Irish Greyhound Board

Scientific Advisory Committee on Doping and Medication Control

# Opinion on Meloxicam

The Committee was requested in January 2016 to advise the Board on the threshold for meloxicam in greyhound urine which could affect the performance of greyhounds.

Following receipt of experimental information from Boehringer-Ingelheim, the authorisation holders for the original product containing meloxicam, and an examination of the available literature, a paper was prepared on the pharmacological threshold of meloxicam in plasma and urine in dogs. That paper is annexed to this opinion and formed the basis of the discussion by the Committee. The objective was to establish the levels in urine which would reflect the likely threshold in plasma/body tissues for pharmacological activity that could affect performance.

Following the discussion and further analysis the Committee agreed that the available data suggested a threshold for meloxicam in urine is between 0.006 and 0.03 µg/ml, that it would therefore be unsafe to take cases to the Control Committee at levels at or below 0.03 µg/ml, and that for risk management reasons the level should be set somewhat above that level. The level suggested was 0.04 µg/ml (otherwise described as 40 ng/ml).

Where positives samples are found at or about such a level, an examination of the creatinine level and of specific gravity of the urine should be considered with a view to determining whether in each case a referral is justified having regard to the degree of concentration of the urine involved.

Finally if further reliable date becomes available the Committee will re-examine its advice in this matter.

# Meloxicam – pharmacological threshold in plasma and urine in dogs

## Objective:

To establish the threshold value for meloxicam in greyhound urine which could affect the performance of greyhounds and to advise the IGB accordingly.

## Pharmacokinetics

In a study by Poulsen & Hörstermann (1999) the pharmacokinetics of meloxicam was examined in 6 dogs. Meloxicam was administered subcutaneously at a dose of 0.2 mg/kg bw the first day followed by a daily oral dose of 0.1 mg/kg bw during 14 days (Figure 1). Cmax was approximately 250 ng/ml and Cmin 150 ng/ml during the dosing period.

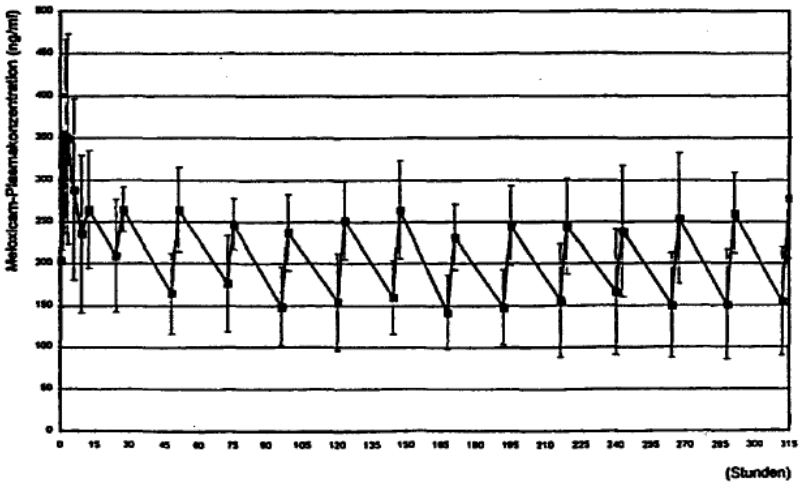


**Figure 1.** Meloxicam concentration in plasma after an initial dose 0.2 mg/kg bw subcutaneously followed by an oral maintenance dose of 0.1 mg/kg bw daily for 14 days (Poulsen & Hörstermann 1999)

The mean plasma concentration of meloxicam after the initial dose of 0.2 mg/kg bw is shown in Figure 2 and the calculated pharmacokinetic variables in Table 1. $C_{max}$ was 351 ng/ml and occurred after 2 hours. Elimination half-life was 20 h.

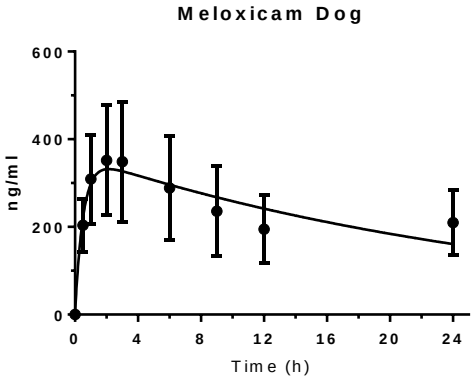


**Figure 2.** Mean plasma concentration of meloxicam after sc administration of 0.2 mg/kg bw (Poulsen & Höstermann, 1999)

**Tabel 1.** Pharmacokinetic variables of meloxicam from the study of Poulsen & Höstermann 1999. Calculations made by Friis

| | |
|---|---|
| FDV | 356,8 |
| Ka, h-1 | 1,922 |
| Ke, h-1 | 0,03393 |
| T½, h | 20.4 |
| Cmax, ng/ml | 351 |
| Tmax, h | 2 |
| AUC, µg/ml*h | 10.5 |
| Cl, l/h/kg | 0.019 |

In a recent study Less et al (2012) tested the bioavailability of a new oral spray formulation against reference product Metacam (Figure 3). Meloxicam was administered 2 mg to beagle dogs weighing 10.1-11.4 kg corresponding to a dose of 0.18 to 0.2 mg/kg bw. Half-life was calculated to approximately 30 h and AUC to 26.8 µg/ml*h. The bioavailability of meloxicam in the study by Lees et al. appears to be higher than in the study by Poulsen and Höstermann.

