Intravenous contrast enhanced computed tomography: dosing and pharmacokinetics in *Cyprinus carpio*

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Background

- Koi carp are colored variety of common carp (*Cyprinus carpio*) that have gained immense popularity as ornamental fish worldwide (Fig. 1).
- Their high monetary and sentimental value, as well as their long life-span, necessitates ante-mortem diagnostic options for veterinary examination.
- Celomic distension is a common abnormal finding in koi (Fig. 2).
- Since few ante-mortem diagnostic methods are reported in fish, exploratory celiotomy and other invasive procedures are typically needed to evaluate abnormal conditions involving internal organs.
- Contrast-enhanced computed tomography (CT) has been widely utilized in veterinary medicine for this purpose, though it has not been documented in fish.
- In a pilot study, the contrast agent iopamidol was found to be safe and effective at producing diagnostic images at a dose of 480mg of iodine/kg (mgI/kg) in koi.

Figure 1. Koi Pond

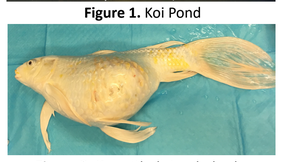


Figure 2. Koi with distended celom

Research Goals

1. To determine if a dose of 150mgI/kg of iopamidol is effective for CT imaging in carp.
2. To compare the efficacy of contrast-enhanced CT imaging in carp at 5min and 1hr post-injection.
3. To determine the pharmacokinetic (PK) parameters following intravenous administration of iopamidol in carp.

Methods

Computed tomography scans

- Protocols for contrast-enhanced CT scanning in fish from Brust et al. (2018) were followed (Fig. 3).
- Six fish were selected to undergo CT scans at 150mgI/kg (n=3) or 480mgI/kg (n=3).
- Fish were scanned prior to receiving contrast, 3-5min post-injection, and 1hr post-injection.
- Blood was drawn from the caudal vein after the 3-5min and 1hr scans (Fig. 4).

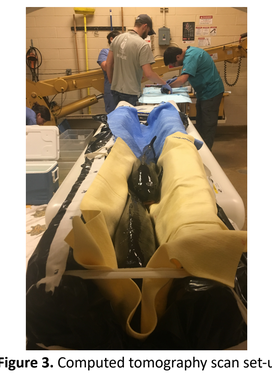


Figure 3. Computed tomography scan set-up

Pharmacokinetic study

- A clinically relevant dose of iopamidol (480mgI/kg IV) was used to establish a clearance curve of the drug.
- Six fish were assigned to each of the following post-injection timepoints for sampling: 5min, 1hr, 6hr, 24hr, 48hr.
- Five controls received saline and were sampled at 48hr post-injection.
- Blood, posterior kidney, gills, and bile were analyzed using liquid chromatography tandem mass spectrometry (Fig. 4, 5).
- Pharmacokinetic parameters were determined using noncompartmental analysis for sparse data.

Figure 4. Injection/blood collection from anesthetized *Cyprinus carpio*

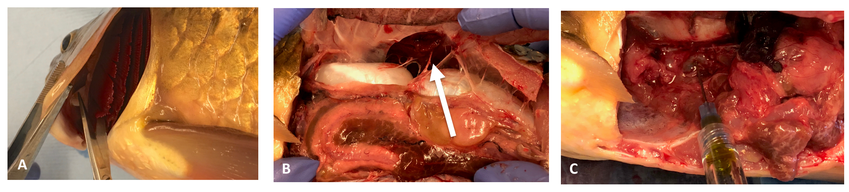


Figure 5. Gill (A), posterior kidney (B), and bile from the gall bladder (C) were collected and analyzed in pharmacokinetic studies

