



INVITED REVIEW

**Antiprogestins; high potential compounds for use in veterinary research and therapy:
A review**

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Özet

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Progesteron nükleer reseptörüne bağlanması transkripsiyonu uyarır. Antagonistler bu reseptöre yüksek affinite gösterirler ama oluşan sinyal iletim sistemi ya kısmen uyarılır ya da hiç uyarılmaz. Bir antagonistin spesifitesi hedef doku ve türe göre farklılık gösterir. Antagonistler mifepriston ve aglepriston için tam antagonist kapasite köpeklerde ve diğer türlerde gösterilmiştir. Progesteronun çok iyi tanımlanmış biyolojik aktiviteleri vardır, ancak birçok biyolojik olaydaki düzenleyici etkileri halen bilinmemektedir. Biz progesteronun köpeklerdeki yalancı gebelik ve luteal fonksiyonlardaki rolünü araştırdık. Bu rol köpeklerde açıkça gösterilirken, ineklerde karunkular progesteron reseptörlerinin uyarılması fetal membranların doğum öncesi olgulaşmasını ve retensiyonunu etkilemediği görülmüştür. Aglepristonun köpeklerde gebeliğin sonlandırılması amacıyla lisansı alınmıştır. Ancak, aglepriston gebeliğin dönemine bağlı olarak düzenleyici mekanizmaları bozar ve geç dönemdeki abortları kritik hale getirebilir. Köpeklerde etiket dışı olarak pyometra tedavisinde ve doğumun uyarılmasında kullanılmaktadır. Başarı için köpek trofoblastlarında Cox2 ekspresyonu verileri benzer şekilde göz önünde bulundurulmalıdır. Kedi, tavşan ve diğer türlerde de etiket dışı kullanımı vardır. Kedilerde antiprogestinler ile fibroadenomatosis tedavisi umut vericidir, ancak gebelik durumunda abort yan etkisi de düşünülmelidir. Fibroadenomatosis tedavisinde eksojen progesteron kullanımında bireysel dozajlama uygulanmalıdır.

Abstract

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Progesterone binding to its nuclear receptor leads to the initiation of transcription. Antagonists show a high binding affinity to the receptor, the resulting signaling cascade, however, is incomplete with transcription not or partially induced. Specificity of a full/partial antagonist may vary, depending on the species and tissue targeted. For the antiprogestins mifepristone and aglepristone full antagonistic activity has been demonstrated in the dog and other species. Progesterone exhibits well defined biological activities. However, its participation as a regulatory factor in many biological processes is still unknown. We have assessed the role of progesterone in overt pseudopregnancy and control of luteal function in the bitch. Its involvement could be clearly demonstrated while interaction with caruncular progesterone receptors in the cow seems not to affect prepartal maturation and retention of foetal membranes. Aglepristone has been licensed for termination of pregnancy in the dog. However, depending on the stage of pregnancy, it interferes with different regulatory mechanisms, making induction of late abortion a critical issue. Off-label use in the dog is for conservative treatment of pyometra and induction of parturition. To be successful, again a critical approach is necessary and recent data on the expression of Cox2 in the canine trophoblast must be considered. Off-label use with similar indications is in the cat, rabbit and other species. In the cat treatment of fibroadenomatosis with antiprogestins is highly promising; however, in case of a pregnancy abortion must be expected. An individual dose regimen must be applied when fibroadenomatosis was induced by exogenous progesterone treatment.

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► Introduction

• Mode of actions and nature of antiprogestins

Antiprogestins are compounds which have been developed to block the actions of the endogenous hormone progesterone. As reviewed by Hoffmann and Schuler (2000, 2006) antiprogestins compete with progesterone as ligands for binding to the nuclear progesterone receptor without or only partially inducing transcription. Due to these partial activities in the latter case also the term “selective steroid hormone receptor modulators” has been introduced.

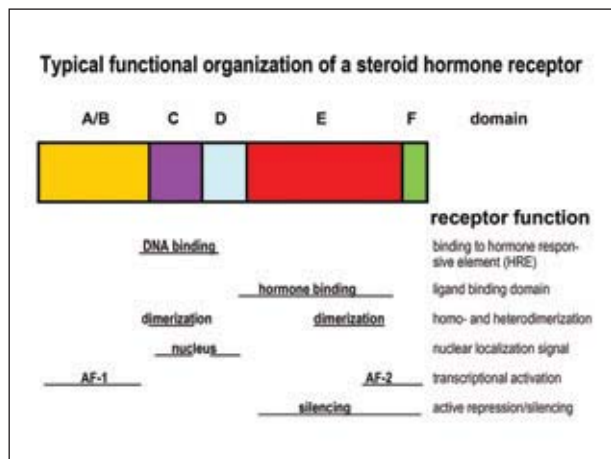


Figure 1. Functional organization of a nuclear steroid hormone receptor; bars indicate localization of receptor functions.

