Article

Estrogen-induced myelotoxicity in dogs: A review

Hasan B. Sontas, Banu Dokuzeylu, Ozge Turna, Hayri Ekici

Abstract — Exogenous estrogens used for therapeutic purposes or endogenous estrogen sources such as functional Sertoli cell or ovarian granulosa cell tumors may cause bone marrow toxicity in dogs. The condition is characterized by hematologic abnormalities including thrombocytopenia, anemia, and leukocytosis or leukopenia. Despite intensive therapy with blood or platelet-rich transfusions, broad-spectrum antibiotics, steroids, and bone marrow stimulants, prognosis is unfavorable. Due to the the risk of stimulating the development of uterine diseases and the potential for inducing aplastic anemia, estrogen use in dogs is best avoided where possible. This paper describes the causes of estrogen-induced myelotoxicity, the clinical presentation of the patients, the diagnosis, and the treatment options in the dog.

Résumé — Myélotoxicité induite par les œstrogènes chez les chiens : étude. Les œstrogènes exogènes utilisés à des fins thérapeutiques ou des sources d'œstrogènes endogènes, telles que des tumeurs des cellules de Sertoli fonctionnelles ou de la granulosa, peuvent causer la toxicité de la moelle osseuse chez les chiens. L'affection se caractérise par des anomalies hématologiques incluant la thrombocytopénie, l'anémie et la leucocytose ou la leucopénie. Malgré une thérapie intensive avec des transfusions de sang ou riches en plaquettes, des antibiotiques à large spectre, des stéroïdes et des stimulants de la moelle osseuse, le pronostic est défavorable. En raison du risque de stimulation du développement de maladies utérines et du potentiel d'induction de l'anémie aplastique, il est préférable d'éviter l'utilisation des œstrogènes chez les chiens dans la mesure du possible. Cet article décrit les causes de myélotoxicité induite par les œstrogènes, la présentation clinique des patients, le diagnostic et les options de traitement pour le chien.

(Traduit par Isabelle Vallières)

Can Vet J 2009;50:1054–1058

Introduction

For many decades, estrogens or synthetic estrogenic compounds have been used in female dogs for the treatment of mismating (1), hormonal urinary incontinence (2), estrus induction (3), or pseudopregnancy (4), and in male dogs for the management of prostatic hypertrophy, perianal adenoma, or testicular neoplasms (5). Development of estrogen-induced myelotoxicity (EIM) and pyometra following the use of estrogens for the management of diseases (6–11) and for experimental purposes have been reported previously (12–16). Furthermore, similar spontaneous myelopoietic damage to bone marrow has been demonstrated in male dogs with testicular tumors of interstitial cell (17) and sertoli cell (18), and in females with ovarian granulosa cell tumor (19).

Clinical signs of EIM include complete loss of appetite, depression, pale mucous membranes, petechial hemorrhages, uni- or bi-lateral epistaxis, vulvar edema, and vaginal bleeding (6–19,20). Typical hematologic changes are nonregenerative anemia, thrombocytopenia, and leukocytosis followed by a leukopenia. Diagnosis of EIM is based on a history of estrogen administration, physical examination, clinical signs, and hematologic findings. Treatment options vary with the cause of the myelotoxicity and include removal of potential estrogen sources, frequent whole blood transfusions or platelet-rich plasma infusions, antibiotics, androgens, corticosteroids and bone marrow stimulants. In untreated dogs, prognosis is always considered to be unfavorable despite early diagnosis. In this paper, etiology, pathophysiology, clinical presentation, diagnosis, and treatment options for estrogen-induced myelotoxicity in the bitch are reviewed.

Estrogens

Estrogens are steroid compounds, synthesized primarily by the ovaries, and to a lesser extent by the testicles, adrenal cortex, and placenta. Other sites of estrogen production include liver, muscle, fat, and hair follicles (5). The immediate precursors to the estrogens are androstenedione or testosterone, and estradiol

Departments of Obstetrics and Gynecology (Sontas, Turna, Ekici) and Internal Medicine (Dokuzeylul), Faculty of Veterinary Medicine, Istanbul University, Avcilar Campus, 34320, Avcilar, Istanbul, Turkey.

