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Brief Communication

Effect of Flunixin Meglumine on the Endocrine Control of Luteolysis in the Porcine Estrous Cycle

The endocrine control of the estrous cycle in the pig has been in the scope of interest of animal reproduction physiologists for a long time. It is established that in sows prostaglandin $F_{2\alpha}$ is luteolytic and that the periodic corpora lutea are brought to regression by series of pulsatile $PGF_{2\alpha}$ release from the uterus during days 13-18 of the estrous cycle. However, attempts to control the luteolysis by injections of prostaglandins have not been successful. This makes the sow unsuitable for hormonal synchronization of estrus for fertilization as is routinely used in e.g. cows.

Flunixin meglumine (Banamine, Finadyne) is a nonsteroidal antiinflammatory drug (NSAID) based on inhibition of synthesis of inflammatory mediators in tissues. $PGF_{2\alpha}$ is among the prostaglandins the synthesis of which flunixin meglumine prevents by inhibition of cyclooxygenase oxidation of arachidonic acid (*Odensvik et al.* 1989). In pregnant gilts flunixin meglumine prevented abortion by inhibition of endotoxin-induced $PGF_{2\alpha}$ release (*Cort & Kindahl* 1990). The purpose of the present study was to test the effect of flunixin meglumine on the luteolytic system of the estrous cycle in gilts.

Five sexually mature crossbred gilts were used. Permanent jugular vein catheters were surgically inserted under general anesthesia (*Rodriguez-Martinez & Kunavongkrit* 1983). At least 1 normal estrous cycle was followed and the first day of the standing reflex set equal to day 1 of the experimental cycle. Flunixin meglumine (FM) (Finadyne, Schering-Plough Corp., Kenilworth, N.J., USA) in dose 1 mg/kg body weight was applied intravenously in different time schedules. The frequency varied between single doses on 1 or several days 8, 10, 12, 14 and an intensive schedule of injections every 6th h between days 14 and 20. Blood samples for hormone analysis were collected in intervals varying between 12 and 2 h. The plasma concentrations of progesterone (*Kunavongkrit et al.* 1983) and 15-keto-13, 14- dihydro-$PGF_{2\alpha}$ ($PGF_{2\alpha}$ metabolite) (*Granström & Kindahl* 1982) were analysed by radioimmunoassay.

The injections of FM caused no clinical response. The plasma concentrations of progesterone in all gilts followed a uniform, stable pattern, rising from below 5 nmol/l during estrus to maximum levels during early diestrus and finally descending to low levels between days 13 and 18 of the cycle. The plasma metabolite of $PGF_{2\alpha}$ maintained concentrations below 1000 pmol/l (base level) from the beginning of the estrous cycle (Fig. 1). Injection of FM immediately decreased the base level of the metabolite to the detection limit of the assay. After a single dose the metabolite concentration returned to base line within 18-24 h (not shown). After days 12-13 of the cycle the metabolite response to FM became more indi-

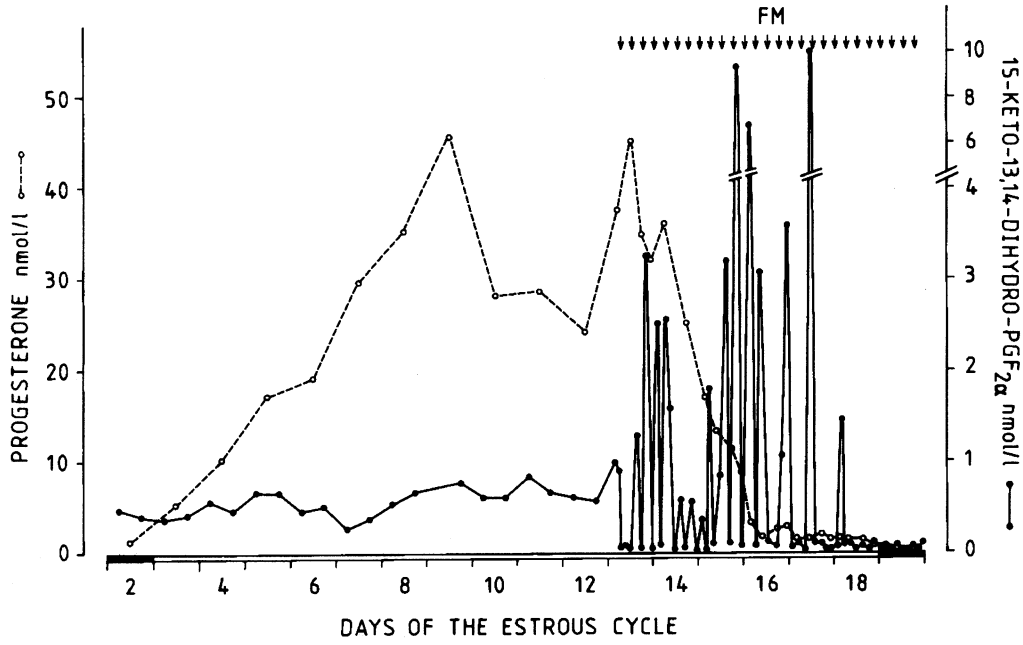

Figure 1: The plasma concentrations of progesterone and 15-keto-13, 14-dihydro-$PGF_{2\alpha}$ in responce to treatment with flunixin meglumine (FM) during an estrous cycle. The black bars illustrate estrus.

vidual and irregular due to the pulsatile release of the endogenous $PGF_{2\alpha}$ during luteolysis. Independent of the intensity of treatment by FM, the decreased base levels of the $PGF_{2\alpha}$ metabolite still broke away with series of pulses of various frequency, duration and intensity. The situation is illustrated by the metabolite pattern in gilt 5 (Fig. 1) where the frequency and intensity of the pulsatile hormone pattern seemed totally unaffected by the prostaglandin synthesis inhibitor. All of the gilts returned to oestrus at 18-22 days of the cycle.

The clinical and endocrine course of the estrus cycle in gilts was not affected by the attempt to inhibit the synthesis of $PGF_{2\alpha}$. Under normal circumstances, even base levels of the $PGF_{2\alpha}$ metabolite are believed to be elevated during luteolysis. In the present study the pulsatile release of $PGF_{2\alpha}$ seemed to proceed with unimpaired intensity despite the base levels being decreased. The character of the metabolite pattern during luteolysis appears to be very individual which may largely depend on the fact that the graphic appearance of the hormonal pattern is dependent on the regime of the sampling.

A similar experiment in heifers resulted in a depression of the $PGF_{2\alpha}$ metabolite concentrations and a prolonged estrous cycle *(Aiumlamai et al.* 1990).

The results of the present study seem to conform with the theory that luteolysis in the estrous cycle in the pig is not controlled by the total concentration of PGF2a as much as by a certain number, frequency and intensity of the pulsatile hormone release which for a still unsolved reason does not let itself be inhibited by prostaglandin synthesis inhibitors such as flunixin meglumine.

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