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THE USE OF SYNTHETIC ANALOGUES OF PROSTAGLANDINS FOR INDUCING LUTEOLYSIS IN MARES

W. R. ALLEN and M. J. COOPER*

*A. R. C., Unit of Reproductive Physiology and Biochemistry,
Animal Research Station, 307 Huntingdon Road,
Cambridge CB3 0JQ, U. K.*

** I. C. I., Pharmaceuticals Division, Alderley Park,
Macclesfield, Cheshire SK10 4TG, U. K.*

SUMMARY

The potency, toxicity and clinical value of two synthetic analogues of Prostaglandin $F_{2\alpha}$ (ICI-79939 and ICI-81008) for inducing luteolysis in mares is discussed. Measurement of peripheral plasma progestagen levels in over 400 Thoroughbred mares has demonstrated that abnormal persistence of luteal function (prolonged dioestrus) is the major cause of the failure of non-pregnant mares to exhibit regular oestrous cycles during the breeding season. Results of the clinical use of ICI-81008 (« Equimate ») for inducing oestrus and ovulation in Thoroughbred mares in prolonged dioestrus in both the Northern and Southern hemispheres are presented.

INTRODUCTION

The mare is a seasonally polyoestrous animal with a distinct breeding season during the spring and summer months (MARSHALL, 1936). Post-mortem examination of large numbers of reproductive tracts of mares has shown that the peak of ovarian activity occurs in July in the northern hemisphere (ARTHUR, 1958) and January in the southern hemisphere (OSBORNE, 1966). However, the breeding season for Thoroughbred horses is restricted in length, and in both halves of the world a sizeable proportion of this arbitrarily delineated mating period lies outside the natural breeding season of the mare.

Reduction in the number of opportunities for advantageous mating of mares to selected stallions due to the failure of individual mares to exhibit regular oestrous cycles within the confines of the covering season, contributes significantly to the low national foaling averages in Thoroughbreds. Non-pregnant mares which are

not exhibiting oestrus may be in anoestrus, where pituitary gland inactivity results in ovarian inactivity, or in dioestrus, where progesterone secreted by an active corpus luteum (CL) suppresses the release of pituitary gonadotrophins.

HUGHES, STABENFELDT and EVANS (1972) demonstrated that varying periods of prolonged luteal function occur spontaneously in many mares and ALLEN and ROSSDALE (1973) and ALLEN *et al.*, (1974) have shown that abnormal persistence of function of the CL (« prolonged dioestrus ») is the most common cause of the failure of non-pregnant Thoroughbred mares to exhibit oestrus during the breeding season. For this reason, a safe, simple and effective method for inducing luteolysis in mares in prolonged dioestrus is desirable in equine veterinary practice.

CONTROL OF THE MARE'S OESTROUS CYCLE WITH PROSTAGLANDINS

DOUGLAS and GINTHER (1972) first examined the luteolytic action of $\text{PGF}_{2\alpha}$ in mares and observed a significant reduction in the length of dioestrus in pony mares given a single subcutaneous (s/c) injection of 1.25-10 mg $\text{PGF}_{2\alpha}$ on the 6th day after ovulation. OXENDER, NODEN and HAFS (1975) similarly found that mares given a single s/c injection of 2-10 mg $\text{PGF}_{2\alpha}$ between the 7th and 9th days after ovulation returned to oestrus within four days. These authors noted that levels of luteinizing hormone (LH), oestrone and oestradiol-17 β in the plasma of mares during the oestrus following $\text{PGF}_{2\alpha}$ treatment were similar to the levels of these hormones measured in mares during a naturally occurring oestrus.

