Specific Populations and Regulatory Considerations – Obese Patients

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Disclaimer : This presentation represents the personal opinions of the speaker and may not necessarily represent the views of the FDA.

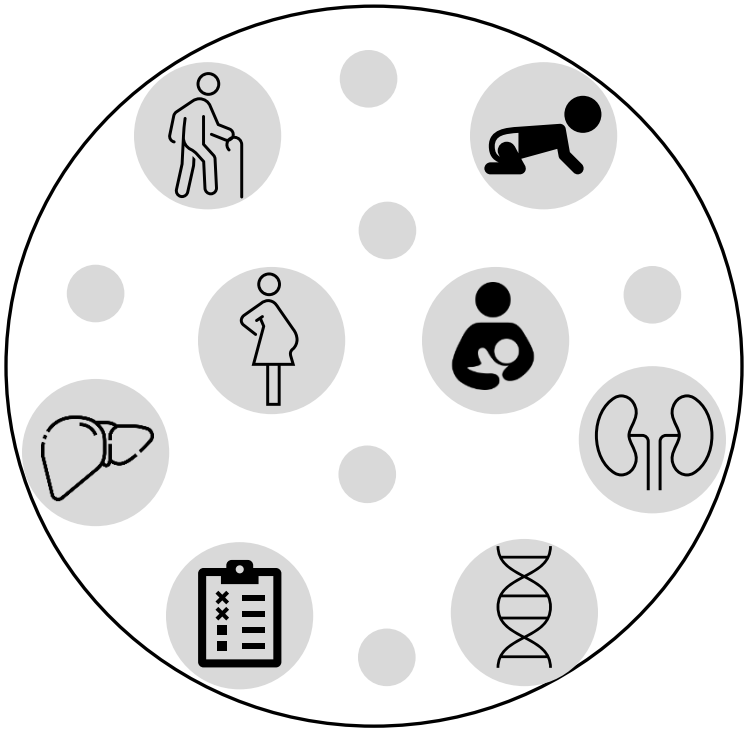
Outline

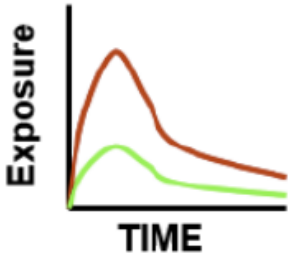
- Specific Patient Populations
- Obese Patients
- Gaps and Opportunities

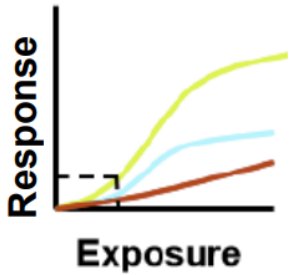
Clinical Trials and Representation

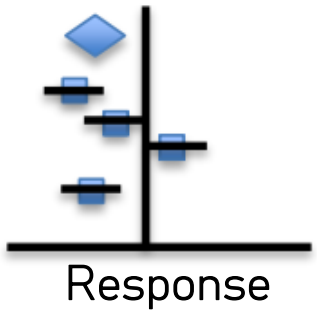
- Pre-market clinical trials aim to limit heterogeneity of treatment effects
- Typically achieved by narrowing of study population
- Often leads to under-representation or exclusion of certain subsets of target population
- Sometimes leads to a gap in prescribing recommendations

Special/Specific Populations
Understanding the Drivers of Response









doi: 10.1038/clpt.2008.144

Special/Specific Populations Regulatory Guidance

- ICH E7 Studies in support of special populations: Geriatrics (1994)
  - ICH E7 Questions & Answers (2012)
- Geriatric information in human prescription drug and biological product labeling [Draft] (2020)

- ICH E11 Clinical investigation of medicinal products in the pediatric population (2000)
  - ICH E11 (R1) Addendum (2018)
  - ICH E11 A Pediatric extrapolation [Draft] (2022)
- General clinical pharmacology considerations for neonatal studies for drugs and biological products (2022)
- General clinical pharmacology considerations for pediatric studies of drugs, including biological products [Draft] (2022)

