Pharmacokinetic appraisal of carprofen delivery from intra-articular nanoparticles: A population modeling approach in rabbits

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INTRODUCTION

Carprofen (CP) is a NSAID, used in veterinary medicine [1] as alternative to corticosteroidic management of osteoarthritis. Drug delivery to synovial fluid lining with the biophase improves local action and reduces systemic effects [2].

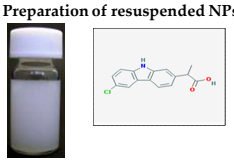
Drug uptake to the cartilage requires high synovial fluid concentrations but distribution towards bloodstream is rapidly achieved [3]. Nanoparticle formulations are promising [4] to extend the drug residence times, bioavailability and duration of effects [5].

PURPOSE

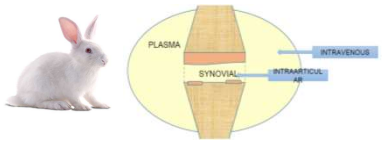
NPs-CP for intraarticular (IA) injection and an intravenous (IV) commercial formulation were administered in rabbits. Plasma pharmacokinetic (PK) profiles and joint levels were obtained. The PK parameters were obtained to compare both profiles.

METHODS

Preparation of resuspended NPs-CP



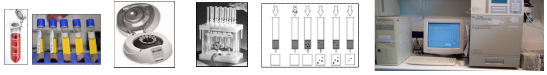
IA administration of NPs-CP in rabbit



Adult New Zeland rabbit. Weight: 3.76-3.94 kg.
1,98 mg/totals NPs-CP resuspended were administered

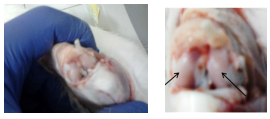
Analytical technique

Sampling
Extraction
HPLC



CP Solid-phase extraction in plasma samples was performed with Discovery® DSC-18 cartridges and Visiprep DL® vacuum manifold (Supelco).
Briefly, technics for extraction of CP: methanol: 1 mL, phosphoric acid: 1 mL, methanol 20%: 1 mL. CP is extracted in different phases. The eluted after is injected in HPLC.

Recovery of CP of joint



Obtaining joint tissue at the end of the experiment

Three different tissues: synovial liquid, femoral articular cartilage (both condyles) and meniscus tissue. Tissues were weighted and extracted (ultrasounds) 50 µl of every sample it is injected into the HPLC. (KH_2PO_4, $Na_2HPO_4.2H_2O$, methanol, H_3PO_4 85%)

Pharmacokinetic analysis

Individual PK parameters [6] were estimated using non-compartmental analysis. PK compartimental analysis was estimated by a population modeling approach. Allometric scaling of PK disposition parameters with weight allowed prediction to other species.

The in vivo CP input rate from the nanoformulation I(t) was calculated by numerical deconvolution [7] with Phoenix-WinNonlin® 64.8.2 Certara Inc).

RESULTS & DISCUSSION

The results obtained in tissue after injection IA are reflected in Table 1

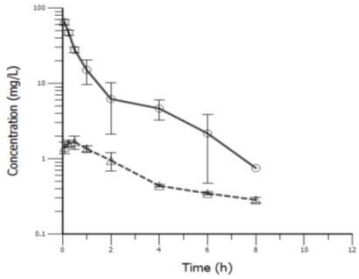
Table 1. Carprofen levels in articular tissues

Tissue Concentration	(µg/g) *
Cartilage	0.997
Meniscus	0.099
Synovial fluid	0.049
Plasma	0.3

The PK study results of the IV and IA injections are depicted in Table 2 .

Table 2. Pharmacokinetics parameters after injection IV and IA . Mean ± SD (n = 3).

PK Parameter	Intravenous	Intra-articular
λz *(h-1)*	0.3565 ± 0.1546	0.1892 ± 0.0436
t1/2λz *(h)*	2.16 ± 0.76	3.78 ± 0.78
AUC *(mg/L)·h*	65.03 ± 20.90	6.73 ± 0.38
AUC/D	4.24 ± 1.36	3.40 ± 0.19
AUCextrap (%)	4.18 ± 4.06	28.29 ± 2.92
CL *(L/h)*	0.2533 ± 0.0831	-
Vi *(L)*	0.2058 ± 0.0273	-
Vss *(L)*	0.4403 ± 0.0758	-
Vdarea *(L)*	0.7963 ± 0.414	-
Cmax *(mg/L)*	75.67 ± 12.40	1.84 ± 0.19
Cmax/D	4.93 ± 0.81	0.93 ± 0.96
Tmax *(h)*	-	0.25 (0.08-0.5)
F (%)	-	94.48 ± 27.83



Individual CP plasma concentration (mg/L) vs. time (h) profiles following IV and IA administration at the doses of 4 mg/kg and 1.98 mg were comparatively assessed.

Figure 2. Overlayed plasma profiles (upper: iv, lower: IA)

Acceptable levels of Goodness-of-fit for the population pharmacokinetic model were obtained and also for the individual model predictions (Figure 3)

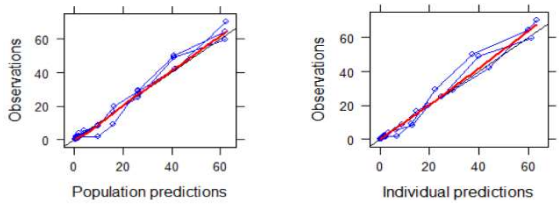


Figure 3. Superimposed values of the observed (OBS, open circles), individual predicted (IPRED, solid line) and population predicted (PRED, dashed lines) CP plasma concentrations (mg/L) vs. time (post-dosing time, h). Dashed line: identity line; Solid line: Smooth line indicating the general data trend.

Based on the population model, two absorption kinetics processes were found (slow and fast). Cartilage levels were 3-times higher than plasma levels at the end of the experiment.

Predicted CP clearance (1.99 L/h/ 70kg) was in agreement with results in healthy volunteers [8] (100 mg IV: 2.916 L/h). However, somewhat higher CL was predicted for 7.1-15.8 kg dogs (0.0447 vs. 0.01487 L/h·kg) and for 1.9-6.0 kg cats (0.058 vs 0.006 L/h/kg).

CONCLUSIONS

In vivo characterization of a new CP nanoformulation for IA administration has been performed in rabbits.

The pharmacokinetic profile was scalable to other species. The CP burst effect inside the joint space enhances its diffusion towards cartilage and plasma.

This rabbit model seems suitable for a predictive evaluation of the release enhancement of CP towards the biophase of arthritic diseases.

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