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Use of Cyproterone Acetate in two aggressive dogs

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Abstract: Canine aggressions remain one of the main reasons for euthanasia or abandonment.

The neurophysiology of aggression is still incompletely known, but several agents have been reported to play a role in its mechanism: androgens, cortisol, and serotonin. This explains why selective serotonin reuptake inhibitors are commonly used as primary pharmacological treatment. Most dogs can improve with environment and behavior modifications associated with such medication. However, in severe cases, they may not completely manage aggressive behavior or underlying anxiety, and multiple medications may be required. That's why cyproterone acetate, a combined androgen antagonist and antigonadotropin, has been proposed. This particular progestin has a wide range of mechanisms of action, including interactions with serotonin and γ-aminobutyric acid, which explains why cyproterone acetate isn't acting like a simple testosterone reducer, but can be used in a similar way as antipsychotics.

We present 2 cases of dogs exhibiting severe aggressive behaviors despite their primary treatment. In each case, the addition of cyproterone acetate led to a decrease in number and intensity of social aggressions; and the aggressions resumed after its removal. In addition, selected cases included male and female, neutered or not, which suggests that cyproterone acetate can be efficient on both male and female, even neutered ones.

The main side effect reported is a mild increase in appetite, which could have been more important without the primary medication (e.g. fluoxetine). Further studies including more cases are needed to investigate these preliminary findings.

Key Words: dog; social aggression; cyproterone acetate; anxiety; fluoxetine.

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Introduction

Dogs with aggression-based behavior problems are commonly presented for behavior consultation (Fatjo et al., 2007; Landsberg et al., 1997). Moreover, behavioral problems remain the primary reason why dogs are abandoned and euthanized (Marston et al., 2004; Reisner et al., 1994). The treatment of aggression in dogs relies on the combination of risk assessment and safety environmental modifications, associated to behavioral modification and medication.

However, some aggressive behavior in dog can be the result of primary psychiatric disorder (e.g. dysthymia[1]) or linked to an underlying anxiety state and controlling them can be a real challenge for veterinarians. This is for those clinical situations where conventional biological interventions and behavior modification are not efficient enough, that cyproterone acetate has been proposed, in a similar way as antipsychotics.

Cyproterone acetate is a synthetic progestogen with a wide range of mechanisms of action (Bolea-Alamanac et al., 2011). Firstly, it acts via a double mechanism: on one hand it blocks

[1] *The behaviourist community has not been able to engage in creating a consensus terminology in veterinary behavioral medicine* (Overall, 2005) *Hence, the authors have decided to use the French nomenclature to describe the symptoms observed in the presented cases.*

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androgens peripherical action via a competitive inhibition to the testosterone cytosolic receptor, and on the other hand it blocks GnRH secretion leading to a secondary blockage of FSH, LH and testosterone (Gruber & Huber, 2003). This double mechanism could result in lower circulating testosterone levels than what is observed with chemical castration (Lieberman, 2013).

Moreover, it has been established that cyproterone acetate interacts with the GABA receptor subtype A, which is known to have anticonvulsant and anxiolytic properties (Bolea-Alamanac et al., 2011; Gruber & Huber, 2003). This progestin may also reduce levels of 5-hydroxy indole acetic acid and homo vanillic acid, metabolites of serotonin and dopamine, resulting in an increase in the availability of these monoamines in the central nervous system (Gruber & Huber, 2003). Another potential mode of action is that cyproterone may modulate the enzyme 5-alpha reductase, thereby altering the brain concentration of allopregnanolone, a neurosteroid that at high doses has anxiolytic properties and is synthesized both in neurons and glia (Pluchino et al., 2006). Finally, it has been demonstrated that cyproterone acetate binds to opiate receptors in mice and may have a role in the endorphin system (Gruber & Huber, 2003).