ALLEN and ROWSON (1973) and ALLEN *et al.* (1974) studied the luteolytic activity in pony and Thoroughbred mares of two synthetic prostaglandin analogues structurally related to $\text{PGF}_{2\alpha}$. These two compounds, ICI-79939 and ICI-81008 (BINDER *et al.*, 1974) have been shown to exhibit over two hundred times the potency of $\text{PGF}_{2\alpha}$ in the hamster and rat (WALPOLE, 1973), and both have proved to be

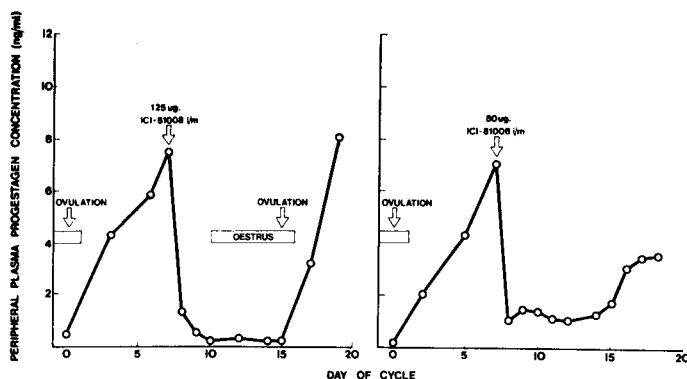


FIG. 1. — Peripheral plasma prostaglandin concentrations in a Welsh Pony mare before and after administration on the 7th day of dioestrus of (a) an effective luteolytic dose of 125 ug ICI-81008 and (b) an incompletely luteolytic dose of 80 ug ICI-81008 (i/m = intramuscular injection) (ALLEN *et al.*, 1974).

extremely effective luteolytic agents in the mare when given as a single dose by either the intrauterine (i/u) or intramuscular (i/m) route. As little as 80 μg ICI-79939 and 125 μg ICI-81008 in the pony and 150 μg ICI-79939 and 250 μg ICI-81008 in the Thoroughbred, given between the 4th and 13th days of dioestrus, consistently induces complete luteolysis and a return to oestrus 2 to 4 days later (fig. 1). ALLEN and ROWSON (1973) demonstrated that complete luteolysis was not induced in mares given ICI-79939 prior to the 4th day of dioestrus (ovulation = Day 0) indicating that, as in cattle (ROWSON, TERVIT and BRAND, 1972), the CL of the mare is refractory to the action of luteolytic agents until it is approximately four days of age (fig. 2). OXENDER, NODEN and HAFS (1975) and DOUGLAS and GINTHER (1975)

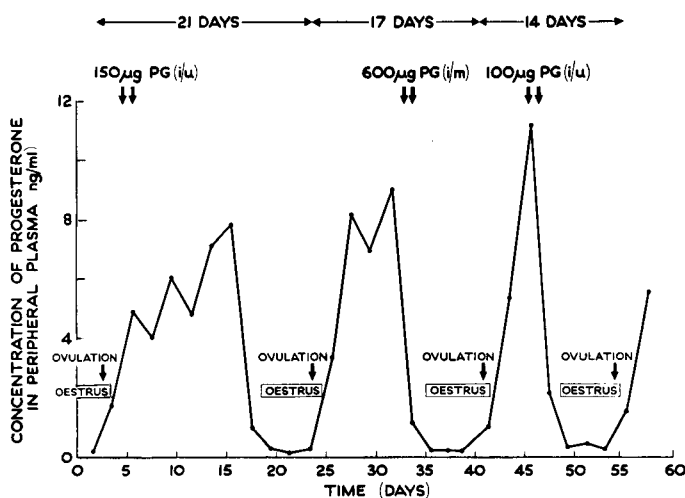


FIG. 2. — Peripheral plasma progesterone concentrations in a Welsh Pony mare treated with ICI-79939 in three consecutive oestrous cycles. Treatment with 150 μg ICI-79939 i/u on the 2nd and 3rd days of dioestrus of the first cycle failed to induce luteolysis and cycle length was normal. However, treatment with 600 μg i/m on the 9th and 10th days of dioestrus and 100 μg i/u on the 5th and 6th days of dioestrus of the second and third cycles respectively, resulted in complete luteolysis followed by a return to oestrus (i/u = intrauterine infusion; i/m = intramuscular injection) (ALLEN and ROWSON, 1973).

have similarly shown that $\text{PGF}_{2\alpha}$ will not induce luteolysis in mares until after the 4th day post ovulation.

