

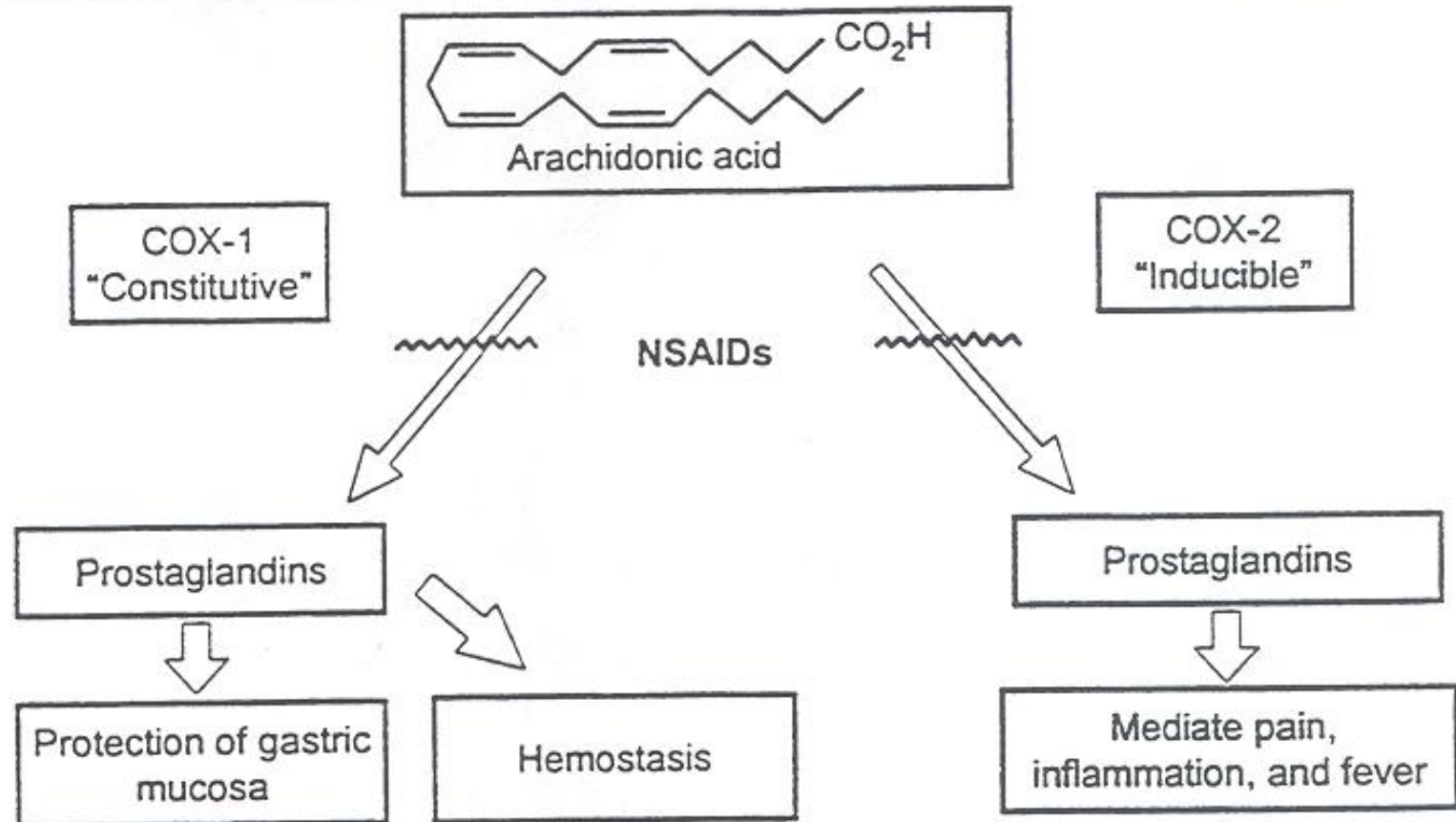
Pharmacovigilance

The Orphan Child of the US FDA

Outline

- Use of two case studies of coxibs & tzds
- A very brief outline of the basic biology for each class known in their development phases that were entirely predictive of eventual adverse cardiovascular outcomes
- Underscore pitfalls inherent in a lack of diligent pharmacovigilance due to FDA infrastructure & relationships to industry

Mechanism of Action of NSAIDs: New Hypothesis



Principles of COX Activity

- COX-1 functions to produce prostaglandins locally that have a constitutive function; providing continuous, maintenance effects (a non-inducible isoform)
- COX-2 functions only in circumstances involving organ stress, locally producing prostaglandins (an inducible isoform)