Considering the inconsistent and controversial reported effects of castration (Farhoody et al., 2018; Hopkins et al., 1976; Maarschalkerweerd et al., 1997; Neilson et al., 1997), it is very likely that the effects of cyproterone acetate on behavior are not only mediated by its effects on testosterone, but rather by its complex and wide mechanisms of action, especially on GABA and serotonin. This is also for this reason that cyproterone acetate cannot be compared to Deslorelin, which is a gonadotropin-releasing hormone (GnRH) agonist that seems to act in a similar way to castration (Beata et al., 2016; Junaidi et al., 2007; Trigg et al., 2006). As a matter of fact, GnRH agonists and cyproterone are used together in humans to nullify the flare-up effect (i.e. temporary increase in circulating LH and testosterone when using a GnRH agonist) observed when initiating the treatment (Le Dare et al., 2015).

However, there are no published data concerning the use of cyproterone acetate to treat social aggression in dogs, even if Pageat (Pageat, 1998) mentioned it as a possible treatment of hypersensitivity-hyperactivity syndrome and sociopathy in association with carbamazepine.

The objective of these cases report was to acknowledge the interest of adding cyproterone acetate for treatment of severe aggressive behaviors, unresponsive to primary medication.

All the aggression and diagnosis listed in this paper come from the French nomenclature of Veterinary Psychiatry initiated by Pageat in 1998 (Pageat, 1998) and developed further in 2003 by Mege and colleagues (Mege et al., 2003).

CASE 1

Presentation

Case 1 is a 5-year-old female German shepherd, weighting 28 kg, presented for multiple aggressions against humans and dogs. Euthanasia is requested by all the family members except the female owner, who is coming to the behavior consultation.

History and presenting signs

The female dog was raised from a working line and was separated from her mother on purpose at 5 weeks of age. She had bitten over 40 times on humans and dogs and the frequency of the aggressions was increasing to reach several episodes per day. Several of these aggressions were severe enough to require surgery on the victims. Every type of aggressive behavior was produced except predation: from the very moment of her adoption at 8 weeks and both towards humans and dogs she exhibited resource holding aggressions around food and toys, accidents during play sessions, without exhibiting submission or deference signals when yelled at. Territorial aggres-

sions appeared with puberty. Overall, the dog's communication signals were so abnormal that she could not establish any normal relationships. Coercive training, including shock-collar, daily physical punishment and aversive communication, led to fear, pain related aggressions (Masson et al., 2018a) and anxiety (Masson et al., 2018b). According to her owner, she never exhibited submission or deference signals when yelled at.

At the time of the consultation, the muzzled dog exhibited increased vigilance, very high level of arousal, and each stimulus triggered aggression attempts.

Physical examination findings and laboratory results

Because of her anxiety and aggressivity level, no exam could be performed without sedation. Blood and urinalysis were in the normal range (including blood count, basic biochemistry, cortisol, fThyroxin and TSH).

Diagnosis

A diagnosis of primary dysocialization was established (Table 1).

Table 1. Diagnosis criteria of primary dysocialization.

The following criteria must be present:
• Aggressions in resource holding situations that are present before puberty (often as early as 3 months old)
• No deference posture can be observed in the dog's communication
• Lack of stop signal
• Lack of bite inhibition
• Intraspecific communication trouble: incapacity to recognize appeasing or deference signals leading to regular aggressions with other dogs

Because brutal aggressions existed from adoption and were not fear-related, they could origin neither from aversive training nor from owners' communication. The dog was hyperactive, but this diagnosis alone does not explain any aggressivity.

Prognosis was guarded considering owner's request, age of the dog, duration of the problem and severity of the diagnosis itself.

Treatment plan

Behavioral treatment: the behavioral part of the treatment plan consisted in safety management measures (Horwitz, 2008), behavioral modification (Herron et al., 2009), training and family strategies (Table 2).

Medication: fluoxetine 4 mg/kg single in day; such dosage is higher than the usual ones described in the literature, but a previous publication reports its use at this dose (Masson & Gaultier, 2018).