Onset of oestrus was well synchronized in mares given ICI-79939 or ICI-81008 with over 70 p. 100 of animals showing oestrus on the 3rd day after treatment and the remainder showing oestrus on the 2nd or 4th days (fig. 3). Ovulation was less well synchronized however and occurred between 7 and 12 days after treatment with a peak on Day 10 (ALLEN and ROWSON, 1973). A marked variation exists between individual mares in the length of time spent in oestrus, and season also exerts a pronounced effect upon this interval. Ovulation normally occurs in mares 24–48 hours prior to the end of oestrus (Day, 1939) and 24–36 hours after an i/m or intravenous (i/v) injection of 3 000–6 000 IU HCG (LOY and HUGHES, 1966). Thus, the « spread of ovulation » which occurs in groups of mares after the induction of oestrus with prostaglandins could be greatly reduced by the concurrent use of HCG or a similar ovulating hormone.

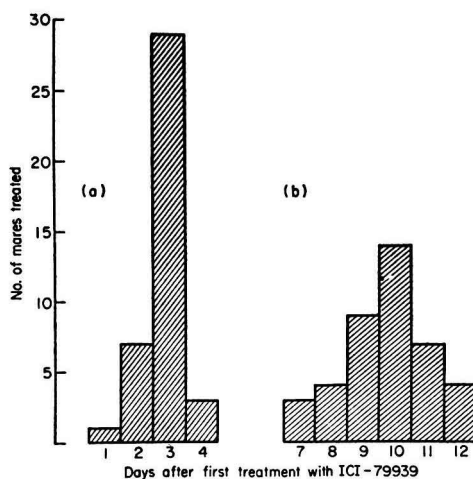


FIG. 3. — Synchronization of oestrus and ovulation in a group of Welsh Pony mares treated with ICI-79939 on two consecutive days between the 4th and 13th days of dioestrus. (a) : Interval between first day of treatment and onset of oestrus. (b) : Interval between first day of treatment and ovulation (ALLEN and ROWSON, 1973).

SIDE-EFFECTS OF PROSTAGLANDINS IN THE MARE

Natural $\text{PGF}_{2\alpha}$ and some synthetic analogues of $\text{PGF}_{2\alpha}$ possess powerful smooth muscle stimulating properties as a result of which they induce a variety of untoward side-effects in the mare. These include profuse sweating on the neck, thorax and ventral abdominal regions of the body, hypermotility of the gastro-intestinal tract, watery diarrhoea, increased rates of pulse and respiration and varying degrees of

TABLEAU I

Adverse side-effects observed in pony mares given high doses of ICI-81008

Number of mares treated	Dose of ICI-81008 given i/m (μg)	Clinical changes
6	250	nil
2	500	nil
9	750	3 mares, very mild sweating
7	1 000	6 mares, very mild sweating
4	1 500	2 mares, mild sweating
		2 mares, no change
5	2 000	3 mares, mild sweating
		1 mare, profuse sweating, and some diarrhoea
		1 mare, no change
3	4 000	3 mares, profuse sweating
		1 mare, diarrhoea and mild colic

abdominal pain and depression. The symptoms are dose dependent and they appear suddenly and are most severe 18-25 min after i/m injection of the compound. They gradually decrease thereafter and have usually disappeared within 2-4 hours.

FRANK (1973) and others have observed profuse sweating and gastro-intestinal hypermotility in Thoroughbred mares given 5 mg PGF_{2α} and ALLEN and ROWSON (1973) observed similar side-effects in Welsh Pony and Thoroughbred mares given ICI-79939 at a dose level of only 150 µg in ponies and 250 µg in Thoroughbreds. With ICI-81008 on the other hand, ALLEN *et al.*, (1974) observed only mild sweating in ponies given a dose of eight times the minimal luteolytic dose of this compound and even with doses as high as thirty-two times the minimal effective luteolytic dose, the side-effects were relatively mild and short-lived (table 1). Thus although ICI-81008 is only slightly less potent than ICI-79939 as a luteolytic agent in the mare, it is a great deal less toxic in many respects.