Special/Specific Populations Regulatory Guidance

- Pharmacokinetics in pregnancy – Study design, data analysis, and impact on dosing and labeling (2004)
- Post-approval pregnancy safety studies [Draft](2019)
- Pregnancy, lactation and reproductive potential: Labeling for human prescription drugs and biological products [Draft] (2020)
- Clinical lactation studies: Considerations for study design [Draft] (2019)

- Pharmacokinetics in patients with impaired hepatic function: Study design, data analysis and impact on dosing and labeling (2003)
- Pharmacokinetics in patients with impaired renal function: Study design, data analysis and impact on dosing and labeling (1998)
  - Revised Draft (2010 & 2020)

Special/Specific Populations Regulatory Guidance

- Pharmacogenomics data submissions (2005)
- Clinical pharmacogenomics: Pre-market evaluation in early-phase clinical studies and recommendations for labeling (2013)
- ICH E18 Genomic sampling and management of genomic data (2018)

- Enhancing the diversity of clinical trial populations – Eligibility criteria, enrollment practices, and trial designs (2020)
  - Broadening eligibility criteria
  - Adopting more inclusive enrollment practices
  - Enhancing the understanding of benefit-risk profile across the patient population likely to use the drug in clinical practice

Special/Specific Populations Regulations

- 21CFR 201.57(c)(9) – Section 8 of the human prescription drug and biological products is "Use in specific populations"
  - 8.1 Pregnancy
  - 8.2 Lactation
  - 8.3 Females and males of reproductive potential
  - 8.4 Pediatric use
  - 8.5 Geriatric use
  - Additional subsections may be included, as appropriate, if sufficient data are available concerning the use of the drug in other specified subpopulations

Obesity

- Obesity is a chronic, relapsing health risk defined by excess body fat.
- Obesity – Individuals with BMI ≥ 30.0 kg/m^2
- Prevalence in the US for 2017 – 2020 is 41.9%
  - Non-Hispanic black adults (49.9%) with the highest age-adjusted prevalence followed by Hispanic adults (45.6%)
- Pediatrics – BMI-for-age & sex ≥ 95^{th} percentile
- Prevalence of childhood obesity is 19.7%

https://www.ncbi.nlm.nih.gov/books/NBK2003/
https://doi.org/10.1542/peds.112.2.424
https://www.cdc.gov/obesity/index.html

Obesity – Physiological Changes

- Increased adipose tissue
- Increased gut wall permeability and gastric emptying time
- Increased cardiac output leading to increased liver blood flow which can decline over time due to NAFLD/NASH in morbidly obese
- Likely induction of phase II metabolism and increase CYP2E1 and likely decreased CYP3A4 activity
- Initial increase in the glomerular filtration rate followed by decrease over time; likely enhanced tubular secretion

doi: 10.1080/17425255.2018.1440287

Obesity and Drug Disposition

Absorption

- Unlikely to affect oral absorption
- Transdermal, subcutaneous, and intramuscular routes may be affected as weight and fat content increases

Distribution

- Changes in drug distribution (Vd) are highly influenced by the intrinsic physiochemical properties of a drug
- Critical for determining loading doses

doi: 10.1080/17425255.2018.1440287

https://doi.org/10.1007/978-3-319-56637-5_7-1

Obesity and Drug Disposition

Metabolism

- A trend for higher clearance for drugs with high hepatic extraction ratio.
- For low-to-medium extraction ratio drugs, phase II conjugation is generally elevated