Monitoring: number of aggressive-related behaviors per day (snarling, lips lifting, growling, biting) was assessed on the day of consultation and the owner was requested to build an agenda of the upcoming aggressions for the weeks coming.

Table 2. Behavioral part of the treatment plan.

	Before consultation	After consultation
Safety management measures	• Basket muzzle occasionally veterinary visit, some of the walks	• Basket muzzle for all walks • Lock the dog in a garage during all visits
Behavioral modification	• Knowledge of all obedience orders	• Continue to train basic orders, insisting on look • Work on calm protocol
Training	• Physical punishment • Shock collar • Assertive communication • Assertive training	• No physical punishment • No shock collar • Calm communication • Positive training
Family strategies	• Avoiding most of the contacts with outside family members • Attempts to obtain submission when aggressions occur	• Avoiding all contacts outside of the owners • Exclusion of the dog when aggressions occur

Follow up

Results of the treatment plan outcome over the course of time are summarized in Table 3.

Table 3. Evolution of the dog behavior as a function of the treatment plan.

Before consultation and since adoption	Under fluoxetine + behavioral treatment	Under fluoxetine + cyproterone acetate + behavioral treatment
• Brutal and severe aggressions towards humans and dogs	• Reduction of frequency and intensity (50%)	• Reduction of frequency and intensity (90%)
• No submissive or deference signals	• No submissive or deference signals	• Deference signals are observed with the owners
• Impossibility to establish normal relationship with humans or dogs	• Impossibility to establish normal relationship with humans or dogs	• Normal relationships with her owners are possible
• Impulsivity	• Reduction of impulsivity (80%)	• Reduction of impulsivity (90%)
• Lack of bite inhibition	• Lack of bite inhibition	• Lack of bite inhibition

First follow-up was conducted 6 weeks after the initial consultation. The dog improved with this treatment protocol and euthanasia was set aside. However, anxiety was still present, and aggressions were reported at 2 to 5 times a week (snarling and growling but no biting), which was still high considering the extreme caution taken to avoid contacts and triggers. The same treatment plan was continued for 6 months with regular laboratory monitoring (blood count and hepatic parameters) but improvement remained mitigated with several weekly aggressions (no bites). The dog communication improved mildly, but the arousal and the motivation to act in an aggressive manner were still very present.

New medication was added after 6 months of fluoxetine alone: cyproterone acetate 2 mg/kg bis in day.

Aggressive behaviors frequency started to decrease in less than a week. Only 4 aggressive episodes happened during the first month and only 2 were recorded in the next month. The owners reported a heavily decreasing in will to react aggressively and vigilance in the house, as well as an increasing ability to settle down and tolerate petting and interactions in general which improved the relationship with the owners. According to them, she was spontaneously engaging less in game and exploration behaviors, but when stimulated by them to do it, she would respond like before.

An increase in the dog appetite was reported. Blood sample showed no modification. Treatment was adapted to 1 mg/kg bid for cyproterone acetate to avoid possible long-term side effects. For over a year, aggressive behaviors stayed stable at 1 per 2 months, and were limited to snarling, with the dog able to engage in another behavior on queue easily. Again, no blood counts and biochemistry were normal.

Owners decided to stop cyproterone acetate for financial reasons.

Consequently, motivation for food decreased and aggressive behaviors increased, going back to the level of aggressions witnesses before cyproterone acetate. This lasted for 2 years, with a bite resulting in hematoma on the owner's arm during a grooming session. Cyproterone acetate was added again with the same dosage protocol resulting in the same clinical improvements as the first time, despite the fact that she had been neutered in between.

This suggests that cyproterone acetate can be efficient on neutered subjects too. Cyproterone acetate was stopped again after 18 months for financial reasons, with the same outcome.

She ended under fluoxetine alone and was euthanized at the age of 13 years after a severe bite on the owner's arm.

CASE 2
Presentation

Case 2 is a 4-year-old neutered male English Spaniel Cocker, weighting 13 kg. He is presented at the consultation for intense aggressions that appeared around the age of ten months. Owners describe him as a gentle dog 95% of the time that suddenly changes his look and becomes very aggressive without reason.