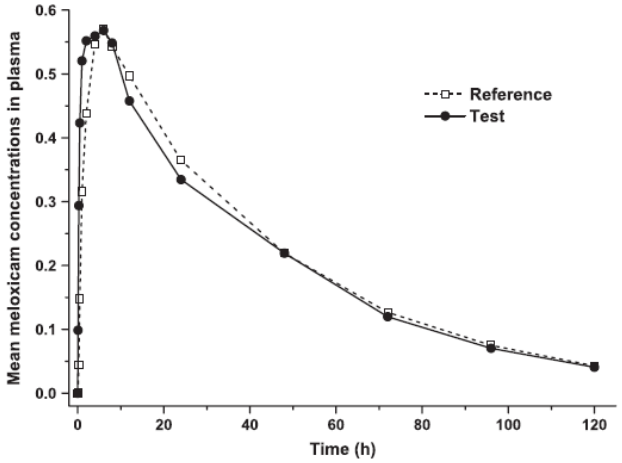


**Figure 3.** Mean meloxicam concentration after dosing a new spray formulation (test) vs conventional Metacam (Reference). Dose: 018-0.2 mg/kg bw PO

**Table 2**. Pharmacokinetic variables of meloxicam after oral dosing of 0.2 mg/kg bw to beagle dogs (Lees et al 2012)

| | Mean |
|---|---|
| Ke, h-1 | 0.0231 |
| T½, h | 30 |
| Cmax, ng/ml | 605 |
| Tmax, h | 6.5 |
| AUC, µg/ml*h | 27.66 |
| Cl, l/h/kg | 0.0072 |

## Excretion profile

*Boehringer Ingelheim* provided data one Beagle dog administered 14C meloxicam IV at a dose of 0.2 mg/kg bw. After 96 h 60% of the dose was found in faeces and 25% in urine (Table 3). No parent drug was identified in urine but only oxamic acid metabolites. Twenty per cent of the radioactivity was identified as parent compound in faeces.

Grude et al. (2010) has examined the excretion of meloxicam in cats. Data are presented in Table 3 and are almost similar to those of the dog except that unchanged meloxicam was found in urine in an amount corresponding to approximately one per cent of the dose.

**Table 3.** Excretion of meloxicam in a Beagle dog dosed 0.2 mg/kg bw intravenously. Data from cats (Grude et al, 2010) are inserted for comparison.

| | Dog (Boehringer Ingelheim) | | Cat (Grude et al, 2010) | |
|---|---|---|---|---|
| Dose | 0.2 mg/kg bw | | 0.75 mg/kg bw | |
| Time after administration | % dose in Urine | % dose in Faeces | % dose in Urine | % dose in Faeces |
| 24 | 10 | 10 | 6 (0.7)* | 29 (20)* |
| 48 | 18 | 26 | 11 (1.1)* | 47 (30)* |
| 72 | 22 | 40 | 15 | 56 |
| 96 | 25 (No parent) | 60 (12)* | 18 | 64 |

*parent compound

## Pharmacodynamics

In a study by Jeunesse et al (2011) a kaolin-induce paw inflammation model previously developed in cats was adapted to the dog. The paw inflammation developed within a few hours, reached maximum values 24 h and up to 3 days after kaolin administration, and then progressively resolved over 2 months. Five end-points of clinical interest (body temperature, creeping time under a tunnel, paw withdrawal latency to a standardized thermal stimulus, lameness score, and vertical force developed during walking on a force plate) were measured regularly over the next 24 h and beyond to characterize the time development of the inflammation either in control conditions (placebo period) or after the administration of meloxicam (test period) according to a crossover design. Pharmacodynamic data were modelled using an indirect response/pharmacokinetic pharmacodynamic model. This model described three effects of meloxicam, namely, classic anti-inflammatory, analgesic, and antipyretic effects. The mean plasma meloxicam IC50 values were 210 ng/ml for the antipyretic effect; 390 ng/ml for the analgesic effect; and 546 ng/ml for the vertical force exerted by the paw on the ground as measured by force plates. These in vivo IC50 values require approximately 80 (antipyretic effect) to 90% (all other effects) cyclooxygenase-2 inhibition as calculated ex vivo whole-blood assay data.

## Rationale to establish a plasma threshold value for no-pharmacological effect of meloxicam

The lowest IC50 value is established for the antipyretic effect of meloxicam, 210 ng/ml. Since there is a large variation between dogs, it will be reasonable to introduce a safety factor of 10. Plasma

threshold of meloxicam can consequently be established to 20 ng/ml which is above the LoQ of the the LC/MS/MS method (Lees et al, 2012). After a single dose of 0.2 mg/kg bw sc 20 ng/ml in plasma will be reached after approximately 96 hours (Figure 4). After repeated doses of 0.1 mg/kg bw 20 ng will be reached after approximately 84 h.