The progesterone receptor belongs to the group of steroid hormone receptors which represent an evolutionary conserved class of transcription factors being present from flies to mammals (Beato et al 1995). In general nuclear steroid hormone receptors possess a highly conserved DNA binding region separating the receptor into a variable amino (N) terminal and a higher conserved carboxy (C) terminal part (Fig.1). The DNA binding region is essential for the sequence-specific recognition of the hormone response elements (HRE) of the target gene by ligand bound receptor dimers.

Concerning the interaction with the receptor different reaction cascades are observed depending whether an agonist, partial antagonist or full antagonist is presented as a ligand (Fig. 2a). Binding of an agonist

induces changes of receptor conformation, loss of heat shock proteins and phosphorylation, followed by dimerization of the hormone-receptor complex, which eventually binds via zinc-fingers of domain C (DNA-binding site) to HREs. The resulting complex interferes with promoters of specific target genes and initiates a reaction cascade, involving - depending on the ligand and cell type - a number of different co-activators and co-repressors. Finally, with the formation of mRNA transcription is initiated.

Also full antagonists show a high affinity receptor binding with dissociation constants in the picomolar to lower nanomolar range (Capony and Rochefort 1978, Katzenellenbogen et al 1981, Hurd and Moudgil 1988, Terakawa et al 1988). However, the reaction cascade following binding of the antagonist is only partially induced and may be terminated at various points. As exemplified in Fig. 2b, also binding of the antagonist induces changes in receptor conformation, loss of heat shock proteins, phosphorylation, dimerization and, as has been shown for antiprogestins (Leonhardt and Edwards 2002), also binding to the HRE. However, due to interference with the action of co-activators and co-repressors, initiation of transcription is blocked.

Also binding of partial antagonists to a receptor induces a similar reaction cascade (Fig. 2c) with, however, an apparently incomplete blocking of the co-activator/co-repressor activity allowing for some initiation of transcription (Chabbert-Buffet et al 2005, Chwalisz et al 2005).

The extent of antagonistic/partial antagonistic activities may be species and organ specific. Some of the underlying mechanisms relate to the cell specific expression of co-activators and co-repressors and receptor isoforms. Thus progesterone may interact with either the progesterone receptor A, B or C, resulting in different transcriptional activities (Kastner et al 1990, Gronemeyer et al 1991, Vegeto et al 1993, Wen et al 1994, Giangrande et al 1997).

A number of antiprogestins has been developed by the pharmaceutical industry. However, so far only mifepristone (RU38486) has been authorized as a drug for human use and aglepristone (RU46534) for

Table 1. Binding of RU 38486 to steroid receptors and plasma proteins in different species (from Baulieu, 1985). +++: $K_D = 10^{-10}$ M; ++: $K_D = 10^{-9}$ M; + $K_D = 10^{-8}$ M; - no affinity, P = Progesterone, D = Dexamethasone; T = Testosterone

Progesterone receptor	rat/rabbit (+++)(> P) ^a	man/monkey (++)(> P) ^a	chicken (-)
Glucocorticoid receptor	rat/mouse (+++)(> D) ^a	man/monkey (+++)(> D) ^a	chicken (+++)(> D) ^a
Androgen receptor	rat (+)(1/4 T) ^a		
Sex hormone binding globulin		man/monkey (-)	chicken (-)
Transcortin		man/monkey (-)	chicken (-)

