TARGETED BP ASSESSMENTS: WHAT FACTORS DETERMINE THE NEED FOR A DEDICATED BP STUDY IN HUMANS?

Mary Jane Geiger, MD, PhD, FACP
Eli Lilly and Company

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The Issues

- Do certain classes of drugs require targeted BP assessments?
- What factors determine the need for a dedicated BP study in humans?

What is the Observed BP Effect?

- A preclinical observation?
- An increase in mean BP?
- A sustained increase in BP (24-hrs) or an transient, short-term increase in BP (e.g., 1 to 3 hrs)?
- An increase in DBP? SBP? Both?
- Effect greatest in outliers (i.e., those at highest risk), such as patients with SBP ↑of >10 or >20 mmHg?
- Do changes matter if SBP remains below 130 or 140 mmHg, for example?

How might these changes influence CV risk?

What is a "Dedicated" BP Study?

- A "Thorough" investigation of BP vs. a "TBP" study?
- An ABPM study?
- Some other BP study?
  - Central vs peripheral measure of BP?
- Is increased variability in BP more important than the actual increases in BP?

Dedicated BP Study – which Drugs?

- All drugs?
- Chronic use drugs?
- Other drugs in class with a known BP effect?
- Drugs for use in populations at high CV risk?
  - Elderly? Diabetes? Renally impaired?
- Drugs with a preclinical BP safety signal?
- Drugs with a early BP "signal" in healthy subjects, when use is intended for a different population?
- MOA – drugs with known or potential off-target BP effects?

Factors to Consider

- Duration of action
- Observed PK/PD relationship
  - Concentration dependent relationship?
- Relationship of observed BP effect to timing of dosing
- SBP, DPB, or both affected?
- BP effect sustained or transient?
- Effect goes away with discontinuation of drug?
- Discontinuation rate due to HTN?
- Potential interaction(s) with antiHTN medications? Need for additional therapy to control BP?

Factors to Consider (cont.)

- Intended use: acute vs. chronic therapy?
- Intended population and underlying CV risk
- Effect in hypertensive vs. non-hypertensive cohorts?
- Is the BP effect in the general study population or observed mainly in outliers?
- Are there other potential cardiac effects?
  - Reflexive heart rate changes?
  - Functional changes (cardiac output)?
  - Postural effects?

Dedicated BP Design Considerations

- Effect size:
  - Define “acceptable or unacceptable” threshold for change associated with CV risk
  - SBP or DBP?
- Control:
  - Placebo vs. Positive control (is one available with sufficient and clear BP response?)
- Statistical assumptions
  - Sample size
  - Standard deviation
- Can a shorter term study evaluate longer term risk?

Summary

- No universal definition of what constitutes an unacceptable BP elevation for all indications, patient populations, or baseline risk factors
- BP effects must be considered in the overall benefit risk assessment of a drug for its intended use (population and disease state)
  - Individual vs Population
- Causality – do the BP changes constitute an increased CV risk (define MOA)? Or are they markers of other pathophysiology?

Conclusions

- **Do certain classes of drugs require targeted BP assessments?**
  - **Yes - Maybe?**

- **What factors determine the need for a dedicated BP study in humans?**
  - **Many!**
  - **Sponsor risk**
    - Go/No-Go development decision

"In my view, a better question regarding ABPM is whether *all systemically available drugs intended* for chronic use merit a careful assessment of their effects on vital signs by ABPM."

Norman Stockbridge

Division of Cardiovascular and Renal Products, CDER, FDA

DIJ 2011 45: 567

Back-Up

BP Assessment Development Considerations