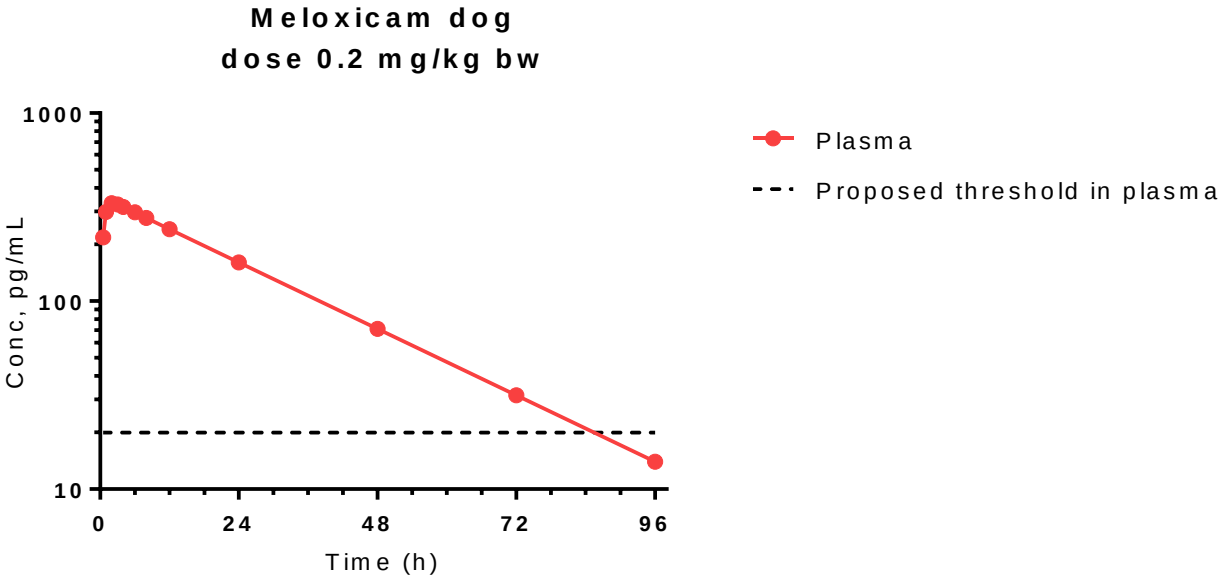


**Figure 4**

## Rationale to establish a urinary threshold value for no-pharmacological effect of meloxicam

Based on the provided data meloxicam is not excreted unchanged in urine in the dog, but approximately 25% of a dose is recovered as oxamic acid metabolites. The metabolites have not been identified further and therefore no marker can be established.

Between 72 and 96 hours after dosing only 3% of the dose is excreted (Table 3). This is equivalent to 0.2 mg/kg*0.03=6 µg/kg/day. According to Merck urine production is 20-100 ml/kg/day in dogs. In the excretion study dogs weighing 27-36 kg. Accordingly concentration of meloxicam metabolites range between 0.3 and 0.06 µg/ml urine (Table 4). No parent meloxicam has been identified in the urine. In cats urinary excretion is similar to that in dog but in cats approximately one tenth of the excreted amount is unchanged meloxicam (Grude et al, 2010).

**Tabel 4**

| Diuresis, ml/kg/day | Body Weight | Metabolites of meloxicam in urine, µg/ml |
|---|---|---|
| 20 | 27 | 0.3 |
| 100 | 36 | 0.06 |

Accepting that one tenth of the excreted dose in urine is present as unchanged drug a pharmacological threshold for meloxicam in urine is between 0.006 and 0.03 µg/ml.

# References

Poulsen & Hörstermann (1999)

Lees, P., Cheng, Z., Keefe, T. J., Weich, E., Bryd, J., Cedergren, R., Cozzi, E. Bioequivalence in dogs of a meloxicam formulation administered as a transmucosal oral mist with an orally administered pioneer suspension product. J. vet. Pharmacol. Therap. 36, 78–84. 2012

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Grude et al. (2010) Grude´, P., Guittard, J., Garcia, C., Daoulas, I., Thoulon, F., Ebner, T. Excretion mass balance evaluation, metabolite profile analysis and metabolite identification in plasma and excreta after oral administration of [14C]-meloxicam to the male cat: preliminary study. J. vet. Pharmacol. Therap. 33, 396–407. 2010

E. C. Jeunesse, I. A. Bargues, C. E. Toutain, M. Z. Lacroix, I. M. Letellier, J. M. Giraudel, and P. L. Toutain: Paw Inflammation Model in Dogs for Preclinical Pharmacokinetic/Pharmacodynamic Investigations of Nonsteroidal Anti-Inflammatory Drugs, J Pharmacol Exp Therapeutics 338:548–558, 2011

Merck