a) in comparison to the affinity of the corresponding agonist

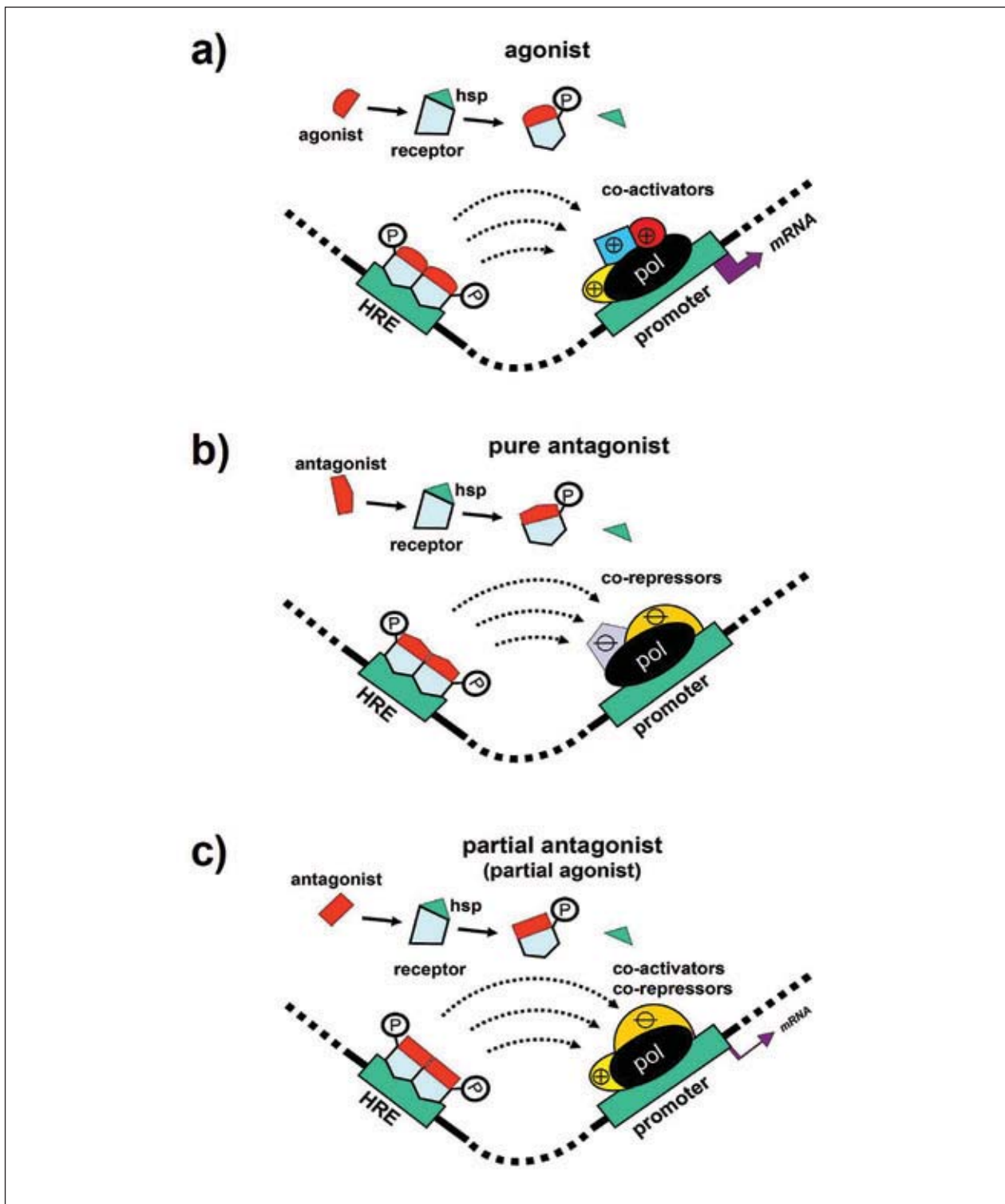


Figure 2. Signal cascade following a) binding of a steroidhormone agonist, b) of a full antagonist and c) of a partial antagonist; HSP (heat shock protein), (P) (phosphorylation), HRE (hormone response element).

use in dogs. For another antiprogestin, onapristone (ZK98299) ample information on its use for experimental purposes is available. As is obvious from Fig. 3 the three antiprogestins are derivatives of testosterone with substitutes at C11, C17 and an additional double bond in ring B (C9 – C10).

The hydrophobic side chain at C17 is responsible for the high affinity receptor binding while the additional aromatic ring at C11 with a dimethyl-amino-group

is responsible for the changes in receptor conformation leading to suppression of transcription (Baulieu 1985, 1987). As indicated above and as is shown for RU38486 in Table 1, binding may not be restricted to the progesterone receptor but is also observed with the glucocorticoid and – to a lesser extent – with the androgen receptor.

