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Flunixin meglumine accelerates uterine involution and shortens the calving-to-first-oestrus interval in cows with puerperal metritis

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The normal uterine involution process involves the expulsion of lochia and the reduction of uterine size. These are achieved through increased uterine contractility caused by sustained high concentrations of prostaglandin $F_{2\alpha}$ (Kindahl *et al.*, 1984). Flunixin meglumine is a potent non-steroidal anti-inflammatory drug, reducing the biosynthesis of prostaglandin $F_{2\alpha}$ through the inhibition of cyclo-oxygenase enzymes in the arachidonic acid cascade; it is licenced (FINADYNE®; Schering-Plough Animal Health, Omaha, NB, USA) for administration to cattle.

Puerperal diseases, such as postparturient metritis – a severe and occasionally life-threatening infection of the uterus, usually occurring within 7 days *postpartum* – have for long been associated with serious delays of uterine involution, leading to a retarded resumption of ovarian activity. Consequently, the fertility of the cow is adversely affected (Morrow, 1969; Fonseca *et al.*, 1983; Hussain & Daniel, 1991).

The objectives of this multicentric field trial were to evaluate the effects of flunixin in the supportive treatment of postparturient bovine metritis and to assess whether the drug would interfere with the subsequent reproductive ability of the animals.

The study was carried out from 1997 to 2000, in 21 dairy farms in northern and central Greece. In total, 259 cows with puerperal metritis were included in the study. These animals, 5–8 days *postpartum*, had a red to brownish, watery or purulent, fetid uterine discharge, fever, reduced appetite, reduced ruminal movements and reduced milk production. Metritis was considered acute ($n = 68$), when the animals were febrile (40.5–41.5 °C), completely off-feed, depressed and with tachycardia, ruminal stasis, diarrhoea, dehydration and minimal milk production. It was considered subacute ($n = 191$), when cows were moderately pyrexic (39.5–40.4 °C), with reduced appetite, ruminal movements and milk production.

All animals entered into the study were intravenously given a broad-spectrum antimicrobial agents' combination. This consisted of long-acting oxytetracycline (ENGEMYCIN™, Intervet (Boxmeer, the Netherlands); dosage: 14 mg/kg on two occasions every 48 h) and a sulphadoxine–trimethoprim combination (DUOPRIM®, Schering-Plough Animal Health; dosage: 15 mg/kg on three occasions every 24 h). The clinical experience of the authors in Greek dairy farms has shown this to be appropriate for the treatment of intrauterine infections. Supportive fluid therapy included intravenous administration of 500 mL 35% dextrose and 3–5 L of Ringer's solution to every cow.

Animals were randomly (by the toss of a coin) allocated into one of two treatment groups. Group A ($n = 128$) cows were intravenously treated with flunixin, at a dosage of 2.2 mg/kg, on six occasions (twice daily on the first 2 days and once daily for the subsequent two). Group B ($n = 131$) cows were controls and received a placebo treatment (15 mL saline 0.9%).

After treatment, rectal temperature was measured every 12 h and until the cow was afebrile. Thirty days *postpartum* the genital system of every cow in the study was examined by rectal palpation, carried out by the principal author, who at the time was unaware of the treatment given to each cow examined. Subsequently, this examination was repeated every 15 days and up to the ninetieth day *postpartum*. Uterine involution was considered complete when the uterine horns were found almost symmetrical and the entire uterus was found positioned into or at the edge of the pelvic cavity. To confirm this, two examinations (initial on the day when complete involution was first considered, subsequently 1 week later) were carried out by means of an ultrasound scanner, with which various measurements of cornual diameter were performed; if no difference in cornual diameter was evident in these examinations, complete involution was confirmed.

During the postparturient period, oestrus detection was carried out by the farmer, by observing the cows twice daily for signs of oestrus. The date when the first oestrus after calving was detected by the farmer, was recorded and the calving-to-first-detected-oestrus interval was calculated.

The effect of flunixin administration on the likelihood of fever 24 h after initiation of treatment and on the likelihood of complete uterine involution until 60, 75 and 90 days after initiation of treatment was investigated in four multiple logistic regression models, respectively. Also, its effect on the mean calving-to-first-detected-oestrus interval was investigated in a

generalized linear model. The acute or subacute nature of metritis was included in the models as a likely confounder or effect modifier. The farm of origin was included in the models as a random effect variable. Hence each model consisted of two fixed-effect variables, the treatment status and the nature of metritis, and a random effect coding for the herd of origin. Model fitting was performed in SAS v.8e GLIMMIX macro and PROC MIXED (Statistical Analysis Systems, 2000). Significance of the treatment effect or of the modification of the treatment effect by the nature of metritis (i.e. the interaction between treatment and nature of metritis) was evaluated by the *F*-test (Littell *et al.*, 1999) and assessed at the 5% or the 10% level of significance, respectively.