Elimination

- Clearance of renally eliminated drugs is higher in obese patients. This increase in CL is likely due to increased glomerular filtration and tubular secretion

doi: 10.1080/17425255.2018.1440287

https://doi.org/10.1007/978-3-319-56637-5_7-1

Obesity and Pharmacodynamics

- Comorbidities and risk factors of obesity include heart disease, stroke, type 2 diabetes, certain types of cancer, high blood pressure, asthma, sleep apnea, etc
- Obese individuals have higher platelet reactivity and ultimately display a blunted response to antiplatelet agents (E.g., aspirin, clopidogrel)
- Obesity has been associated with changes to immune system and is hypothesized as the reason for worse outcomes across several infectious disease
- Benzodiazepines and opioid analgesics may have increased effects on respiratory depression and increase the risk of sleep apnea

https://doi.org/10.1007/978-3-319-56637-5_7-1

Obesity Labeling

FDA Drug Labeling NLP Tool used to search for “obesity” or “obese” or “BMI” or “lean” or “ideal” in the “Dosage and Administration” and “Use in Specific Population” sections of US Package Inserts*

32 drug labels with information relevant to obese patients

- **13** Alternative body weight-based dosing in obese
- **07** No dose modification
- **08** Alternative body weight metric to compute creatinine clearance
- **04** Alternative needle length

** As of Sep 2022*

Obesity Labeling

- Obese definition
  - Lean weight is abnormally small fraction of their total body mass
  - TBW 30% over IBW
- Dose modification in obese patients
  - Ideal body weight, lean body weight, adjusted ideal body weight, estimated lean body mass
- Estimating Creatinine Clearance in obese patients
  - Ideal body weight, lean body weight, adjusted body weight

Obesity Labeling

2.9 Dosage Modifications in Obese Patients

The starting doses of ULTIVA should be based on ideal body weight (IBW) in obese patients (greater than 30% over their IBW) *[see Use in Specific Populations (8.6)]*.

8.6 Use in Morbidly Obese Patients

As for all potent opioids, caution is required with use in morbidly obese patients because of alterations in cardiovascular and respiratory physiology *[see Dosage and Administration (2.2)]*.

8.7 Overweight Women

The effectiveness of the etonogestrel implant in women who weighed more than 130% of their ideal body weight has not been defined because such women were not studied in clinical trials. Serum concentrations of etonogestrel are inversely related to body weight and decrease with time after implant insertion. It is therefore possible that NEXPLANON may be less effective in overweight women, especially in the presence of other factors that decrease serum etonogestrel concentrations such as concomitant use of hepatic enzyme inducers.

8.10 Obese Patients with a BMI ≥40 kg/m^2

A trial of 188 obese patients, with a body mass index ≥40 kg/m^2, investigated the time to recovery from moderate or deep neuromuscular blockade induced by rocuronium or vecuronium. Patients received 2 mg/kg or 4 mg/kg BRIDION, as appropriate for level of block, dosed according to either actual body weight (ABW) or ideal body weight (IBW) in random, double-blinded fashion. Pooled across depth of block and neuromuscular blocking agent, the median time to recover to a train-of-four (TOF) ratio ≥0.9 in patients dosed by ABW (1.8 minutes) was statistically significantly faster compared to patients dosed by IBW (3.3 minutes).

The adverse reaction profile was generally similar to the profile in adult patients in pooled Phase 1 to 3 studies *[see Adverse Reactions (6.1)]*. No dosage adjustment is necessary *[see Dosage and Administration (2.2)]*.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020630s020lbl.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021529s019s020lbl.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022225s008lbl.pdf

Obesity – Gaps/Opportunities

- Enable adequate representation of obese patients
  - Information on the eligibility and enrollment of obese participants in oncology clinical trials is dramatically underreported.
  - Enrollment expectations laid out for hormonal contraceptives intended to prevent pregnancy
- Develop best practices and guidelines
  - Study design considerations for evaluation in obese patients
  - Considerations for renal function estimation
- Ensure consistent translation of information to dosing
  - Information about use in obese patients not consistent and often heterogenous

https://doi.org/10.1093/annonc/mdy138

https://www.fda.gov/media/128792/download

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