Inhaled Drug Therapy: Challenges and Opportunities

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Outline

- Rationale for inhaled therapy in general
- Rationale for inhaled therapy for tuberculosis
  - Efficacy
  - Safety
- Pharmaceutical Product Development Approach
  - Background
  - General
  - Specific
- Conclusion
Rationale for Inhaled Therapy in General

- Primarily for local action (e.g. low dose - asthma and COPD; high dose – infection in CF)
- Occasionally systemic action (e.g. diabetes and migraine)
- Poor bioavailability following oral administration
  - Sparingly soluble
  - Not absorbed from GI tract
- To avoid first pass metabolism (or liver tox)
- As alternative to parenteral administration
  - Avoid formulation difficulties
  - Avoid invasive procedure
Inhaled Antibiotics

- 1960s off-label use of a variety of antibiotics in nebulizers
- More recently a number of nebulizer products:
  - Pentamidine (PCP treatment in AIDS patients)
  - Amikacin (MAC treatment)
- Tobramycin (Treatment of infection in CF) established example of:
  - Dose
  - Formulation
  - Device
  - Product approval strategy (?)
Rationale for Inhaled Therapy

When could aerosols be used?

- Prevent transmission / prophylaxis.
- As supplement to standard of care (SOC) to enhance therapy for MDR-TB.
- As replacement for one element of the regimen in SOC for convenience and minimally the same efficacy.
- As replacement for one element of the regimen with the intention of improving efficacy.
- As combination therapy to supplement or replace more than one element of the regimen with the intention of improving efficacy.
- For delivery of new drugs that cannot be delivered by other routes.
Safety and Efficacy Considerations

- High local dose/low systemic dose
  - If circulating doses not above MIC or not used to supplement drug by other route of administration risk periods of sub-therapeutic systemic doses BUT

- Can use multiple daily doses (based on PK) to increase times at Cmax and duration above therapeutic concentration
  - Risk poor compliance/adherence BUT

- May shorten regimen by adopting a more effective therapy.
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Streptomycin Aerosol Study

- twelve children with advanced tuberculosis were treated with aerosols of streptomycin
- all except three children with atelectatic lesions responded to therapy by healing
- the most rapid response occurring in the children with the greatest amount of infiltration, consolidation and cavitation
- This is a remarkably positive outcome for an early study.

Panel C. Courtesy of Prof. H. Frijlink, University of Groningen
Number of viable bacteria (CFU/mL), in lung and spleen of TB-infected guinea pigs following capreomycin administration (average ± standard deviation, n=6)(* significantly smaller than untreated controls, ** significantly smaller than placebo and untreated control, # significantly smaller than any other treatment).

Capreomycin PK

- 20 mg/kg of CMIP delivered by insufflation to guinea pig
- Lung concentrations of drug after single dose reached 4-100 times the MIC of m.tb in BAL and 40-100 times the MIC in lung tissue (100-fold higher than plasma levels)
- AUC/half-life/lung residence time longer/higher concentration after 2 and 3 doses
- Study data suggest that high doses daily of powder will treat TB systemically
- More drug is available in lungs also to kill mycobacteria for a longer period (still present at 8 hours, last time point tested)
Single Dose Tolerability and PK Study

- Completed preclinical inhalation toxicology study
- Phase 1a clinical program (single, escalating dose and plasma PK in healthy volunteers)
  - Successfully dosed 4 cohorts (n=5) each at doses of 25, 75, 150 & 300 mg. Well tolerated with no significant adverse events (SAE). Minor coughing (dose independent)
- Study conducted at Brigham & Women’s Hospital in Boston, MA

Clinical Trials Design?

- Repurposing old drugs
  - Supplementing existing regimen or replacing one component of the regimen in MDR-TB would tie the regulatory approval to the specific combination. Limits application but establishes relevance.
  - Rapid regulatory review as safety already established for original route of administration and systemic exposure.
- Development of a new drug by the inhaled route will require a standard NDA full development program.
Safety Considerations

- Most toxicities relate to consistently high circulating doses of drug at sites that are susceptible to off target effects and duration of therapy. The most serious of these
  
  - Hepatotoxicity
  - Nephrotoxicity (aminoglycosides)
  - Ototoxicity (aminoglycosides)

may be minimized by inhaled therapy.
Conclusion

- Inhaled therapy for tuberculosis may have a number of objectives; prevent transmission; supplement therapy by other routes of administration; offer completely new therapeutic strategy for drugs that show efficacy but cannot be delivered by other routes.
- High local dose, low systemic dose may impart some safety benefit.
- Inhaled drug product development poses some unique challenges but a number of products exist for asthma therapy for which regulatory testing is clear.
- A dry powder aerosol product of the antibiotic tobramycin is available to treat infections in cystic fibrosis as a model product.
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