History and presenting signs

From the adoption at 2 months old to the age of ten months, the dog behaved perfectly normally. Communication and training were of good quality.

At 10 months, the dog's mood changed by crises lasting a few hours, sometimes happening two days in a row and sometimes not happening for several weeks. Between those episodes, the dog was perfectly normal. During the crises the owners could see his pupils dilated and brutal aggressions could then occur: the dog would growl snarl and attempt to bite around specific resources depending on the episode (a friend's dog, a seatbelt, a sport bag). He could also seek petting and suddenly threaten the owner. According to the owners there was no regular pattern or logical explanation to the aggressive events.

For instance, one day the dog was in the car, on the backseat as always and when the male owner moved his hand to grab the seatbelt, the dog jumped on it, shredding it apart. The owner managed to not get bitten. The dog continued to growl, being very agitated and barking at any attempt to approach the car with dilated pupils for over 10 minutes. The owners waited him to calm down, took a few minutes to walk him out of the car, after which the dog acted normal for the rest of the day.

The owners never reacted in an aversive manner to the guarding episodes: they were waiting the mydriasis to stop, and they could tell when they could interact with the dog again. They looked for solutions: neutering was advised by their veterinarian but did not consistently changed the dog behavior or mood changes.

At the time of the consultation, they had been able to habituate their dog to wear a basket muzzle for each car travel, which made their living possible without too many risks.

Physical examination findings and laboratory results

The physical examination was perfectly normal. The dog was brought to the car and out, manipulated for the examination, but no aggressive reaction was observed during the exam. A recent complete blood analysis had already been done by the referring veterinarian without any abnormal findings.

Diagnosis

In this case, the diagnosis criteria were quite caricatural and dysthymia was the most probable diagnosis (Table 4). This mood disorder is often compared to human bipolar disorder.

Table 4. Diagnosis criteria of dysthymia.

One mandatory criterion: brutal and repeated apparition of productive episodes, characterized by an elevation of vigilance level and activity. In addition, 3 symptoms amongst the following must be present:
• Irritation aggression, brutal, severe and without control from the first episode
• Stereotypic behavior
• Fixity phases with mydriasis
• Object guarding
• Search for contact and petting accompanied with threatening
• Hyperphagia
• Hyposomnia

Differential diagnosis included neurological disorder (partial epileptic crisis, brain tumor) and the interest of MRI was discussed with the owners. Communication trouble was ruled out because of the high quality of the relationship between the dog and the owners

Treatment plan

Behavioral treatment: the behavioral part of the treatment plan consisted in safety management measures (Horwitz, 2008), behavioral modification (Herron et al., 2009), training and family strategies (Table 5).

Medication: the first drug prescribed was fluoxetine at 2.3 mg/kg single in day.

Monitoring: the owners were asked to record every mood change, including starting context, duration and ending context.

Table 5. Behavioral part of the treatment plan.

	Before consultation	After consultation
Safety management measures	• Basket muzzle during car rides • Inconsistent isolation of the dog when a crisis started	• Basket muzzle during car rides • Systematic isolation of the dog in a specific room during crises
Behavioral modification	None	• Track for subtle physical changes announcing a crisis • Use postural communication to be able to isolate him without touching him
Training	• Knowledge of all obedience orders using positive training	• Continue practicing of all obedience orders using positive training
Family strategies	• Renouncement to certain activities because of the fear of the dog's reactions	• Inclusion of the dog in all family activities outside of the crises to maintain a good relationship

Follow-up

Results of the treatment plan outcome over the course of time are summarized in Table 6.

Table 6. Evolution of the dog behavior as a function of the treatment plan.

Before consultation and since the age of 10 months	Under fluoxétine + behavioral treatment	Under fluoxétine + cyproterone acetate + behavioral treatment
• Brutal aggressions without control towards humans occurring during "crises"	• Reduction of intensity but not frequency of the crises	• Disappearance of the crises

After 2 months, the treatment seemed to affect only intensity but not frequency of the crises.