One day after initiation of treatment, 124 (97%) group A cows and 105 (80%) group B cows were afebrile. The odds of fever 24 h after initiation of treatment were 10 times lower ($P < 0.0001$) in cows treated with flunixin than in controls. This effect was not modified by the acute or subacute nature of metritis.

In no case was complete uterine involution recorded before 30 days *postpartum*, whilst four (3%) treated and 10 (7%) control cows did not have uterine involution by 90 days *postpartum*. Results for complete uterine involution and calving-to-first-detected-oestrus interval are in Table 1. Animals treated with flunixin were 4.3 ($P = 0.001$), 2.6 ($P = 0.0002$) and 2.7 ($P = 0.04$) times more likely to have uterine involution until 60, 75 and 90 days *postpartum*, respectively, than controls. This effect was independent of the acute or subacute nature of metritis. Also, flunixin-treated cows showed oestrus 7.3 days earlier ($P = 0.0002$) than controls.

The clinical signs recorded suggest that all cows entered into the study, suffered an endotoxaemia of varying degree. Broad-spectrum antimicrobial therapy was given in order to treat the infection, whilst supportive fluid therapy was necessary to avoid dehydration and to prevent ketosis, which are common sequellae of such cases. Cows treated with flunixin had an earlier decrease of rectal temperature and more rapid clinical improvement than controls. These findings are consistent with the antipyretic, anti-inflammatory and antitoxic properties of flunixin. In cattle, flunixin reduces the plasma concentration of thromboxane B_2 and prostaglandin E_2 and thus, is effective against inflammatory response to endotoxins (Anderson & Hunt, 1989; Espinasse *et al.*, 1994; Odensvik & Magnusson, 1996).

The process of normal uterine involution is usually completed within 4–5 weeks *postpartum* and is associated with a massive and sustained release of prostaglandin $F_{2\alpha}$ (Morrow, 1969; Okano & Tomizuka, 1987; Zain *et al.*, 1995). One may therefore postulate that administration of flunixin, although beneficial in reducing the clinical signs, could also hinder the involution process and the subsequent reproductive performance of cows, as it also reduces to some extent the release of prostaglandin $F_{2\alpha}$. The finding that flunixin is a non-selective cyclo-oxygenase inhibitor (Landoni *et al.*, 1995) would lend further support to that argument.

This apparently reasonable hypothesis was not confirmed by the findings of the reproductive performance (uterine involution data and calving-to-first-observed-oestrus interval). No adverse effects of flunixin on the process of uterine involution and subsequent ovarian resumption were found. In fact, flunixin-treated cows had a faster uterine involution than controls and showed the first *postpartum* oestrus earlier than controls. We may therefore postulate that either the minimal prostaglandin $F_{2\alpha}$ concentration after flunixin administration is sufficient to sustain involution or alternatively, the 4-day administration of the drug is not long enough to interfere with the involution process, but still capable to reduce inflammatory reaction. It has been reported that in healthy cows, the suppressive anti-prostaglandin effect of flunixin is maximal 4 h after administration and lasts approximately for 8 h. During this period prostaglandin concentration decreases by more than 80%, but is never completely suppressed (Thun *et al.*, 1993). In addition, Odensvik and Fredriksson (1993) found that in healthy cows uterine involution is not compromised by flunixin, even when repeated daily administration is applied for a prolonged time period.

Therefore, as the suppression of prostaglandin is short-term (in our case it could not have lasted after the thirteenth day *postpartum*), an adverse effect on the interaction of prostaglandin with luteal function and progesterone concentration, which is important in the resumption of cyclical ovarian activity and takes place approximately 3 weeks after calving (King, 1993), is unlikely.

Table 1. Proportions of cows with complete uterine involution and calving-to-first-detected-oestrus interval of 259 dairy cows with purperal metritis

	Cows (*n*), with uterine involution completed until			Mean calving-to-first-detected-oestrus interval (days)
	60 days *p-p*	75 days *p-p*	90 days *p-p*	
Group A cows				
With acute metritis ($n = 36$)	4 (11%)	21 (58%)	35 (97%)	69.3 ± 12.7
With subacute metritis ($n = 92$)	14 (15%)	71 (77%)	89 (97%)	61.2 ± 16.0
Group B cows				
With acute metritis ($n = 32$)	1 (3%)	15 (47%)	29 (91%)	78.8 ± 17.2
With subacute metritis ($n = 99$)	4 (4%)	50 (51%)	92 (93%)	68.3 ± 16.6

p-p: *Postpartum*, ± refers to standard deviation.

