Contractility Assessment in Safety Pharmacology: An FDA Reviewer’s Perspective

Philip J. Gatti, Ph.D.
Pharmacologist
FDA/CDER/OND/ODE1/DCRP
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ICH S7A and S7B

• CV safety studies recommended: Arterial Blood Pressure, HR and hERG/QT analysis.

• Optional studies: Ventricular contractility, Cardiac Output, Vascular Resistance and Testing the effects of endogenous/exogenous substances on CV responses.
Causes of Drug-Induced Heart Failure

- Beta-1 receptor blockade
- Calcium channel blockade
- Cardiac necrosis
- Edema formation
- Increased afterload (Increase in Arterial Blood Pressure)
- Valve pathology
- Coronary Artery Disease
Drug Classes Known to Cause Heart Failure

• Antifungals
• Thiazolidinediones
• Antiepileptics
• MEK Kinase Inhibitors
• RAF Kinase Inhibitors
• Tyrosine Kinase Inhibitors
Could Safety Pharmacology studies have predicted this effect?

Case Studies
Antifungal

• Yes, an antifungal does produce acute effects to decrease dP/dT *in vitro* and *in vivo* in several species.

• Not initially tested in SP studies because previous antifungals did not produce this effect on contractility.
Thiazolidinedione

- No acute effects on contractility in SP studies
- Increased heart weights in rat 13-week repeat-dose toxicology study, and in dog 4, 13 and 52-week repeat-dose toxicology studies
- Cardiac hypertrophy is believed to be a consequence of increased afterload due to an increase in plasma volume.
Antiepileptic

• No effect on contractility in SP study
• In 4-week monkey study, enlarged hearts were noted at autopsy along with LV and septal necrosis and fibrosis.
• Exacerbates HF in patients with low EF, but can induce HF in patients w/o history of CV disease.
• MOA: CCB?, vasodilation leading to edema? Suggestive of increased afterload.
ICH-S9 Guidance (Oncology Drugs)

• “Conducting stand-alone-safety-pharmacology studies to support studies in patients with advanced cancer is not called for. In cases where specific concerns have been identified that could put patients at significant additional risks in clinical trials, appropriate safety pharmacology studies described in ICH S7A and/or S7B should be considered.”
MEK Kinase Inhibitor

• Decrease in contractility (using high concentrations) observed in rabbit wedge preparation. Also, negative inotropic effect in vivo in mice, not dog or monkey (doses in dog and monkey were limited because of other toxicities, which could explain the apparent lack of negative inotropic effects)

• In clinic, drugs produce high incidences of drug-induced heart failure. Warning in label.
RAF Kinase Inhibitor

• Contractility not measured in SP studies
• In the 4-week rat repeat-dose study, valve pathology observed in males at highest dose.
• In the 13-week dog study, this pathology was observed in both sexes at all doses.
• Label: cardiomyopathy warning and precaution when taken with MEK Kinase inhibitors.
Tyrosine Kinase Inhibitor

• Decrease in contractility when administered i.v. to domestic pigs. Many in this class do not acutely decrease contractility, only with chronic use.

• Many in this class can produce cardiomyopathy characterized as cardiac failure, LV dysfunction or decreased EF in clinic and has been included in label
Summary

- Sometimes, SP (when studies are performed) can detect drug-induced changes in contractility (when it is measured).
- In many instances, DIHF was detected in repeat-dose toxicology studies even when no acute changes were observed in SP studies.
Conclusions

• Need to look at both SP studies and repeat-dose toxicology studies to fully assess potential DIHF adverse effect.

• Better utilization of in vitro systems (Langendorff or wedge preps) or use of animal models of HF which would enhance sensitivity to such drug effects.