Cyproterone acetate was added at the dose of 1.9 mg/kg bis in day for 2 months and fluoxetine was lowered to 1.5 mg/kg single in day. Two months later, no new aggressive episode was reported but a change in the dog behavior was observed: he was apathic and the owners reported that their dog was not really willing to engage in play activities. His affiliative behavior was changed too: he was not willing to interact with owners and was staying still in his basket if no one was stimulating him. His appetite increased slightly with the treatment adjustment. The dosage of cyproterone acetate was divided by two, putting the new dosage at 1 mg/kg bis in day.

The dosage seemed to fit the dog well and the owners reported a will to play close to its initial level before treatment. Affiliative behavior came back to normal as well.

A blood count and chemistry were required every 6 months to monitor a possible elevation in hepatic enzymes. Safety measures were maintained. Decision was made to keep the care this way unless some aggression reappears or blood analysis changes, and until now, two years later, the dog remained stable and no new crisis happened.

Summary box: Danger

Before accepting to treat such dangerous dogs, it is mandatory to establish a contract between the veterinarian and the owner explaining in detail the safety measures to follow. No medical care

should be engaged without such contract. Systematic use of a muzzle when the dog is in contact with people at risk and an isolation zone inside the house are a minimum to require.

Discussion

In dogs, serotonin reuptake inhibitors are used frequently in the pharmacologic treatment of canine aggression (Dodman et al., 1996). In these clinical cases, dogs were given a high dose of fluoxetine (2.3 to 4 mg/kg per day) as first-intent treatment, which is higher than the recommendation of the European Medicines Agency (i.e. 1 to 2 mg/kg per day). The reason for this dosage was the severity of the symptoms, along with the emergency of the situation, which involved possible euthanasia or rehoming if the clinical status of the dogs did not improve quickly (case 1). Until recently, no published study was providing evidence on the safety of fluoxetine at 2-4 mg/kg per day, but the French behaviorist specialists edited a textbook in 2003 (Mege et al., 2003) for the use of fluoxetine at such dosage.

Recently, the use of fluoxetine at a dose of 2-4 mg/kg per day a was presented for the treatment of HSHA syndrome (Masson & Gaultier, 2018). Such treatment is also supported by several studies in humans (Barrickman et al., 1991; Carlisi et al., 2016; Chantiluke et al., 2015) without adverse effects, even on patients with epilepsy (Kanner, 2016).

Those 2 clinical cases illustrate two severe diagnosis that lead to lifelong treatments, where monotherapy with fluoxetine was insufficient to control the symptoms. Carbamazepine (Meyer et al., 2016), which has anti-epileptic and anti-depressant activities, has been reported to control explosive aggression in humans, but can have profound side effects that include agranulocytosis (Avinash et al., 2016).

In humans, cyproterone acetate was used in the treatment of prostate cancer and is now used for androgen-dependent indications in women and precocious puberty in boys. It is also used to control unresponsive aggression, in aggressive dementia, and sex offender treatment (Le Dare et al., 2015). Cyproterone acetate has a weak glucocorticoid activity, which renders its use safer than other progestins; however, several authors report mild adverse effects such as weight gain, loss of libido and gynecomastia, which are due to the lowered serum testosterone concentrations and are mostly reversible (Turner et al., 2013).

For these cases, adding cyproterone acetate was chosen and appeared useful to decrease the dog's arousal and consequently the frequency of the aggressive episodes. In dysthymia, it even acts as an anti-psychotic, able to decrease significantly the number of episodes.

From a phenotypical description of the dog behavior, fluoxetine and cyproterone acetate seem to have complementary roles: fluoxetine is targeting impulsivity and lowers the intensity of the aggression, whereas cyproterone acetate seems to act on arousal and the motivation to perform the aggression. In our two cases, the dogs improved under fluoxetine, exhibiting problematic behaviors less often and with less impulsivity. Nevertheless, their motivation to perform it was nearly intact and it seems that cyproterone acetate was able to act on this part of the behavior.

