

Blood Pressure Effects of COPD Therapy

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Difficulties of Evaluating Cardiovascular and Blood Pressure Effects of COPD Drugs (1)

1. Pre-existing CV pathology due to long history of smoking
2. Multiple drugs are often required for CV indications
3. Arteriosclerotic changes due to smoking can increase basal variability of BP changes and mask drug effects

Difficulties..... (2)

4. Most patients are at age where hypertension is common and are receiving antihypertensive agents that can hide or modify BP effects of COPD drugs
5. Thus, best data on possible BP effects of COPD drugs might come from studies in normal volunteers, though extrapolating findings to an older and less healthy treatment population may be difficult

Major Classes of Drugs Used in COPD

- Inhaled selective beta-2 agonists
- Inhaled antimuscarinic agents
- Inhaled corticosteroids
- Oral corticosteroids

BP Effects of COPD Therapy

Beta-2 Agonists (1)

- Remarkably little detailed information available about BP effects
- These agents produce classical adrenaline-like actions:
airway dilation; tachycardia; vasodilation
- Both “hypotension” and “hypertension” are listed as potential adverse effects – but no details provided

Beta-2 Agonists (2)

Effects of age and concomitant disease are important:

Reduced beta-2 receptors in older people

Possibility that peripheral vasodilation may not fully compensate for tachcardia

Other drug classes may affect baroreflex mechanisms

Interaction with beta blockers

Some early beta-2 agonist labels warned of increased BP with beta blockers, but no firm evidence

Selective beta-1 blockers should not affect BP in COPD

Recent reports that beta-1 blockers might improve survival and reduce exacerbations in COPD; no BP effect reported (Rutten, Arch Intern Med 2010; 170:880)

BP Effects of COPD Therapy

Selective muscarinic agents

- Central effects include tachycardia and stimulation of vasomotor center that could increase BP, though negative feedback usually compensates
- Effects on AV node shorten resting potential (PR interval) but no direct cardiac effects on BP
- Increased parasympathetic activity might mediate the normal BP dipping pattern at night, so it's theoretically possible that muscarinic antagonists could attenuate the circadian BP pattern. ABPM would be the best tool to study this effect.
- There are no available data to indicate that these agents have meaningful effects on office BP during clinical use

BP Effects of COPD Therapy

Inhaled corticosteroids

Long-term effects on pulmonary function are not fully established, but these agents reduce the frequency of exacerbations and improve quality of life

Effects on BP: No major changes reported

Oral Corticosteroids

Agents like prednisolone are effective in managing COPD exacerbations.

Prolonged use of these agents is known to affect BP, but intermittent use in COPD should not normally produce meaningful BP changes

Blood Pressure Increases Caused by Drugs Under Development

Information needed to guide research and clinical use (1)

- Do BP increases actually occur?
- What is the incidence of this effect?
- What is the effect size and range?
- When does it occur in relation to dose?
- When does it occur in terms of therapy duration?
- Is it PK dependent or unpredictable in timing?
- Is it reversible upon drug discontinuation?

Blood Pressure Increases Caused by Drugs Under Development

Information needed to guide research and clinical use (2)

- Does the drug convert normal BP into hypertension?
- Does it occur mainly in hypertensive patients?
- Could the effect be due to interaction with antihypertensive drugs?
- What patient characteristics are predictive? Age, sex, concomitant conditions, other drug types?
- What are the likely mechanisms of effect: volume, vascular, SNS/RAS/endothelin vasoconstriction?
- What simple measures can be used to treat the increased BP?
- Does it affect heart rate or other risk factors? e.g. glucose, lipids

Systematic Evaluation of Blood Pressure Increases Caused by New Drugs

Duration of effect?

(Reversible after each dose? Duration > inter-dose interval; partly or completely permanent?)

How best measured? --- ABPM, Office

During which phase of development? --- All 3
standard phases

Systematic Evaluation of Blood Pressure Increases Caused by New Drugs

Is circadian BP profile altered?

(Are patients who are dippers made into non-dippers?)

How best measured? --- ABPM

During which phase of development? --- All 3 standard phases

Systematic Evaluation of Blood Pressure Increases Caused by New Drugs

How often does drug convert patients to hypertension (<140 to \geq 140 mmHg)

How best measured? --- Office

Note: If using ABPM this would be <130 to \geq 130 mmHg for 24 hour period

During which phase of development? --- All 3 standard phases and post-approval. Consider ABPM in long-term safety studies in patients identified by office BPs

Summary Slide: Blood Pressure Events

Weight of Evidence LABA/SAMA/LAMA/ICS and combinations are associated with	No clear evidence for adverse BP effects
What (if anything) was required to evaluate perceived “risk”	Routine BP measurements. ABPM not done. BP changes difficult to identify due to antihypertensive therapy in many patients
Presence of a Likely MOA for Risk LABA/SAMA/LAMA/ICS	Both LABA and LAMA agents have potential BP effects (beta receptors, muscarinic receptors), but these effects have not been clearly demonstrated in clinical testing.
Is perceived risk: Generalizable to Other Drugs with Same Efficacy MOA?	Since the risk hasn't really been demonstrated it's unlikely to affect other drugs like these
Lessons Learned	Generally negative findings as far as BP concerned, but uncertainty as to whether sufficient rigor was applied in searching for BP effects