Implications of Differential COX Isoform Activity

- Basal/maintenance generation of TXA2 by COX-1 isoform to produce platelet-aggregation
- COX-2 upregulation of PGI2 production under conditions of endothelial laminar shear (organ stress) to prevent vascular smooth muscle proliferation & promote endothelial dilatation (clearly documented effects from 1981, Moncada, et.al. & confirmed by FitzGerald, et.al. 2000)

Organ-Based Conclusions (I)

- Intense marketing to physicians & direct-to-consumer advertising over-emphasized gastric-sparing effects & false claims of superior anti-inflammatory effects vs. nsaid
- Effects on both gastric erosions & outcomes of trauma & dental pain relief require only short term exposure to document efficacy allowing for rapid approval by FDA

Organ-Based Conclusions (II)

- Labeling & marketing also emphasizes less bleeding risk (preserved TXA2 activity to allow platelets to aggregate), but downplays effect favoring vascular smooth muscle proliferation & vasoconstriction by inhibition of PGI2
- Requires long-term exposure (≥ 18 mos) to show clinically-relevant impact of imbalance
- Enter polyp & dementia studies requiring daily long term exposure to uncover adverse CV events

- Rofecoxib first to show definitive increase in adverse cardiovascular outcomes (CVA/MI), roughly 2 times greater in treatment group (3%) vs. placebo
- Valdecoxib follows showing an increased risk in small group of high-risk individuals post cardiac surgery
- Longer time interval and more patient-exposures required for celecoxib to show risk due to weaker COX-2 selectivity

Generic/ Brand Name	Chemistry	COX-1 / COX- 2 Ratio	Status in U.S.	Status in E.U.
Celecoxib / Celebrex	Sulphonamide	30	Approved by FDA in May 1999. On April 7, 2005 FDA asked Pfizer to include a boxed warning in the celebrex label.	Approved by EMEA. Label revised in February 2005. Ongoing safety review.
Valdecoxib/ Bextra	Sulphonamide	261	Approved by FDA in November 2001. Label revised by FDA in December 2004. On April 7, 2005 FDA voluntarily withdrew Bextra from the market.	Following discussions with EMEA and FDA decision Pfizer suspended the use of Bextra in the E.U. on April 7, 2005.
Parecoxib/ Dynastat	Sulphonamide	261	Not approved by FDA Approved by FDA in May 1999.	Approved by EMEA for short-term post-operative pain. Label revised in December 2004. Ongoing safety review.
Rofecoxib/ Vioxx	Sulphonyl	276	On September 30, 2004 Merck voluntarily withdrew Rofecoxib. On April 7, 2005 FDA stated that will carefully review any proposal from Merck for resumption of marketing of Vioxx.	On September 30, 2004 Merck voluntarily withdrew Rofecoxib from E.U. and worldwide market.
Etoricoxib/ Arcoxia	Sulphonyl	344	Not yet approved. Under consideration by FDA	Approved by EMEA. Label revised in February 2005. Ongoing safety review.
Lumiracoxib/ Prexige	Phenyl Acetic Acid	433	Not yet approved. Under consideration by FDA	Not yet approved by EMEA.

FDA Advisory Panel, 2/18/05

- All to remain on market: cel: 31-1 (19-1), val: 17-13 (5-13), rof: 17-16 (5-16)
- Black box for all, no marketing
- Lack of ability to use in the populations that would be indicated (i.e.: older, long term use in DJD, same at risk of gastropathy), low potency of celecoxib plus dose ceiling of 200 mg/day limits utility

TZDs

Lessons In Moderation of PPAR-
gamma activation

Conflicting Data on Atherogenesis

- Salutory effects of a cholesterol efflux from macrophages & repression of pro-inflammatory cytokines: Chinetti, 2001; Chawla, 2001
- Equally concerning effects to promote internalization of oxLDL & thereby promote atherogenesis in models of DM: Nagy, 1998; Lankin, 2005

Discrepancy in Specific TZDs

- Muraglitazar (EC50 of 0.11 $\mu\text{mol/L}$ on PPAR)-robust on insulin sensitivity with increase in adverse atherosclerotic events
- Rosiglitazone (EC50 of 0.13 $\mu\text{mol/L}$ on PPAR)-improves surrogates, but evidence accumulating on atherosclerotic ADRs
- Pioglitazone (EC50 of 0.49 $\mu\text{mol/L}$ on PPAR)-neutral to protective on CV events

Likely Explanation

- Improved insulin sensitivity that drives surrogate markers (serum lipids, A1C) is largely due to enhanced uptake in adipose
- Thus, the usual way of assessing interim benefit of these drugs may be separate from those that process lipids in arterioles

Pharmacogenetics

Polymorphic variation in PPAR-
gamma activity as guide to confusing
effects of TZDs