One of the 2 cases presented resulted in euthanasia. In this case, the dog would have been euthanized at 5 years if she had been unresponsive to treatment. Instead, the behavioral care offered her 8 years, with a good quality of life despite the safety measures taken to make sure that humans other than her owners would be in complete security.

In the presented cases, the main side effect reported was an increased appetite, which is consistent with the cyproterone acetate mode of action (i.e. the inhibition of a testosterone effect). This side effect should be carefully considered before prescribing cyproterone acetate, because it could lead to food-related aggressions. The counterbalance provided by fluoxetine in the presented cases probably prevented such side-effect.

In our study, no dog exhibited any liver enzymes increase. However, hepatotoxicity has been

described and can lead to fatal acute liver failure induced by cyproterone acetate (Bessone et al., 2016; Nour et al., 2017). For this reason, the authors would like to highlight the importance to keep cyproterone acetate as a secondary line treatment, in cases where single fluoxetine therapy does not provide sufficient results, especially when arousal and excessive motivation are still exhibited despite the first medication and only for diagnosis such as primary dysocialization and dysthymia.

Conclusion

The clinical improvement reported in these 2 cases suggest that using cyproterone acetate may be useful for the treatment of severe social aggressive behavior in dogs low responsive to primary fluoxetine medication. The main side effect reported in this study concerned an increase in appetite which was partly balanced by the loss of appetite induced by the primary treatment (e.g. fluoxetine). Further studies including a larger number of dogs are needed to confirm these preliminary findings.

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Conflict of interest

Authors declare no conflict of interest

Authorship statement

The idea of the paper was conceived by Sylvia MASSON and Gerard MULLER
The cases were handled by Sylvia MASSON
The paper was written by Sylvia MASSON and Gerard MULLER
All authors have approved the final article

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Utilizzo del Ciproterone acetato in due cani aggressivi

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Sintesi

L'aggressività canina rimane una delle principali ragioni di eutanasia ed abbandono del cane.

La neurofisiologia dell'aggressività è ancora parzialmente sconosciuta ma diversi agenti rivestono un ruolo importante nel suo meccanismo: androgeni, cortisolo e serotonina.

Questo spiega perché gli inibitori del reuptake della serotonina sono usati comunemente come trattamenti farmacologici primari. La maggior parte dei cani migliora con modificazioni dell'ambiente e tecniche di modificazione comportamentale associate a questi farmaci.

In alcuni casi particolarmente gravi, questi farmaci non sono in grado di gestire perfettamente il comportamento aggressivo o l'ansia sottostante e possono essere necessari altri farmaci.

Questo è il motivo per cui è stato proposto il ciproterone acetato, un composto antagonista degli androgeni e con attività anti-gonadotropinica.

Questo farmaco ha un ampio meccanismo d'azione, includendo le interazioni con la serotonina e l'acido γ-aminobutirrico, che spiega perché il ciproterone acetato non si comporti come un semplice depressore del testosterone ma possa essere utilizzato in maniera simile agli antipsicotici.

Sono presentati due casi di cani che mostrano aggressività grave, nonostante il trattamento farmacologico primario.

In entrambi i casi, la somministrazione di ciproterone acetato ha portato ad una riduzione del numero e dell'intensità delle aggressioni sociali che sono ricomparse dopo la sua sospensione

Inoltre, i casi selezionati includevano maschi e femmine, sterilizzati e non, fatto che suggerisce che il ciproterone acetato possa essere efficace in entrambi i sessi, a prescindere dalla castrazione.

Il principale effetto collaterale riportato è un aumento dell'appetito che può diventare cospicuo, in assenza della fluoxetina.

Ulteriori studi che includano un maggior numero di soggetti sono necessari per approfondire questi risultati.