In animals treated with flunixin, oestrus was detected earlier than in controls. This delay in ovarian resumption could be explained by the fact that *postpartum* infections either suppress the hypothalamic secretion of gonadotrophin releasing hormone causing retarded follicular development (Bosu *et al.*, 1988) or distract a neuronal opioid system, which partially regulates the release of luteinizing hormone (Dobrinski *et al.*, 1991).

REFERENCES

Anderson, K.L. & Hunt, E. (1989) Anti-inflammatory therapy in acute endotoxin-induced bovine mastitis. *Veterinary Research Communications*, **13,** 17–26.

Bosu, W.T.K., Peter, A.T. & DeDecker, R.J. (1988) Short term changes in serum luteinizing hormone, ovarian response and reproductive performance following gonadotropin releasing hormone treatment in postpartum dairy cows with retained placenta. *Canadian Journal of Veterinary Research*, **52,** 165–171.

Dobrinski, V.I., Aurich, J.E., Grunert, E. & Hoppen, H.O. (1991) Endogenous opioid peptides in cattle during pregnancy, parturition and the neonatal period. *Deutsche Tierarztlichte Wochenschrift*, **98,** 205–226.

Espinasse, J., Thouvenot, J.P., Dalle, S., Garcia, J., Schelcher, F., Salat, O., Valarcher, J.F. & Daval, S. (1994) Comparative study of the action of flunixin meglumine and tolfenamic acid on prostaglandin E2 synthesis in bovine inflamatory exudate. *Journal of Veterinary Pharmacology and Therapeutics*, **17,** 271–274.

Fonseca, F.A., Britt, J.H., McDaniel, B.T., Wilk, J.C. & Rakes, A.H. (1983) Reproductive traits of Holsteins and Jerseys: effects of age, milk yield, and clinical abnormalities on involution of cervix and uterus, ovulation, estrus cycles, detection of estrus, conception rate and days open. *Journal of Dairy Science*, **66,** 1128–1147.

Hussain, A.M. & Daniel, R.C.W. (1991) Bovine endometritis: current and future alternative therapy. *Journal of Veterinary Medicine A*, **38,** 641–651.

Kindahl, H., Fredricksson, G., Madej, A. & Edqvist, L.E. (1984) Role of prostaglandins in uterine involution. *Proceedings of the 10th International Congress on Animal Reproduction and Artificial Insemination (1984)*, Vol. IX. Urbana, USA.

King, G.J. (1993) Reproductive performance and problems. In *Reproduction in Domesticated Animals*. Ed. King, G.J. pp. 531–565. Elsevier, Amsterdam.

Landoni, M.F., Cunningham, F.M. & Lees, P. (1995) Determination of pharmacokinetics and pharmacodynamics of flunixin in calves by use of pharmacokinetic/pharmacodynamic modeling. *American Journal of Veterinary Research*, **56,** 786–794.

Littell, R.C., Milliken, G.A., Stroup, W.W. & Wolfinger, R.D. (1999) *SAS System for Mixed Models*. SAS Institute, Cary, NC.

Morrow, D.A. (1969) Postpartum ovarian activity and involution of the uterus and cervix in dairy cattle. *Veterinary Scope*, **14,** 2–24.

Odensvik, K. & Fredriksson, G. (1993) The effect of intensive flunixin treatment during the postpartum period in the bovine. *Journal of Veterinary Medicine A*, **40,** 561–568.

Odensvik, K. & Magnusson, U. (1996) Effect of oral administration of flunixin meglumine on the inflammatory response to endotoxin in heifers. *American Journal of Veterinary Research*, **57,** 201–204.

Okano, A. & Tomizuka, T. (1987) Ultrasonic observation of postpartum uterine involution in the cow. *Theriogenology*, **27,** 369–376.

Statistical Analysis Systems (2000) *SAS Release 8e*. SAS Institute, Cary, NC.

Thun, R., Kunding, H., Zerobin, K., Kindahl, H., Gustafsson, B.K. & Ziegler, W. (1993) [Uterine motility of cattle during late pregnancy, labor and puerperium. III. Use of flunixin meglumine and endocrine changes] (De). *Schweizer Archiv Tierheilkunde*, **135,** 333–344.

Zain, A.E.D., Nakao, T., Raouf, M.A., Moriyoshi, M., Kawata, K. & Moritsu, Y. (1995) Factors in the resumption of ovarian activity and uterine involution in postpartum dairy cows. *Animal Reproduction Science*, **38,** 203–214.