ATRIAL FIBRILLATION IN DRUG DEVELOPMENT

Is drug induced AF a real phenomenon?

What role does patient population / substrate have on the incidence of drug induced AF?

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Disclosures

- Employee and shareholder of GlaxoSmithKline
- Contents of this presentation are solely my personal opinions and not necessarily shared by GSK

Can drugs cause atrial fibrillation?

- Why do we care?
  - AF is associated with hospitalization, morbidity and mortality
  - Identifying modifiable risk factors is a priority for AF prevention, including the possibility of drug-induced AF (DIAF)
- Little mention of DIAF in the current AF guidelines
  - Perhaps due to limited evidence?
  - Is DIAF just a myth? Or is it a real clinical problem?

The evidence – or lack thereof

- Literature mostly contains individual case reports; lacking in well controlled prospective study data
- We each have our own clinical experiences
  - Pt with sepsis in the ICU on dopamine who develops rapidly conducted afib
  - Afib during a dobutamine stress echo
  - College student with afib on a Sunday morning
  - Elderly female with COPD exacerbation receiving IV methyprednisolone, inhaled albuterol, and oral theophylline
  - But what about less obvious cases – the healthy 52yo taking just NSAIDs for an ankle sprain?
- We need to consider a potential association with both cardiovascular and non-cardiovascular drugs

Can ibuprofen really cause AF?

- Retrospective case control study in northern Denmark (BMJ 2011)
  - ~3000 cases matched to ~22,000 controls
  - Current use vs no use - RR 1.33 (95% CI 1.26-1.41)
  - Adjusted for age, sex, CV risk factors - RR 1.17 (95% CI 1.10-1.24)
  - For new users, adjusted RR 1.46 (1.33 – 1.62). Equivalent to 4 extra cases of AF per 1000 new users of NSAIDs

- Population based prospective cohort study in the Netherlands (BMJ 2014)
  - ~8500 in analysis population; ~850 cases of Afib during 12.9year follow-up
  - Current use of NSAIDs for 15-30 days associated with increased risk of afib compared with never use: adjusted HR 1.76 (95% CI 1.07-2.88)
  - Similar result even when adjusting the LVEDD or LA size
  - Trend towards increased risk with higher doses of NSAIDs

Mechanisms of drug-induced AF

- We know AF results from different underlying mechanisms, so we expect DIAF may also occur through different mechanisms
  - Direct EP effects– adenosine, theophyline, dopamine
  - Changes in autonomic tone – alcohol, acetylcholine (nicotine, atropine), sympathomimetics
  - Drug induced hypotension - verapamil
  - Direct myocardial damage – chemotherapeutic agents
  - Myocardial ischemia – coronary vasoconstrictors, triptans
  - Electrolyte disturbance – diuretics, glucocorticoids

- NSAIDS – cardio-renal effects – inhibit cyclo-oxygenase enzymes leading to fluid retention and increased BP, attenuation of diuretic effect and other anti-hypertensive medication effects

What role does patient population have on incidence of AF?

- Based on these different mechanisms of DIAF, underlying substrate *may* impact an individual's susceptibility
- Generally would anticipate an increased incidence of drug-induced afib in the elderly
  - Background rate is already increased
  - Generally treated with multiple concomitant medicines
  - Have multiple co-morbidities to increase their risk
- What about "healthy" patients with occasional PACs?
- Data to support this expected impact of substrate on occurrence of DIAF are lacking
- Is new onset AF a reflection of the patient's disease, or is it an adverse effect of a recently started drug?
  - Without randomized data, this may be a challenging question to answer

Susceptibility to DIAF

- Are risk factors for AF the same as risk factors for DIAF?
  - Recent cardiac surgery, age, hypertension, valvular disease, cardiomyopathy, electrolyte disturbance, thyroid disease, chronic lung disease, sleep apnea, alcohol use, . . .
- Some patients are more susceptible to drug induced torsades on the basis of substrate (inherited channelopathies, acquired structural heart disease, etc.) – it is reasonable to expect the same may apply to DIAF

Challenges in diagnosis of DIAF

- Temporal association may not be obvious
- Symptoms are often lacking - "silent AF"
- Episodes may be paroxysmal and quite short – limiting ability to document the arrhythmia
- Even if temporal relationship fits with the PK profile, the AF episode is captured, and a plausible mechanism exists, in a high risk patient it still could be "chance" and just reflect the underlying disease

Concluding thoughts…

- More questions than answers
- Will application of novel monitoring technologies help us generate the data we need?

References

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