Address all correspondence to Dr. Besim Hasan Sontas; e-mail: bhsontas@istanbul.edu.tr

17-β and estrone are the main endogenous estrogens in most species (21). Estrogens are necessary for many physiological actions in the body including: normal growth and development of female gonads; development of secondary sexual characteristics including duct growth of the mammary glands, changes in body conformation and hair growth; production of clinical signs of estrus; normal contractility of the uterus; promotion of bactericidal activity of the uterus during estrus by increasing the rate of migration of leucocytes into the uterine lumen; sensitization of the uterine muscle to oxytocin; relaxation of the pelvic structures, softening of the pubic symphysis and enlargement of general perineal area during parturition; regulation of skeletal growth and maintenance of the skeleton; vasostimulation and health of the skin; and increasing the coagulability of the blood.

Natural estrogens such as estradiol, estrone, and estriol are produced from natural sources such as the urine of pregnant mares and women, the adrenals and testes of stallions, and the human placenta and amniotic fluid (21). Synthetic estrogens exerting the same effect as natural estrogens including diethylstilbestrol (DES), ethinyl estradiol, and esters of estradiol such as benzoate, cypionate, propionate, valerate, enanthate, and undeclynate are produced from coal-tar derivatives and other steroids (21). Clinical use of estrogens in humans and dogs is given in Table 1.

In small animal practice, immediate treatment of unwanted matings is the most common reason for the administration of estrogens, which prevent conception by closure of the tubal-uterine junction or their effect on the oviduct and uterus (22). Today, the use of estrogens for mismating is no longer recommended because 1) uterine disturbances including pyometra may develop; 2) most mismated dogs are reported to be nonpregnant at the time of examination; 3) availability of progesterone-receptor blockers such as aglepristone that enable clinicians to terminate pregnancies during any stage of gestation with less side effects; 4) safe and efficacious doses of estrogens do not exist; and 5) fatal myelotoxicity due to the administration of estrogens has been reported. However, a study by Tsutsui (23) demonstrated that a single treatment of estradiol benzoate at 0.2 mg/kg on day 5 post-ovulation effectively prevented pregnancy without causing any side effects. Tsutsui et al (23) indicated that side effects would be more common in animals treated with repeated administration of estradiol benzoate.

Pathophysiology of estrogen-induced myelotoxicity

Early studies in the 1940's clearly demonstrated the myelotoxic effects of exogenous estrogens in dogs (12,13). After the use of estrogens, neutrophil production increases in the bone marrow, resulting in an increase in white blood cells in the peripheral blood and a left shift. Leukocytosis is followed by leukopenia, but persists until day 21 (12,13,24). According to Chiu (25), the effects of estrogens on the hematopoietic system occurs in 3 stages. Stage 1 (days 0–13) is associated with a brief increase in platelet numbers followed by a severe thrombocytopenia. Stage 2 (days 13–20) is characterized by bone marrow granulocyte hyperplasia with neutrophilia. Stage 3 (days 21–45) may be associated with marrow recovery or marrow aplasia depending on the dose used. The mechanism of EIM is not fully understood, but studies have confirmed estrogen-induced production of a myelopoiesis-inhibitory factor by thymic stromal cells of dogs in vitro (26) and in vivo (27).

Table 1. Clinical use of estrogens in humans and dogs

Uses in humans	Uses in dogs
Contraception	Pregnancy termination
Post-menopausal hormone replacement	Urinary incontinence
Primary hypogonadism	Pseudopregnancy
Senile or atrophic vaginitis	Induction of estrus
Prostatic cancer	Anal adenoma
Dysfunctional uterine bleeding	Prostate hypertrophy
Acne	Testicular tumors
Hirsutism	Lactation suppression
Prevention of heart attacks	
Osteoporosis	
Breast cancer	
Suppression of post-partum lactation	

Exogenous estrogens administered at excessive or repeated doses or at recommended dosages to dogs with idiosyncratic sensitivity and estrogen-producing ovarian or testicular neoplasms induce toxicity (10,17–19). However, most of the reported cases had an over-dosage of estrogens. In the reported cases, myelotoxicity was associated with administration of estradiol cypionate, estradiol benzoate or diethyl stilbestrol in excess of or at the recommended doses (6–11). The response of the bone marrow to estrogens varies from one dog to another, because some dogs may have fatal bone marrow suppression, whereas others have only mild to moderate damage after the administration of the same dose (13). This individual sensitivity does not depend on breed, nutrition, route of administration, or the reason for use of the drug but it is highly correlated with age, type of estrogen used, total dose, and physical condition of the animal (6,13). A summary of the previously reported cases is given in Table 2.

