMP/EWP/QWP/1401/98

NOTE FOR GUIDANCE ON THE INVESTIGATION OF BIOAVAILABILITY AND BIOEQUIVALENCE

For products for local use (after oral, nasal, inhalation, ocular, dermal, rectal, vaginal etc. administration) intended to act without systemic absorption the approach to determine bioequivalence based on systemic measurements is not applicable and pharmacodynamic or comparative clinical studies are in principle required.

Conclusive regulatory concept?

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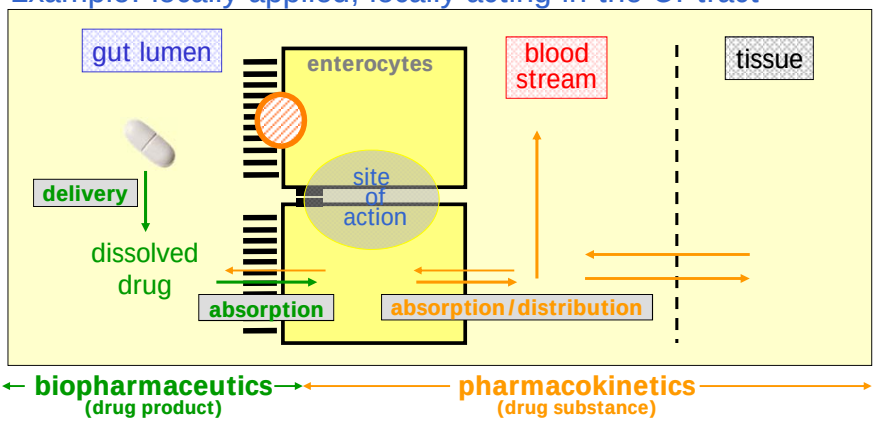
Example: locally applied, locally acting in the GI tract



Plasma concentrations in exchange with site of action (determined by PK) ⇨ why BE concept not applicable?

Focus on oral non-systemic drugs

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Examples (different categories)

- treatment of inflammatory bowel disease: "colon targeting"
  - different galenical concepts (controlled release by pH/time/pressure/...)
  - pro-drugs (sensitive for bacterial enzymes, e.g. sulfasalazine)
  - combination of both
- drugs intended to interact with nutrition/metabolism
  - acarbose for treatment of Type-2 diabetes
  - phosphate-binders for therapy in patients with renal failure
  - orlistat – "life-style medication" (?) designed to treat obesity

Challenging the regulatory concept

- BE concept appropriate, e.g. in case of IBD ...
  ... thus, additional Phase-III studies not necessary
- PD surrogate (for PK?/ for clinical?) endpoints sufficient ...
  ... in order to conclude on therapeutic equivalence

Just an interjection ...

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Suggested concept in case of therapeutics for IBD

- assessment of bioequivalence
  - after absorption into the enterocytes ...
  - ... API performance no more affected by drug product properties
  - thus, plasma concentration *vs.* time profiles ...
  - ... should reflect concentration-time course at the site of action
- conclusion on therapeutic equivalence (efficacy/safety)
  - extrapolation from superimposible plasma profiles ...
  - ... to superimposition of concentration-time courses at the site of action

Supported by localisation study

- goal: demonstration of comparable *in-vivo* performance
  - characterisation of gastric residence time & intestinal transit
  - identification of site of drug delivery
- conclusion on similarity/equivalence of drug targeting

Example: orlistat (alli®, Xenical®)

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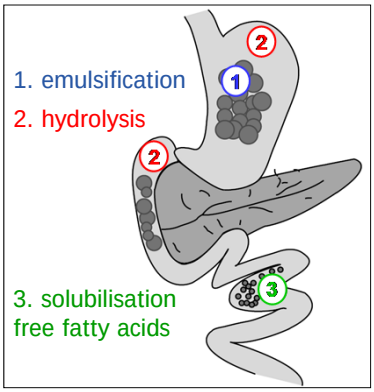
Use for treatment of obesity

- locally applied, locally acting
- irreversible inhibition of lipases in saliva/gastric juice, or secreted from pancreas (dosed to chyme)
- consequences
  - reduction in fat absorption ... (nota bene: not exceeding 35%!!)
  - ... and thus, uptake of calories
- reduction in BW (5-10% per year)



Administration conditions

- surprising advice given by the SmPC:
  "capsules taken before, during or one hour after a meal ..."

Abridged (generic) application

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Conditions according to CHMP concepts

- BE concept (equivalent systemic exposure) not applicable
  - rationale: concentrations at site of action not in exchange with plasma
  - moreover, systemic exposure very low (not appropriate for profiling)
- suggested approach for non-systemic drugs
  - comparative PD surrogate/clinical studies to assess efficacy ...
  - ... systemic exposure for safety reasons (if appropriate/needed)

Development of alternative concept for orlistat

- scientific considerations
  - clinical effect developed locally, i.e. in the lumen of the GI tract ...
  - ... should be appropriately reflected by faecal fat excretion (FFE)
- conclusion supported by studies accepted by Authorities for bridging during development of EU and US innovator product

Faecal fat excretion

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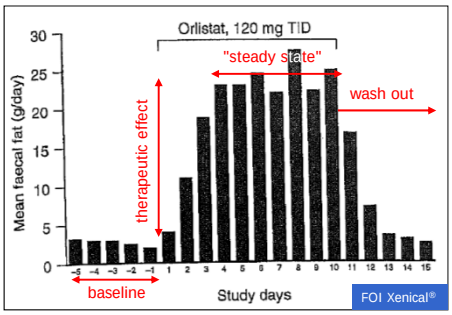
Information derived from published data