Binding affinity may vary between species and other

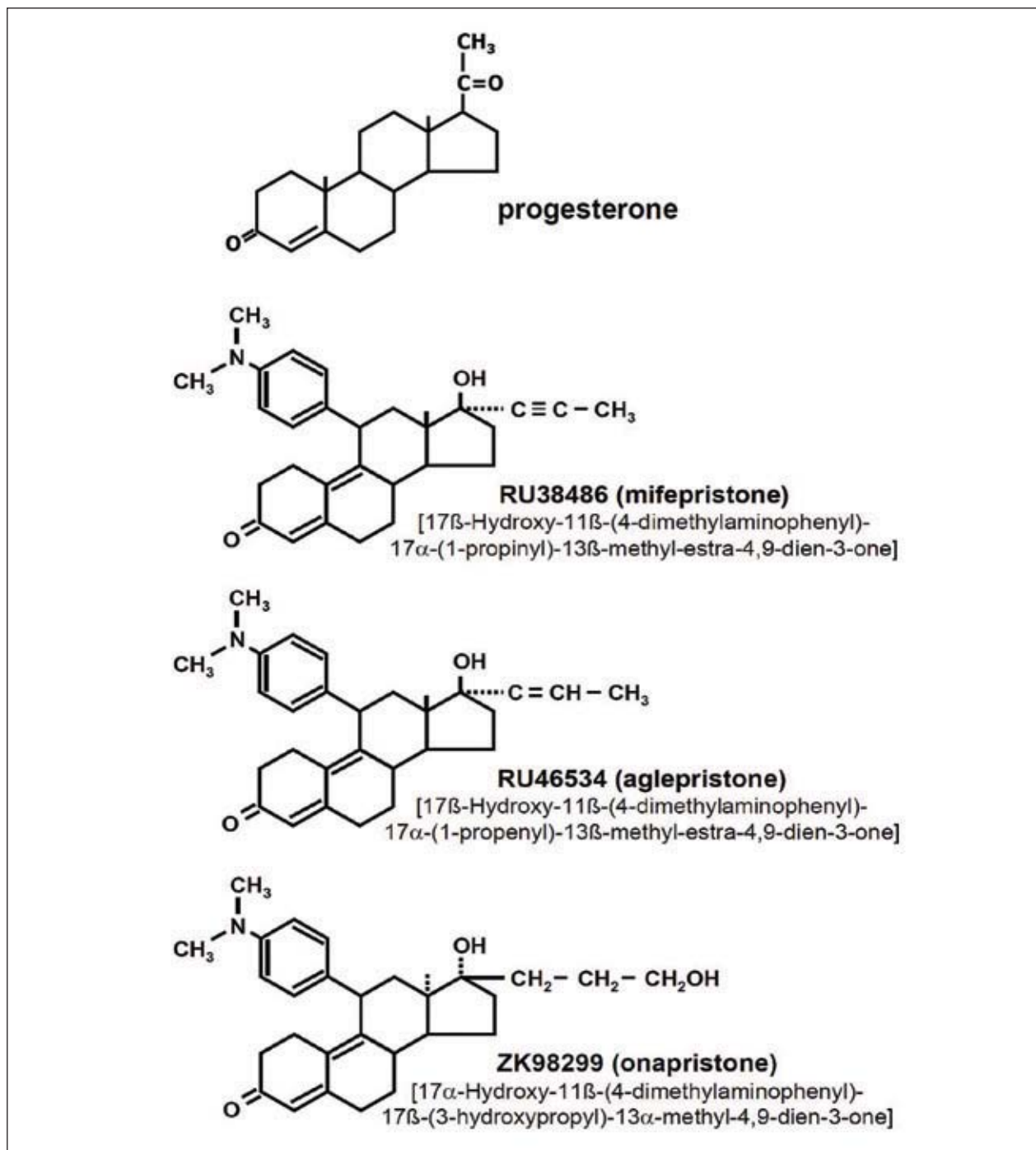


Figure 3. Molecular structure of progesterone and antiprogestins.

than progesterone no binding was observed to transcortin in the human, monkey and chicken (Baulieu 1985) and – as shown in own studies –in the dog (Gerres 1991). Clearly RU38486 was shown to act as a full antagonist in the dog (Hoffmann and Gerres 1989) and no interference with glucocorticoid activity could be observed.

• *Hypothesis underlying the use of antiprogestins*

Based on the assumption that antiprogestins block the activity of progesterone at the receptor level two different types of application can be envisaged:

- to further define and elucidate the role of proges-

terone in reproductive processes and disorders and

- to interfere (block) with a well established action of progesterone either for biotechnological purposes or to achieve a therapeutic effect.

Attempts to further define and elucidate the role of progesterone in reproductive processes and disorders of domestic animals

A classical approach to study the function of a given hormone has been the removal of the respective endocrine gland and the study of the resulting effects. However, by such an intervention in general not only

one endocrine factor but a whole array of factors is removed, rendering the resulting observations to be of multifactorial origin. More specific approaches for example are passive or active immunization against a given hormone, the use of specific enzyme blockers or – limited to the rat and mouse – the development of knock out models.

Also the use of antiprogestins acting via blocking receptor mediated transcription must be seen in line with these more specific approaches. However, apart from having established the pharmacodynamic profile of a given receptor blocker, also the pharmacokinetic properties (e.g. distribution volume, half life, effective dose) must be considered when designing an experiment. By making use of this approach we have tried to get more information on the role of progesterone in three specific situations.