INDUCTION OF OESTRUS IN NON-CYCLING THOROUGHbred MARES WITH PROSTAGLANDIN ANALOGUES

ALLEN and ROSSDALE (1973) and ALLEN *et al.*, (1974) observed that prolonged dioestrus is the single biggest cause of the failure of non-pregnant mares to exhibit regular oestrous cycles during the spring and summer months. In an extensive survey of Thoroughbred mares in the Newmarket area, conducted between April and July during the 1972 and 1973 breeding seasons, no fewer than 93 p. 100 of the 362 non-pregnant, non-cycling mares examined were found to be in prolonged dioestrus. Diagnosis of the condition was based upon the clinical history that the mare was not pregnant, had not exhibited oestrus during the preceding 28 days and showed a concentration of > 1 ng progesterone/ml plasma in the peripheral blood. The mares fell into four main categories :

- (i) Mares which had resorbed or aborted their conceptus during the first 100-days of gestation.
- (ii) Mares which had not returned to oestrus after mating but which were found to be empty when examined manually for pregnancy at 19-45 days after service.
- (iii) Foaling mares which were not covered at the « foal heat » and subsequently failed to return to oestrus.
- (iv) Barren and maiden mares which were not showing regular oestrous cycles.

The results of treating a total of 207 Thoroughbred mares in one or other of the above categories with ICI-81008 or ICI-79939 are shown in table 2. Complete luteolysis with a return to oestrus followed by ovulation occurred in 91 p. 100 of the treated mares and of the 171 animals which were mated during the induced oestrus, 43 p. 100 conceived to this service. This conception rate was considered entirely satisfactory in view of the fact that many of the treated mares had very bad breeding histories and it confirmed earlier findings in pony mares that the ovulation which follows treatment with prostaglandin analogues is no less fertile than a naturally occurring ovulation.

TABLEAU 2

Treatment of non-cycling Thoroughbred mares with ICI-81008 and ICI-79939 (U. K. 1973)

Prostaglandin analogue	Number of mares treated	Number which returned to oestrus and ovulated	Number mated during induced oestrus	Number for which subsequent history known	Number pregnant from mating during induced oestrus
ICI-81008	63	55	52	45	18 (40 %)
ICI-79939	144	134	119	110	51 (46 %)

Further extensive clinical trials upon the efficacy of a single i/m injection of 250 µg ICI-81008 (« Equimate ») for inducing oestrus in noncycling Thoroughbred mares at stud, were conducted in Australia and New Zealand during the 1973-74 southern hemisphere breeding season (SHEPHERD and FINDLAY, 1974; BERWYN-JONES and IRVINE, 1974). It was not possible to measure peripheral plasma progesteragen concentrations in these trials so that the selection of mares suitable for treatment (*i.e.* in prolonged dioestrus) was based entirely upon oestrous history and clinical examination of the ovaries and cervix. The mares were classified simply as barren, maiden or lactating and all were known to be non-pregnant and had not displayed oestrus during the preceding 28 days or longer. Of the total of 448 mares treated with ICI-81008, 359 (80p. 100) showed oestrus within five days after treatment and subsequently ovulated normally. The majority of mares were covered and of the 261 mares for which results are known, 121 (46 p. 100) conceived to service during the induced oestrus (table 3).

TABLEAU 3

Treatment of non-cycling Thoroughbred mares with ICI-81008
 (« Equimate ») Australasia 1973-74 ⁽¹⁾

Category of mares	No. of mares treated	No. which returned to oestrus in 5 days and subsequently ovulated	No. tested for pregnancy after mating in induced oestrus	No. diagnosed pregnant
Maiden	128	98	69	28
Barren	183	149	113	49
Lactating	137	112	79	44
Totals	448	359 (80 %)	261	121 (46 %)

⁽¹⁾ Figures taken from Shephard and Findlay (1974) and Berwyn-Jones and Irvine (1974).

