The Nephrotoxicity of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

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Outline

• Introduction: the kidney and nephrotoxicity

• Why predict nephrotoxicity?

• Nephrotoxicity in Derek Nexus
  • Endpoint status in Derek Nexus (v4.0, April 2014)
  • Case study: the nephrotoxicity of NSAIDs

• Challenges in nephrotoxicity prediction
The Kidney and Nephrotoxicity

- The kidney performs vital body functions including regulation and elimination

- The kidney is an essential organ for excreting pharmaceutical agents, diagnostics and metabolites → high exposure and susceptibility

- Acute Kidney injury (AKI) results from pre-renal, renal or post-renal effects
  - Pre-renal: hemodynamic alterations
  - Renal: nephritis, nephrosis, tubulopathies, necrosis
  - Post-renal: crystal nephropathy

- Many drug-related factors contribute to AKI
  - Poor solubility when concentrated in urine
  - Clinical mode of action
  - Prolonged therapy at high dose
Why Predict Nephrotoxicity?

• Drugs are responsible for a significant number of community and hospital acquired renal complications\(^1\)

• Drug induced AKI is a major reason for the late-stage failure of drugs in development\(^2\)

• **Addressing the potential for drug-induced AKI early in drug development ensures both patient safety and efficient, successful clinical development**

• Few *in silico* methods or *in vitro* assays for the prediction of nephrotoxic hazard

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1. Naughton, American Family Physician, 2008, **78**, 743-750
2. Redfern et al, The Toxicologist 2010, **114**, 231
Nephrotoxicity in Derek Nexus (v4.0, April 2014)

- 4 full alerts for the nephrotoxicity of nucleoside/nucleotide drugs
- 1 full alert for the nephrotoxicity of an NSAID sub-class
- 54 RapidPrototype alerts for urinary tract toxicity endpoints
  - Based on an FDA CDER dataset relating to post-marketing adverse events in man

- 1 full and 34 RapidPrototype alerts for nephrotoxicity prediction from other projects

- Lhasa Limited aim to use the existing RapidPrototype alerts as the basis for expanding the number of full nephrotoxicity alerts in Derek Nexus
1. **NSAID sub-classes** were identified and evaluated for **publicly available in vivo reports** of nephrotoxic events in **man and other mammals**.

2. **Expert assessment** and **peer-review** of toxicity data and suitability for development into a nephrotoxicity alert. **Plausible mechanisms** investigated.

3. **Expert activity calls** made and added to internal nephrotoxicity dataset.

4. **Structure activity relationships (SAR) defined** and toxicity alerts implemented in Derek Nexus.

5. **Alert validation** against **FDA CDER urinary tract toxicity dataset**.³

6. **Mechanistic knowledge** used to construct tentative **AOPs** to describe the nephrotoxicity of NSAIDs.

³ Ursem et al, Regulatory Toxicology and Pharmacology (2009), 54, 1-22
The Nephrotoxicity of NSAIDs

- **107 NSAID** compounds given **peer-reviewed expert call**
  - **62 NSAIDs (58%)** - nephrotoxic, weakly nephrotoxic or equivocal
  - **45 NSAIDs (42%)** - no nephrotoxicity data (active or inactive) → equivocal
  - Based on the available data, it was not possible to give any NSAID compound an unequivocal ‘inactive’ expert call for nephrotoxic hazard in man or mammals

- **6 full nephrotoxicity alerts for NSAIDs implemented in Derek Nexus**
  - 1 alert implemented in the last Knowledge release (v4.0, April 2014)
  - 5 alerts prepared for the next Knowledge release
## The Nephrotoxicity of NSAIDs

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- Validation against the **FDA CDER dataset** of compounds with reported **post-marketing adverse nephrotoxic events in man** (496 positive/1113 negative)

→ **Confirmed NSAIDs are one of the most nephrotoxic classes in the dataset**
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- **Expert assessment** of the inactive (FP) compounds in the FDA CDER dataset showed:
  - 9 compounds → reported nephrotoxic in man or mammals
  - 5 compounds → no nephrotoxicity data → equivocal
  - 4 compounds → pro-drugs of active compounds
  - 2 compounds were not NSAIDs
The Nephrotoxicity of NSAIDs

- NSAIDs → acute renal failure (ARF), with or without nephrotic syndrome, occasionally secondary to acute interstitial nephritis.

![Diagram showing the mechanism of NSAID nephrotoxicity](image)

- Interact with organic anion transporters on the basolateral membrane
- Accumulate within proximal tubule cells
- Uncouples and/or inhibits mitochondrial oxidative phosphorylation
- → Acute tubular necrosis and ARF

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W Drewe and MB Surfraz, SOT 2015 Poster, abstract 1326 – available through the Lhasa Limited website
The Nephrotoxicity of NSAIDs

- NSAIDs → acute renal failure (ARF), with or without nephrotic syndrome, occasionally secondary to acute interstitial nephritis.

- Glomerular filtration and/or efflux from proximal tubule cells → NSAID concentration at the renal papillary tip
- Long-term use or excessive consumption of NSAIDs → renal papillary necrosis and irreversible renal failure

W Drewe and MB Surfraz, SOT 2015 Poster, abstract 1326 – available through the Lhasa Limited website
**The Nephrotoxicity of NSAIDs**

- NSAIDs → **acute renal failure (ARF)**, with or without **nephrotic syndrome**, occasionally secondary to **acute interstitial nephritis**.

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**Diagram:**

- Basolateral membrane
- Proximal tubule cell
- Renal tissue/tubule
- Renal adverse outcome

**NSAID cyclooxygenase (COX) inhibition**
- Reducing prostaglandin (PG) synthesis
- Uncontrolled renal vasoconstriction
- Reduced glomerular filtration rate (GFR)
- Ischaemia of renal tissues
- Necrosis of renal tubules and/or the renal papilla and ARF

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**Abbreviations:** Non-steroidal anti-inflammatory drug (NSAID), Cyclooxygenase (COX), Prostaglandins (PGs), Glomerular filtration rate (GFR), Blood urea nitrogen (BUN), Serum creatinine (SrCr).

W Drewe and MB Surfraz, SOT 2015 Poster, abstract 1326 – available through the Lhasa Limited website
How may these toxicity alerts and AOPs be used?

• Highlight the **nephrotoxic hazard** posed by chemicals **structurally or mechanistically related to NSAIDs**
• Aid **read-across** to predict the nephrotoxic hazard of related chemical classes
• Applied in a **nephrotoxicity screening strategy** for establishing nephrotoxic hazard

• Improve **understanding of the mechanistic rationale** for alerting compounds
• Identification of **in vitro/in vivo testing strategies** to probe nephrotoxic hazard

**Improve patient safety and reduce nephrotoxic liability during late-stage drug development**
Challenges in Nephrotoxicity Prediction

- Complex endpoint

- Limited quantity and variable quality of publicly available data

- There is a recognised need for improved preclinical screening and clinical diagnosis/reporting

- New data sources may allow improved *in silico* nephrotoxicity predictions to be made in the future
Acknowledgements

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Questions?