Clinical signs

Due to the individual sensitivity to estrogens, clinical signs may vary from completely normal to collapse. The affected animals may show complete loss of appetite, exercise intolerance, vulvar edema, vaginal bleeding, pallor, dyspnea, hematuria, melena, fever, uni- or bi-lateral epistaxis, and petechiation of the skin or mucous membranes (6–11,15,16,28). Less common clinical signs include edema around the mouth and perineal area, alopecia, mammary hypertrophy, head tilt, bilateral nystagmus, signs of feminization in males and estrus behavior and coitus with failure to conceive in females. Furthermore, development of type III vaginal prolapse has been recently reported in a young, 40-kg, cross-breed dog which had a 24-h history of estradiol benzoate administration at a dose of 0.3 mg/kg for estrus induction (29). Clinical signs including vulvar discharge, abdominal distention, vomiting, polyuria, and polydipsia may be observed, if pyometra is also induced by estrogen administration (30).

Diagnosis

Diagnosis is based on the history of estrogen administration, clinical symptoms, physical examination findings, laboratory analysis, and bone marrow cytology (6). A complete blood (cell)

Table 2. Characteristics of previously reported cases of estrogen-induced myelotoxicity in bitches

Reference	Breed	Age (y)	Reproductive status	BW (kg)	Drug/Dose	Route, Frequency	Reason for use
6	Cross-bred shepherd	6	intact	57	ECP/10 mg	IM, once	mismating
6	St. Bernard	4	intact	NS	a) ECP/10 mg b) DES/90 mg	a) IM, 2 times 1 wk apart b) 50 mg, IM once + 5 mg PO, q24h for 8 d	infertility
8	NS	NS	NS	NS	ECP/0.22 mg/kg	IM 2 times at 21 d interval	urinary incontinence
8	NS	NS	NS	NS	ECP/0.08 mg/kg	IM 2 times at 15 d interval	urinary incontinence
8	NS	NS	NS	NS	NS	IM once	mismating
9	Airdale terrier	4	intact	20	ECP/2 mg	IM 3 times at 48- to 72-hour interval	mismating
10	Old English sheepdog	6	spayed	28	a) DES/18 μg/kg b) DES/36 μg/kg c) ECP/0.14 mg/kg	a) PO, q24h for 15 mo b) PO, q12h for 3 wk c) IM 2 times at 1 wk intervals	urinary incontinence
11	Glen of Imaal terrier	2	intact	NS	EB/10 μg/kg	SC 3 times at 2–3 d intervals	mismating
20	Poodle	2	intact	3.6	ECP/1 mg	IM 2 times at 1 wk intervals	mismating

NS — not specified, ECP — estradiol cypionate, DES — diethyl stilbesterol, EB — estradiol benzoate, IM — intramuscular, SC — subcutaneous, PO — per os.

Table 3. Summary of treatment and outcomes of cases of estrogen-induced myelotoxicity in bitches