EFFECT OF PMSG UPON OVARIAN ACTIVITY

One category of non-cycling mares which do not respond satisfactorily to treatment with prostaglandins are those animals which possess active endometrial cup tissue in the uterus and therefore have high levels of gonadotrophin (PMSG) circulating in the blood. Such a situation arises in some mares which have aborted after 40 days of gestation and in all mares from which twin conceptuses have been deliberately removed from the uterus after Day 40. The PMSG-secreting endometrial cups are composed of specialized foetal trophoblast cells which invade the maternal endometrium around the thirty-sixth day of gestation (ALLEN, HAMILTON and MOOR, 1973). Once the invasion process has been completed, the cups will continue to develop normally and secrete high levels of PMSG for many weeks despite the subsequent loss of the conceptus by either spontaneous or deliberate abortion (ALLEN, 1970). Luteal function is maintained in most mares following loss of pregnancy but not all. However, whether active luteal tissue persists in the ovaries or not, the mares will only return to oestrus and ovulate normally when the endometrial cups finally regress and PMSG has disappeared from the blood (ALLEN, 1970; MITCHELL, 1971).

Mares carrying twin conceptuses have two sets of endometrial cups and therefore show double the normal levels of PMSG in their serum (ROWLANDS, 1949). Twins are a major cause of infertility in Thoroughbred mares as the majority are aborted between five and nine months of gestation due to placental insufficiency which results in the death of one or both foetuses. They are normally diagnosed by rectal palpation of the uterus between 42 and 45 days after ovulation and are often deliberately aborted at this time in an attempt to get the mare pregnant again in the same breeding season. This practice rarely succeeds, however, as the mare does not return to oestrus while the endometrial cups remain functional and continue to secrete PMSG.

ALLEN *et al.*, (1974) examined a total of 12 mares from which twins had been removed from the uterus after 42 days of gestation and 3 mares which had resorbed spontaneously but continued to show high levels of PMSG in their serum. Treatment of all these animals with ICI-79939 or ICI-81008 on one or more occasions successfully induced luteolysis as judged by peripheral plasma progesterone measurements. However, the ovaries of all the mares became increasingly small and inactive after treatment and, although some animals showed intermittent oestrous behaviour when teased, none showed normal follicular development or ovulated until PMSG had disappeared from the blood. In contrast, one mare treated with ICI-81008 following removal of twins from the uterus at 35 days of gestation (and therefore prior to the development of endometrial cups) returned to oestrus 3 days after treatment and ovulated normally. Thus, the paradoxical situation appears to occur in the mare when, in the absence of the conceptus, high concentrations of PMSG in the blood suppress ovarian activity rather than stimulate it. For this reason, twin conceptuses must be diagnosed and removed from the uterus prior to 36 days of gestation if the mare is to respond satisfactorily to treatment with prostaglandins and return to oestrus and ovulate normally.

CONCLUSIONS

The advent of stable and potent synthetic prostaglandin analogues which can be administered by the i/m route has provided a much-needed tool in equine stud management. These compounds give a safe and effective means of inducing luteolysis in the mare and thus allow a good measure of control of her oestrous cycle. Prostaglandin analogues have an immediate clinical use for treatment of prolonged dioestrus in mares. They have an even greater future potential in stud management for the control and synchronization of oestrus in normal mares. This action is especially applicable to those countries and in those breeds of horses where artificial insemination is permitted and practised widely. But even in Thoroughbred mares where A.I. is not permitted by the breed registration authorities, the planned administration of prostaglandin analogues should prove most useful for shortening the oestrous cycle of individual mares when desired.

*Colloque : Control of sexual cycles in domestic animals
October 27-30, 1974, Nouzilly.*

RÉSUMÉ

UTILISATION DES ANALOGUES DE PGF_{2α}
POUR INDUIRE LA LUTÉOLYSE CHEZ LA JUMENT

Dans cet article, les auteurs discutent l'activité, la toxicité et la valeur clinique de deux analogues de PGF_{2α} (ICI-79939 et ICI-81008) pour induire la lutéolyse chez la jument. La détermination des niveaux plasmatiques périphériques de progestagènes sur plus de 400 juments pur-sang a montré que la persistance anormale de la fonction lutéale (dioestrus prolongé) est la principale cause de la non extériorisation de cycles oestriens réguliers pendant la saison sexuelle par les juments non gestantes. Les résultats de l'utilisation clinique de ICI-81008 (« Equimate ») pour induire l'oestrus et l'ovulation chez des juments pur-sang en dioestrus prolongé sont présentés par les auteurs, aussi bien dans l'hémisphère Nord que dans l'hémisphère Sud.

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