- baseline relatively stable under continuous diet
- active treatment increases fat excreted in faeces
  - maximum effect achieved after 3-4 days of active treatment ("steady state")
  - after end of treatment back to baseline after three days



Consequences for equivalence study

- placebo control: baseline represents "placebo" treatment
- active treatment: 3 days to steady-state; 3-5 days sampling
- wash-out/back to baseline between treatments (min. 3 days)

Assessment of faecal fat excretion

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Day-to-day variability

- not only between subjects but also intra-individually
  - separate measurements over 3 (-5) consecutive days ...
  - ... calculation of means (in order to reduce impact of day-to-day variation in physiology)

Assessment of PD/clinical effects

- baseline corrected values
  - differences between active treatment and baseline/"placebo" phase
- alternative (suggested in literature): direct calculation
  - fat excreted in faeces vs. fat taken up with meals (fat content)

Testing for equivalence

- baseline corrected mean (3-5 days) values
- 95% confidence intervals & conventional acceptance criteria

Understanding PD surrogate ...

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Dispute on confidence intervals: 90% *vs.* 95%

- Agency: FFE as surrogate for clinical endpoint (efficacy) ...
- ... thus, 95% confidence intervals need to be calculated
- alternative position: FFE as PD surrogate endpoint for BE ...
- ... thus, 90% confidence intervals appropriate

Final solution/consensus not achieved (so far) ...
... however, no problem as results met both criteria

More essential: sensitivity of surrogate parameter?

- requirement: should exhibit sufficient discriminative power ...
- ... in order to detect (relevant) differences between products
- essential: selection of appropriate dose/dosing regimen

FFE: sensitive surrogate endpoint?

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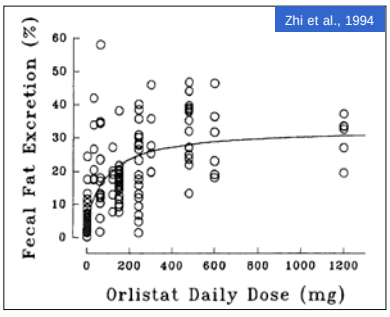
Information on dose-response relationship

- retrospective population based (meta) analysis in obese patients
  - 11 db, pc, pg studies; N=171
  - daily doses between 30 and 1200mg
- E_{max} model used for assessment
  - maximum effect: 32% of ingested fat (for comparison: 5% in placebo phase)
  - $E_{50\%}$ was assessed as 98mg/day
- Zhi: "steep part up to 400mg/d"



Open question remaining

- FOI: "mixing with a meal ⇨ drastic increase of efficacy ..."

Why ??

Kicking against the pricks ...

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GI physiology responsible for "ceiling effect"

- role of stomach: pre-digestion; storage; but not mixing (!)
  ⇨ orlistat dose gets in contact with maximum 1/3 of a meal
- chyme is emptied from stomach in portions ...
- ... and pancreatic lipase is "dosed" to fat containing portions

Efficacy of orlistat is determined by its (limited!) presence in (not all!) chyme portions emptied from the stomach

Consequence

- application of E_{max} (or other dose-response) model imperfect
- inhibition of fat absorption limited by API distribution
  ⇨ all portions emptied with orlistat inhibit lipase completely

Reason for significantly increased efficacy when mixed with meal

Rationale for product optimization

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Development goals

- improved distribution of orlistat throughout a meal ...
- ... in order to be present in all portions leaving the stomach
- expectations: improved efficacy, reduction of dose

Proof of concept [B. Sternby, Clin. Nutrition, 2002]

- 12 male subjects
- determination of lipase activity in GI aspirates (intestinal tubes)
- fat-rich liquid meal
- 60 mg capsule given with/after the meal
- API mixed with the meal before ingestion
- placebo (in capsule)

Results

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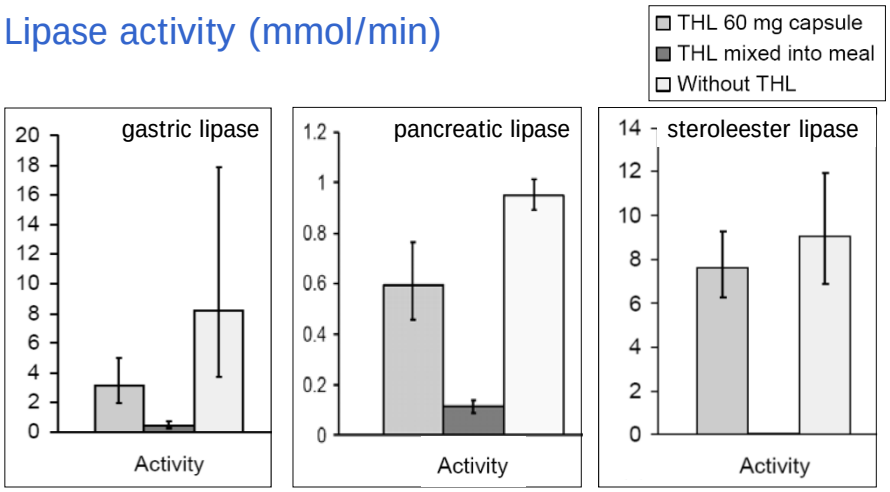
Lipase activity (mmol/min)



Conclusions

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Importance of PD surrogate parameters

- more precisely quantifiable than clinical endpoints
- may be used with different intention(s)
  - as surrogate parameter for clinical efficacy
  - as surrogate parameter for PK characteristics/BE assessment

Essential requirements

- development of gradually quantifiable parameters
- measurement in discriminative part of dose-response curve
- appropriately validated procedure

Potential applications

- proof-of-concept/candidate selection studies
- BE/therapeutic equivalence assessment for Hybrid Application