Pseudopregnancy in the dog: Pseudopregnancy is an inherent phenomenon of the reproductive cycle of the dog, where luteal function in the non pregnant bitch in general exceeds that of the pregnant bitch, where a precipitous decline of progesterone precedes parturition (Fig. 4). Only overt pseudopregnancy (Chakraborty 1987) may result in clinical problems like mammary gland hyperplasia without or with secretion, sometimes even developing into mastitis, increased aggressiveness and nesting behaviour. Symptoms may appear as early as 30 days after ovulation and may last up to 90 days (Arbeiter and Winding 1977). After having confirmed the antigestagenic properties and defined an effective dose of RU38486 for the dog (Hoffmann and Gerres 1989), overtly pseudopregnant dogs were treated in 2 to 3 day intervals with 2 mg RU38486/kg bw. Treatment commenced on days

24, 35 and 43 after onset of pro-oestrous bleeding and lasted until progesterone had declined to levels between 1 to 2 ng/mL; the dogs served as their own controls. Treatment resulted in an earlier onset of overt pseudopregnancy. However, clinical symptoms were distinctly reduced and duration of pseudopregnancy was shortened when treatment commenced on days 24 and 35. These observations clearly point to a role of progesterone in onset and maintenance of overt pseudopregnancy. The advanced onset was seen as a result of the mimicked progesterone withdrawal due to treatment with the antiprogestin, the reduced clinical symptoms suggest that maintenance of pseudopregnancy - at least in part - depends on the availability of progesterone (Gerres and Hoffmann 1994).

Progesterone as an important factor regulating luteal function in the dog: In a series of experiments we have addressed the mechanisms responsible for luteal regression in the non pregnant and for luteolysis in the pregnant dog. Clearly the corpus luteum (CL) of non pregnant and pregnant dogs expresses the progesterone receptor (Hoffmann et al 2004) with the effect of time being highly significant in pregnant dogs (Kowalewski et al 2009). This observation suggests that progesterone of luteal origin might be involved in the regulation of luteal function as a paracrine/autocrine factor. To test for this hypothesis midpregnant dogs (days 40 to 45 of pregnancy) were treated with two times 10 mg aglepristone/kg bw 24 hrs apart. The resulting changes in the expression of the prostaglandin system [cyclooxygenase2 (Cox2), prostaglandin F- (PGFS) and E- (PGES) synthase, the PGF2 α - (FP) and PGE2- (EP2, EP4) receptors], of the progesterone receptor; of 3 β -hydroxysteroiddehydrogenase Δ 4/5 -isomerase (3 β HSD) and of steroidogenic acute

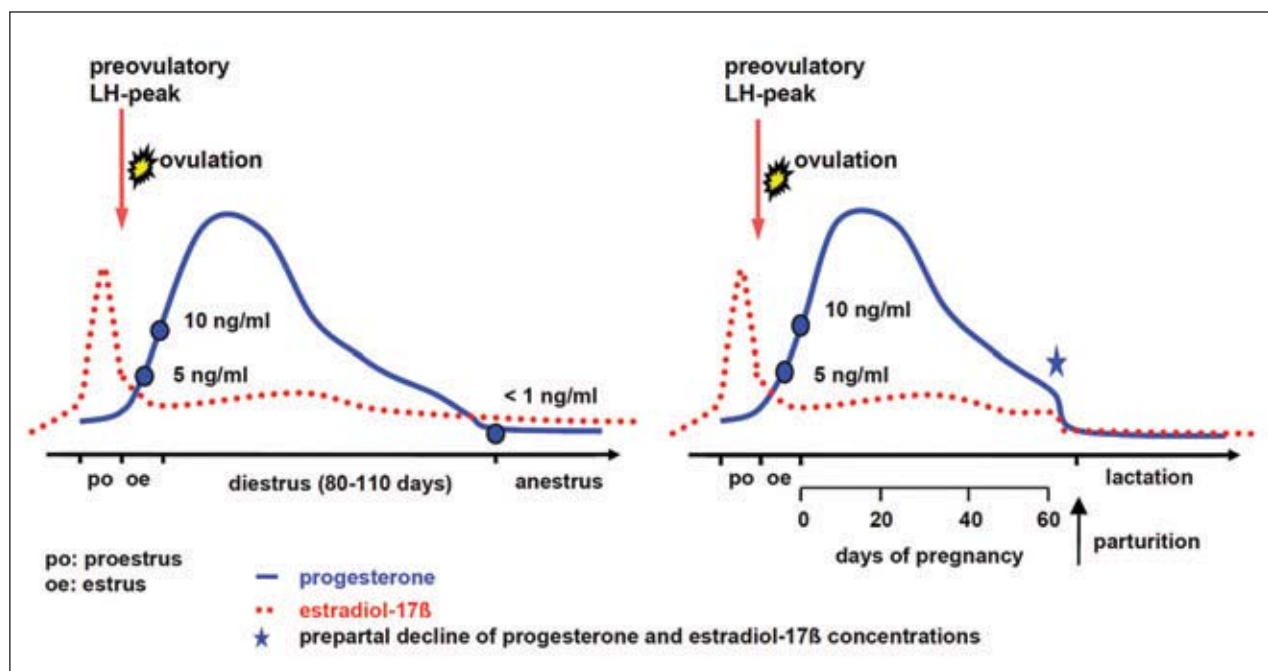


Figure 4. Scheme of the course of progesterone and estradiol concentrations in pregnant and non pregnant bitches (according to Hoffmann et al 1999).