Results

Computed tomography

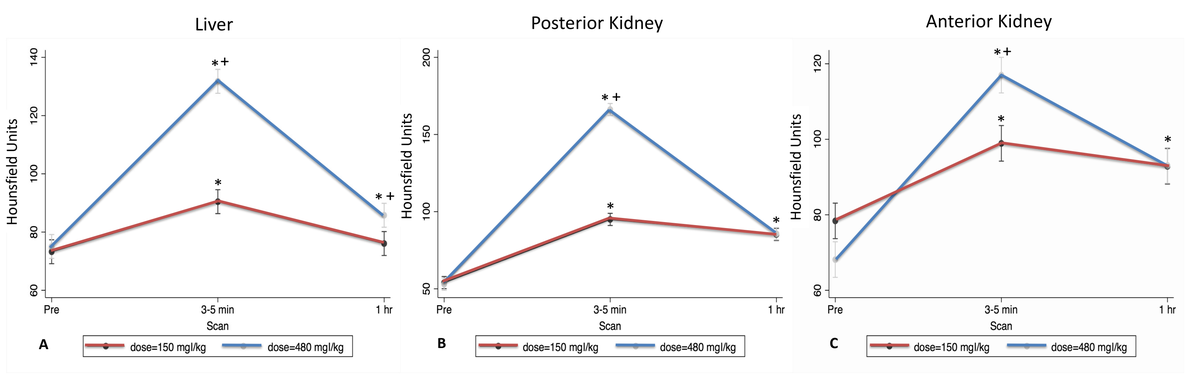
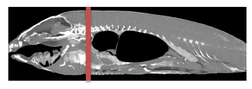


Figure 6. Average of triplicate measurements of Hounsfield units (HU) in three representative organs; liver (A), posterior kidney (B), and anterior kidney (C) across scan timepoints and iopamidol dosages. The error bars represent standard errors.
*; denotes significantly higher HU when compared to pre-contrast measurement ($p<0.05$).
+; denotes significantly higher HU quantified in fish injected with 480mgI/kg when compared to fish injected with 150mgI/kg ($p<0.05$) .

Results Continued

Computed tomography scans



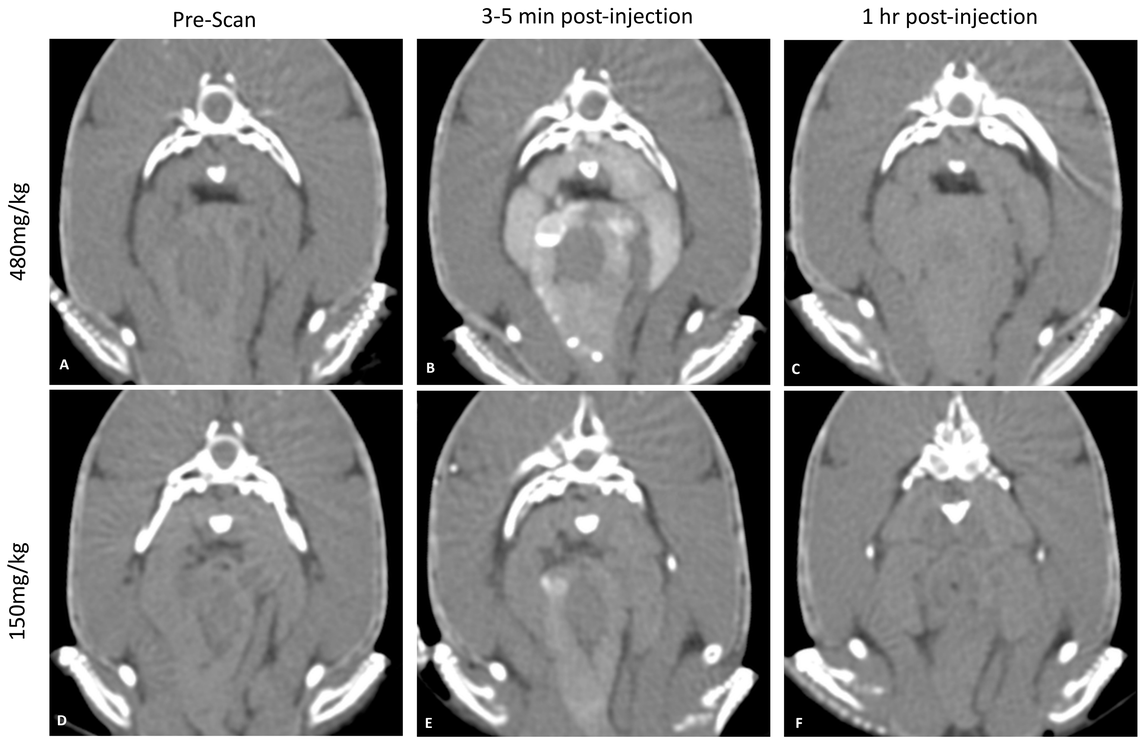
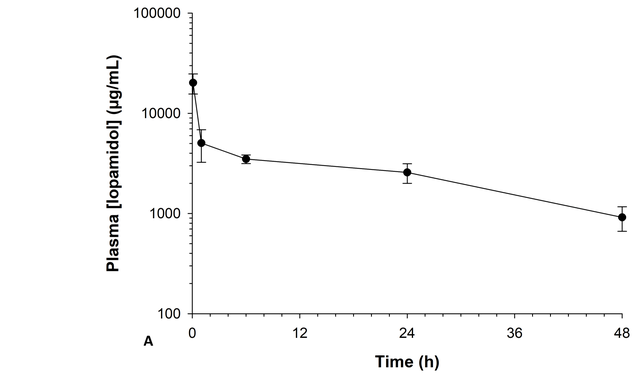


