From the cortex to the tip of the papilla: A pathological journey through the kidney

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Introduction

Renal toxicity represents a frequent observation in pre-clinical toxicity studies.

Mostly, alterations of the proximal tubules and/or the glomeruli

In this presentation, additionally:

- Subcapsular lesions
- Distal renal tubular epithelium
- Collecting duct epithelium
- Lesions of the papilla
(Sub-)Capsular Findings
Cynomolgus Monkey, Biologic, i.v.

Control  Acute death, day 2
(Sub-)Capsular Findings
Cynomolgus Monkey, Biologic, i.v.

Low Dose, 7 days

High Dose, 7 days
Cortical lesions

Rat, interstitial nephroblastematosis
Glomerular Lesions
Cystic dilation of Bowman’s Capsule, Amyloidosis

CD-1 Mouse
Glomerular Lesions
Pigment deposition with glomerulo-sclerosis, minipig
Lesions of the proximal tubular epithelium
Rat, vacuolation/“osmotic nephrosis“, cyclodextrin, i.v.

Male rat, control, 14 days, NaCl i.v.; normal appearance

Male rat, control, 24 h HP-β-CD, i.v.; minimal to slight apical vacuolation of proximal tubular epithelia.
Lesions of the proximal tubular epithelium
Rat, vacuolation/“osmotic nephrosis”, cyclodextrin, i.v.

Control, 14 d days  High Dose, 14 d
Lesions of the proximal tubular epithelium
Rat, vacuolation/“osmotic nephrosis“, cyclodextrin, i.v.

High Dose, 14 days  Control, 4 wks and 4 wks Recovery
Lesions of the proximal tubular epithelium

Dog, vacuolation, cyclodextrin, i.v.
Lesions of the distal tubular epithelium

4-wk rat: Hypertrophic distal tubular epithelium in 10/10 m and 6/10 f: Is this finding adverse?

Control, male  High dose male
Lesions of the Distal Tubular epithelium

13-wk rat: Kidney Weight (abs. / rel.) ↑

Gross Observation: enlarged, discoloration
Lesions of the Distal Tubular epithelium
Hypertrophy of distal convoluted tubules, tubular dilation

Kidney, High Dose
Lesions of the Papillary Collecting Ducts

Same study: Rat 13 wks: Epithelial hyperplasia, intraluminal sloughing of epithelial cells

Control  High Dose
Lesions of the Papillary Collecting Ducts

Same study: Rat 13 wks: Epithelial hyperplasia with papillary projections
Question:

Are these findings considered as adverse?

Next steps: 13-wk rat study with different interim sacrifice time-points

- Female Wistar (Hsd Cpb:WU) rats (n = 10)
- Necropsy time points: d 3, 14, 28, 47, 56, 70, 91
- Survival was most likely not affected
- Urinalysis: Volume ↑, density, protein, urea and creatinine ↓
- Urine enzymes: LDHc and NAGc ↑, γGTc ↓
- Gross observations occurred beginning with d 47: enlarged, discoloration
- Histopathology: see next slides

LDH = L-Lactatdehydrogenase, NAG = N-acetyl-β-D-glucosaminidase, gammaGT = Urinary gamma-glutamyl transferase
Cortical distal tubule hypertrophy

Control | Day 3 | Day 14 (?) | Day 28 | Day 47
Papillary Collecting Ducts

And what about Recovery?
Conclusion

• Renal lesions observed in the 13-wk study were confirmed
• Possible early onset
• Cellular lesions are reflected in urinary enzyme data
  • LDHc and NAGc reflect cellular damage
  • Pathogenesis of $\gamma$GTc decrease remains open
• Distal convolute tubule and collecting ducts: Active Na$^+$ re-absorption which is Aldosteron-regulated and K$^+$ secretion
• Passive H$_2$O re-absorption which is ADH-regulated
• DCT and CD are impermeable for H$_2$O w/o ADH
• Further progression to hypertrophic and hyperplastic lesions due to exaggerated regeneration?
Lesions of the Collecting Ducts and Renal Papillary Necrosis (RPN)

- Various regulatory and mechanistic rat studies performed with a Serotonin (5HT$_{1A}$-receptor) agonist intended for treatment of general anxiety in humans


Main Metabolite:

1PP = 1-(2-pyrimidinyl-butyl)-Piperazin)
Lesions of the Collecting Ducts: Vacuolation

Swelling of Medullary Collecting Duct Epithelia (MCDE) Pap. Base

5-HT-1a Agonist, 1 Wk.

Moderate swelling of MCDE, reaching mid of papilla

5 Wks.
Lesions of the Collecting Ducts: Vacuolation

Severe Vacuolation of MCDE Mid of Papilla
5 Wks.

Renal papillary tip still o.k.
5 Wks.
Lesions of the Collecting Ducts: Vacuolation

Vacuolation of MCDE reaching the tip of papilla

9 Wks.

Vacuolation of MCDE reaching the tip of papilla

14 Wks.
The Renal Papilla

Control

Papillary Tip

Normal Interstitium
The Renal Papilla

Technique:
Optimal Cut:
Complete papillary tip
Technique: Optimal cut with complete papillary tip. Note collecting ducts ending in the renal pelvis!
The Renal Papilla

**Technique:** Suboptimal cut with only partial papillary tip. The contralateral transverse slide is even worse!
The Renal Papilla

Technique: Inacceptable cuts!
You would miss any papillotoxin!!!
Renal Papillary Necrosis

1. Early Papillary Necrosis, characterized by multifocal necrosis of interstitial cells, thin limbs of Henle and vasa recta, degeneration and detachment from the basement membrane of collecting tubule epithelium, occurrence of calcium granules within the renal papillary interstitium, basement membrane of thin limbs and the cytoplasm of degenerating cells,

2. Intermediate Papillary Necrosis, characterized by coagulative necrosis of all elements of renal papilla with sparing of the collecting tubules and calcium granules as described under 1, and

3. Total Papillary Necrosis, showing necrosis of all elements of the renal papilla, including the collecting tubules that might appear only as „ghost“ cells.
The Renal Papilla

9 Wks.

Interstitial swelling, "loss of staining detail"

13 Wks.

Interstitial swelling, "loss of staining detail"
Interstitial swelling, „loss of staining detail“
9 Wks.

Early renal papillary necrosis
13 Wks.
The Renal Papilla

Total Papillary Necrosis

2 yrs. treatment

No cellular demarcation
The Renal Papilla

Complete renal papillary necrosis

Complete renal papillary necrosis, note inflammatory demarcation

Spontaneous Infection

Spontaneous Infection
Experimental RPN: Bromethylamine 50 µl/kg i.p., 3 d

125 µl/kg i.p., 3 d
Experimental RPN:

Total renal papillary necrosis, Propylenimine 10 µl/kg i.p., 4 days

Total renal papillary necrosis, with re-epithelialisation Propylenimine 10 µl/kg i.p., 4 days
Experimental RPN:

Renal papillary necrosis, epithelial proliferation
Propylenimine 10 µl/kg i.p., 4 days

Renal papillary necrosis, epithelial proliferation
Bromethylamine 125 µl/kg i.p., 3 d
What about the common Metabolite?:

1PP = 1-(2-pyrimidinyl-butyl)-Piperazin)

Kidney damage has not been reported as a direct result of taking buspirone. However, patients with chronic kidney conditions are not candidates for taking buspirone…
Köszönöm szépen!

CD-1 Mouse / Amyloidosis of the papilla