regulatory protein (StAR) - as observed on the mRNA and protein level - allowed us to conclude that luteal progesterone acts as an autocrine factor in a positive loop feedback mechanism via controlling the availability of StAR and 3 β HSD (Kowalewski et al 2009). In a follow up study changes in the expression of the prostaglandin system (see above) and of the progesterone receptor were assessed in utero/placental tissue samples of the same dogs (Kowalewski et al 2010). These studies clearly showed that the only cell located in the placenta expressing the progesterone receptor are the decidual cells (which are of maternal origin) and that the prepartal PGF2 α increase results from a strong up-regulation of Cox2 in the trophoblast allowing the conclusion that the withdrawal of luteal progesterone has a signalling function with the decidual cells playing a key role in the underlying cell-to-cell cross talk.

Placental release in the cow: In our studies on placental function in the cow we have observed the expression of the progesterone receptor in caruncular stromal cells, capillary pericytes and - only at the time of parturition - in arterial walls (Schuler et al 1999, Hoffmann and Schuler 2002). Thus there is an immediate proximity between the site of receptor expression and the cotyledonary trophoblast which, among other hormones, also synthesizes progesterone. Thus the hypothesis was put forward that progesterone originating from the trophoblast might act as a paracrine regulatory factor controlling caruncular proliferative activity and - at the time of parturition - placental release due to a seizure of progesterone synthesis. In order to test this hypothesis we have treated 3 pregnant cows on day 270 and 271 with an abortifacient dose (10 mg/kg) of aglepristone (RU46534). As was observed in the dog (Kowalewski et al 2010) the mimicked withdrawal of progesterone was accompanied by luteolysis commencing 33 resp. 49 hrs after the last treatment and complete cervical opening; however labor was not initiated and the calves had to be extracted at still high or decreasing progesterone levels. All cows developed a pronounced and persistent retention of fetal membranes indicating that - other than hypothesised - a complete withdrawal of progesterone in caruncular tissue is not a prerequisite for a timely placental release (Shenavai et al 2010).

Interference of antiprogestins with well described actions of progesterone either for biotechnological purposes or to achieve a therapeutic effect; basic aspects

The present use of antiprogestins in veterinary medicine is based on receptor-mediated activities of progesterone and is thus bound to the expression of the progesterone receptor in various cells and organs, respectively. The most prominent activities of progesterone result in the following effects:

- Cervical closure at the end of oestrus.
- Adaptation of the endometrium from the prolifera-

tive phase into the secretory phase following oestrus and conception.

- Termination of the oestrogenic activity at the external genitalia and vaginal epithelium.
- Control of motility and secretory activity of the uterine tube as a prerequisite for a successful transport of the early embryo from the ampulla into the uterus resp. the uterine horns.
- Inhibition of myometrial contractility during pregnancy.

It may be expected that application of an antiprogestin using a dosage allowing for effective competition at the progesterone receptor will lead to a termination of these progesterone mediated effects. As reviewed by Hoffmann and Schuler (2000, 2006) this assumption could be confirmed in a number of studies with the dog being the main target animal.

Thus it is not surprising that aglepristone has been licensed as a veterinary drug for use in dogs in quite a number of countries since 1996. The brand name is Alizin[®] (Virbac, France) with the authorized indication: "Pregnant bitches: For termination of pregnancy up to day 45 from mating".