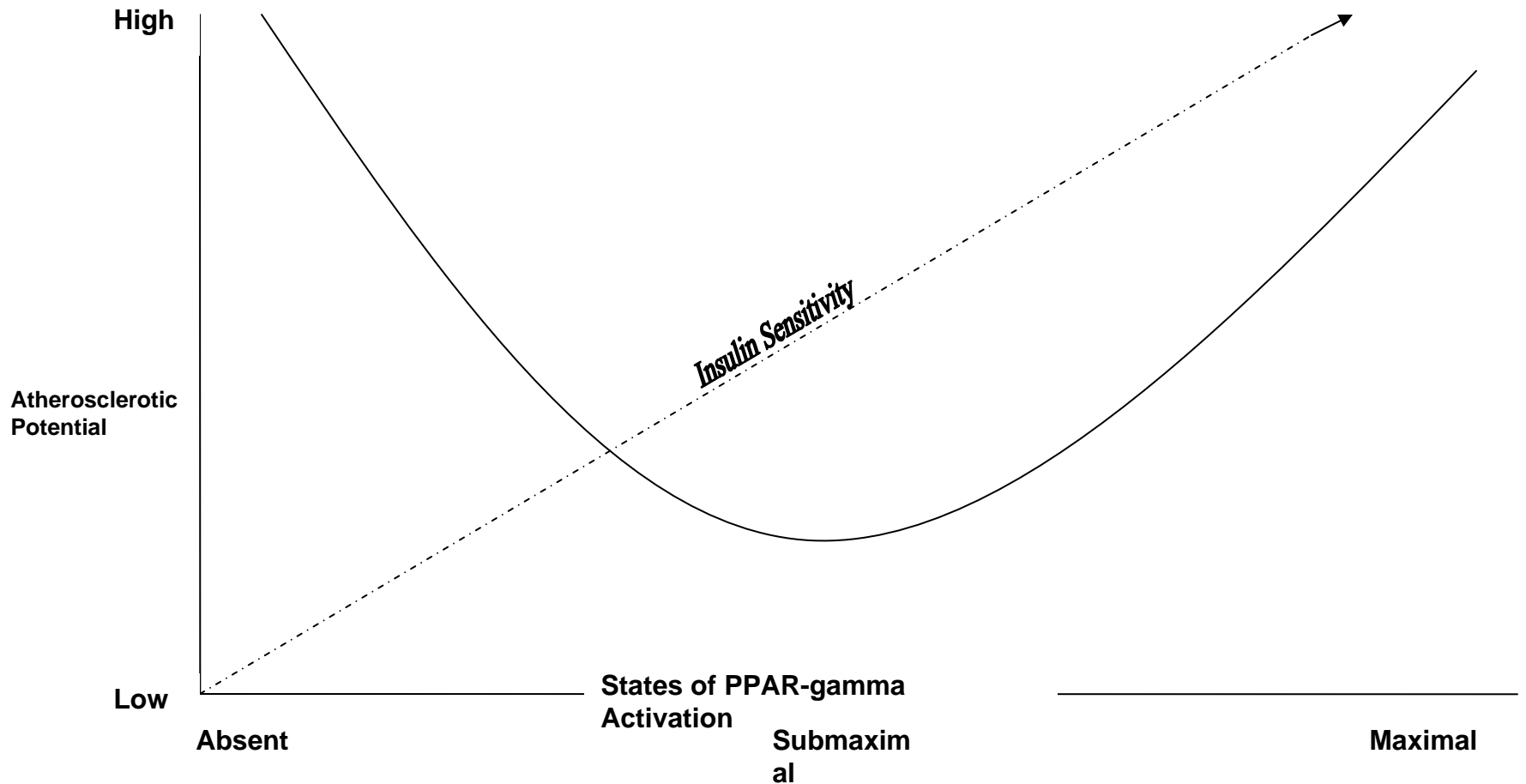


Figure 1: Graphic representation of the conceptual relationship between the state of PPAR-gamma activation, the potential for atherosclerosis and their relationship to the level of insulin resistance. The 3 states of PPAR-gamma activation correspond to the Pro495Leu, Pro12Ala and Pro113Gln genetic mutations, respectively.

Summary: TZDs

- Like coxibs, evidence of potential for harm from enhanced oxLDL accumulation present in early in-vitro studies
- Mistake made to assume that decrease in insulin resistance & surrogate markers correlates with improved hard outcomes
- Role of tzd pharmacodynamics mimicking variable states of PPAR activation is key

Overall Summary

- Tunnel vision of drug development: focus on molecular biology: identify drug effects on single biological process
- Other pathways or broader implications of drug effect neglected (clin pharm expertise)
- Makes imperative pharmacovigilance, especially when ADR also occurs from primary disease being treated