Figure 7. Cross sectional computed tomography images at the level of the anterior kidney from one representative fish at 480mgI/kg (A, B, C) and 150mgI/kg (D, E, F), prior to contrast (A, D), 3-5min post-injection of iopamidol (B, E), and 1hr post-injection (C, F).

Pharmacokinetics of iopamidol in carp



Plasma Pharmacokinetic Parameters	
Half-life	20.4hr
Total systemic clearance	0.051mL/min/kg
Volume of Distribution	79.9mL/kg

Table 1: Terminal phase half-life, total systemic clearance, and volume of distribution at steady state of iopamidol in plasma calculated using noncompartmental analysis for sparse data.

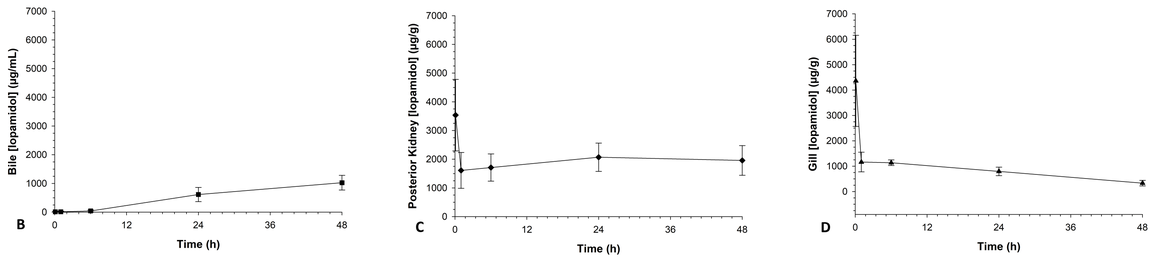


Figure 8. Mean +/- standard deviation of iopamidol concentration over time curves in plasma (A), bile (B), posterior kidney (C), and gill (D) following intravenous administration of 480mgI/kg. Samples acquired at 5min, 1hr, 6hr, 24hr, and 48hr post-injection and analyzed via liquid chromatography-mass spectrometry.

Conclusions and Future Directions

1. Our results corroborate those by Brust et al. (2018) that a dose of 480mgI/kg of iopamidol administered intravenously is effective for contrast-enhanced CT imaging in carp, and further conclude that a dose of 150mgI/kg of iopamidol is not clinically useful (Fig. 6, 7).
2. Imaging 3-5 minutes post contrast injection produced vascular to parenchymal phase images, while imaging 1hr post-injection is not clinically useful (Fig. 6, 7).
3. The plasma pharmacokinetic parameters of iopamidol in fish are notably different from that of mammals, including a markedly prolonged half-life in fish (Fig. 8, Table 1).

Application

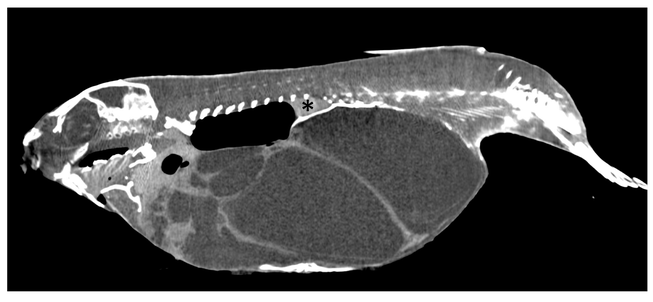


Figure 9. Contrast enhanced computed tomography of koi carp 5min post intravenous injection with iopamidol (480mgI/kg). There is a large cavitary gonadal mass, the non-cavitary portions of the mass are contrast enhancing. The CT was used to for surgical planning. The * denotes the left caudal kidney, the gas filled viscus cranial to this is the swim bladder, and the remainder of the imaged celom is filled with cavitary mass.

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