Basic considerations and experiences concerning the use of aglepristone

- *Application in the dog*

Termination of pregnancy: Progesterone plays a key role in the processes of early embryonic development and implantation. This conclusion is substantiated by our observation of a high expression of the uterine progesterone receptor during the pre-implantation period in the dog (Kowalewski et al 2010). The prevention of nidation and induction of early embryonic death by use of antiprogestins must therefore be considered an effective way leading to termination of pregnancy up to around day 20. The mechanisms underlying induction of termination of pregnancy beyond that point of time are more speculative and must be seen in connection with the observation that antiprogestin treatment also induces luteolysis (Concannon et al 1990, Hoffmann et al 2000) which perpetuates the effect of antiprogestin treatment. We have observed heart beat of the fetuses for several days following treatment with the recommended dose of 10 mg/kg bw, two times 24 hrs apart. Thus foetal death is a rather delayed response to treatment. Late treatments may or may not be accompanied with abortions. After implantation expression of the progesterone receptor is restricted to the endometrial stroma and to nuclei of both glandular and superficial epithelial cells, the smooth muscle cells of the myometrium and - on the foetal side but of maternal origin - the decidual cells (Kowalewski et al 2010). Thus progesterone withdrawal targets several organs and it only can be speculated that interference with de-

cidal cells might be the prime target to bring about placental dysfunction. Ample clinical experiences when using Alizin for termination of pregnancy has first been published by Fieni et al (1996); Wehrend and Georgiev (2006) report about some special precautions to be observed.

Induction of parturition: In accordance with drug legislation this would be an off label use. Induction of parturition in the dog is a rare indication and prior to treatment confirmation must be obtained if and to what extent length of pregnancy might be exceeded. Reports about induction of parturition in the dog seem to be somewhat controversial. First attempt to induce parturition by a series of treatments with 6 mg mifepristone (RU38486)/kg bw, starting on day 56 of pregnancy, showed that onset of parturition with cervical opening was achieved; however, due to the lack of the prepartal PGF 2α increase no labor was induced and parturition had to be completed by caesarean sections. In this study using a lower dose treatment with the antiprogestin did not interfere with luteal function (Nohr et al 1993). Based on these observations we have developed a protocol for induction of parturition in the dog with aglepristone in combination with ecboolic support (Hoffmann et al 1999). A protocol based on similar assumptions was developed by Fieni et al (2001, 2009) with good clinical results also obtained by Fontbonne et al (2009). On the other side Baan et al (2005) report about induction of parturition without ecboolic support; apart from using a higher dosage (15 mg aglepristone/kg bw, 9 h apart) recent data by Kowalewski et al (2010) have shown that expression of Cox2 in the trophoblast seems to be up-regulated immediately prior to parturition. Thus it may be assumed that the need for ecboolic support decreases with the time point of induction of parturition approaching the physiological end of pregnancy.

Pyometra in the dog: The cystic endometrial hyperplasia-pyometra complex is an acute or chronic gynaecological disorder of the in general elderly bitch. Pyometra may occur at any stage of the reproductive cycle, however, according to Blendinger and Bostedt (1991) 80% of the bitches are presented within 16 weeks after onset of dioestrus with the majority of them presented within the first four weeks when the CL are still fully functioning. A distinction can be made between an open and closed cervix pyometra. When presented the dogs in general show distinct clinical symptoms like vulval discharge in cases of an open cervix pyometra, polydipsia and renal failure especially in cases of a closed cervix pyometra. In a series of experiments we have tested the hypothesis that progesterone might be an important factor maintaining the state of pyometra in those cases when dogs are presented in the stage of dioestrus as verified by progesterone analysis. An initial pilot study on dogs with closed cervix pyometra (Blendinger et al 1997) clearly showed that treatment with RU38486

in a dose of 6 mg/kg bw, twice on day 1 and once on days 2, 3 and 4, led to a complete evacuation of uterine contents; the quick recovery observed, however, should also be attributed to the initial treatment with antibiotics. These first observations were confirmed in an open clinical study using aglepristone in the recommended dose of 10 mg/kg bw, on days 1, 2, 24 h apart. A third treatment was given on day 7 and - depending on the individual case - a fourth treatment on day 14 (Hoffmann et al 2000). This study showed that clinical success depends on progesterone concentrations ≥ 1 ng/mL at onset of treatment and an otherwise undisturbed ovarian function with the latter observation being confirmed by Trasch et al (2003). Also treatment of pyometra would be an off label use.

- *Application in the cat*

Aglepristone has not been licensed for use in cats. However, as a registered veterinary drug at a given situation off label use may be in accordance with drug legislation, however, all responsibility being with the treating veterinarian.

Termination of pregnancy: A distinction must be made between "prevention of pregnancy" and treatment during mid- and late gestation. Following formation of the zygote the early embryo migrates from the oviduct into the uterus 4 to 5 days after fertilization. The blastocyst forms and attachment to the endometrium occurs around day 15 following mating (Feldman and Nelson 2004). None of the 17 cats treated during this period, i.e. on days 5 and 6 after mating with 10 mg aglepristone/kg bw were found pregnant on day 25 when examined by ultrasound (Goericke-Pesch et al 2010). Thus implantation and early embryonic development were blocked by treatment with the antiprogestin and prevention of implantation (rather than prevention of pregnancy) seems to be a highly rational indication.

In using the same dose regimen abortion may also be induced at mid-gestation (Fieni et al 2006, Georgiev and Wehrend 2006) and at late gestation (Georgiev et al 2010). As reported by Georgiev and Wehrend (2006) the success rate was 87% when treatment for abortion was on days 25/26, the success rate was 67% when treatment was on days 45 and 46 (Georgiev et al 2010). However, from a clinical point of view the results must be seen critically. The time span between the first treatment and occurrence of abortion was 4 to 9 days with puppies still alive until abortion and some of them born alive. Late gestation abortion was associated with mammary gland development and lactation. Monitoring by transabdominal ultrasound was considered essential to examine for non expelled fetuses. Based on these observations the authors recommend to refrain from late gestation abortions using antiprogestins (Georgiev et al 2010).

At least from a theoretical point of view the use of dopamine agonists (e.g Cabergoline) might be a better

approach; dopamine agonists inhibit the release of prolactin which acts as a luteotropic hormone in the cat and is also responsible for mammo- and lactogenesis prior to parturition (Jöchle et al 1989).

Treatment with the antiprogestin showed no inhibitory effect on Cl function during early and mid-gestation (Goericke-Pesch et al 2010, Georgiev and Wehrend 2006) while preterm luteolysis was observed at late gestation treatment (Georgiev et al 2010). These observations are conflicting and presently no conclusions on a role of luteal progesterone as a paracrine/autocrine factor in the cat is possible.

Fibroadenomatosis: As reviewed by Jurka and Max (2009) fibroadenomatosis is a rapid but not malignant proliferation of cells in the ducts and stroma of the mammary gland, leading to a significant enlargement of - in general but not always - all mammary complexes. It is most commonly observed in young queens during pregnancy or pseudopregnancy. Progesterone plays an essential role in the etiology of fibroadenomatosis and consequently also treatment with synthetic gestagens may induce fibroadenomatosis in both, male and female cats. The rationale to treat fibroadenomatosis with antiprogestins was first developed by Blendinger et al (1994) who reported about the successful treatment of a pregnant cat with RU46534 (aglepristone) and - as was to be expected - treatment associated abortion. A number of reports confirm this initial observation (Wehrend and Bostedt 2000, Wehrend et al 2001, Görlinger et al 2002, Meisl et al 2003). According to own observations and as stated by Wehrend and Georgiev (2006) treatment of fibroadenomatosis induced by application of synthetic progestagens needs special considerations due to the in general depot formulation of the progestagen applied.

Pyometra: In analogy to the situation in the dog also in the cat treatment of pyometra with antiprogestins should be reasonable in case there are no ovarian disorders and if it occurs while the reproductive cycle is under the dominance of progesterone. First results about a successful treatment with aglepristone have been reported by Hecker et al (2000).

- *Application in other species*

In 1996 Dudley et al report about successful induction of preterm birth in mice following treatment with RU38486, Özalp et al (2008, 2010)) report about the successful termination of pregnancy during mid-gestation and the prevention of implantation in the rabbit.

According to own experiences (Goericke-Pesch et al, unpublished data) off-label use of aglepristone is also suitable for treatment of pyometra in the hamster, rat, rabbit and guinea pig, especially when patients are presented in a bad general condition so that the anaesthetic risk in case of an intended ovario-hysterectomy would be significantly increased.

The treatment scheme is the same as in the dog (days 0 and 1, 24 h apart, day 7). In rabbits and guinea pigs the dose applied is, as in the dog, 10 mg/kg bw; in the hamster and rat a general dose of 1.5 mg/animal has shown to be effective. Success rates are good provided there are no other uterine or ovarian disorders.

► Conclusions

Antiprogestins have been shown to be valuable tools in reproductive research aiming at the further elucidation of the role of progesterone at physiological and pathophysiological situations. With the availability of Alizin® as a veterinary drug with aglepristone as the active ingredient new perspectives have opened up to treat reproductive disorders and to manipulate reproduction. The official use of Alizin® relates to termination of pregnancy in the dog. Thus the use of oestrogens for prevention of nidation has become obsolete. A high clinical efficacy has been observed when Alizin® was used for conservative treatment of open and closed cervix pyometra in the dog. As there is no other drug licensed for this indication this off label use is in accordance with animal drug legislation, however, responsibility is with the treating veterinarian and not the pharmaceutical entrepreneur. Aglepristone has been shown to be similarly effective in the cat for termination of early and mid pregnancy, it is the first drug allowing for a rational and successful treatment of fibroadenomatosis. Based on the underlying mechanisms of action aglepristone has also been effective in the rabbit and other pet animals. All these indications would require off label use with the above mentioned restrictions.

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