Reference	Delay[a]	Hematologic findings	Clinical signs	Treatment	Outcome
6	14	Anemia, leukocytosis, thrombocytopenia	Petechial hemorrhages, lethargy, decreased appetite	Corticosteroids, antibiotics, whole blood transfusions	Died 16 d after administration of ECP (2 days after diagnosis)
6	21	Leukocytosis	Vulvar swelling, vaginal discharge	Antibiotics	Full recovery in 90 d
8	47	Leukopenia, thrombocytopenia	Cutaneous ecchymotic hemorrhages	No treatment	Euthanized
8	15	Leukopenia, thrombocytopenia	Vulvar swelling	Platelet-rich plasma transfusions	Full recovery in 70 d
8	7	Anemia, leukocytosis, thrombocytopenia	Bloody vulvar discharge	No treatment	Euthanized
9	15	Anemia, thrombocytopenia, leukopenia	Lethargy, anorexia, fever, ocular discharge, lameness, vaginal discharge	Fresh blood, antibiotics, vitamin-mineral supplement, anabolic steroid	Full recovery in 81 d
10	30	Anemia, leukopenia, thrombocytopenia	Lethargy, vaginal discharge, attraction to male dogs	Antibiotics, vitamin-mineral supplement, lithium carbonate	Full recovery in 42 d
11	10	Anemia, thrombocytopenia, leukocytosis	Collapse	Fluid therapy, whole blood transfusion, platelet-rich transfusion, antibiotics	Full recovery in 14 d
20	21	Anemia, thrombocytopenia, normal leukocyte count	Hematuria, uncoordination, head tilt, scleral hemorrhage	Corticosteroids, antibiotics, vitamin-mineral supplement, platelet-rich plasma, lithium citrate	Full recovery in 48 d

[a] Days between estrogen administration and presentation. ECP — Estradiol cypionate.

count after estrogen administration demonstrating nonregenerative anemia, thrombocytopenia and leukocytosis (until week 3) may aid in confirming the diagnosis. Although the history of estrogen administration, clinical signs, and laboratory findings are sufficient to establish the diagnosis, abdominal radiography or ultrasonography should be performed for locating and staging estrogen-producing tumors and for diagnosis of pyometra, if the physical condition of the affected animal allows. Examination of bone marrow aspirate may be performed to support the diagnosis and to evaluate the prognosis. Necrotic lesions and an inflammatory response have been demonstrated in the bone marrow of dogs receiving high doses of estrogens (13). In an advanced stage, bone marrow biopsy may reveal hypocellularity with depletion of all hematopoietic cell lines. Differential diagnosis of EIM includes other conditions that cause pancytopenia such as toxins, drugs, infection, neoplasia, immune-mediated diseases, myelodysplasia, bone marrow necrosis, osteosclerosis, and myleofibrosis (31).

Treatment

Reported cases of estrogen toxicity have either ended in death of the patient (7,17,18) or in a long recovery period (9–11,20). Treatment options depend on the underlying cause of the myelotoxicity. In cases of estrogen-producing testicular or ovarian tumors, surgical removal of the source may be curative with long-term intensive care. Treatment includes 1) correction of the anemia and thrombocytopenia, 2) protection against infections, and 3) stimulation of the remaining bone marrow elements (10). Prolonged treatment with periodic fresh blood or platelet-rich transfusions, broad-spectrum antibiotics, steroids and bone marrow stimulants is essential in affected animals (6,10,11,17,18). Hemograms should be obtained weekly during the treatment, but care should be taken during venipuncture or other invasive procedures since bruising may occur in highly thrombocytopenic animals.

Androgen therapy to stimulate bone marrow recovery has given remarkable results in humans with aplastic anemia (32,33). A prolonged treatment with combined testosterone and corticosteroid therapy provided complete recovery of approximately 50% of patients with chloramphenicol-induced or idiopathic acquired aplastic anemia (32). An anabolic steroid, nandrolone decanoate (2.5 mg/kg, intramuscularly, once weekly) was used to stimulate bone marrow activity in a female Airedale terrier with a history of estradiol cypionate treatment for mismating. On day 81, hematologic values of the dog had been within reference ranges. In another report, methyltestosterone provided complete recovery in a dog with EIM (34).

Lithium carbonate, which has been known to stimulate neutrophil production in humans, has been used with success for canine cyclic hematopoiesis (35). Furthermore, the use of lithium in dogs with EIM has also provided full recovery (10,20). Lithium stimulates division of pluripotential stem cells by an unknown action. Maddux and Shaw (20) used lithium citrate at a dose of 21 mg/kg PO, q24h in divided doses in a dog with a history of EIM. On day 46, normal values of erythrocyte, leukocyte, and platelet numbers were obtained. However, it was difficult to assess the efficacy of lithium therapy in this case, because the dog was also medicated with prednisolone. Furthermore, serum lithium concentrations never reached an optimum therapeutic level. In another case (10), a dog with a history of DES therapy for urinary incontinence made full recovery with lithium carbonate therapy (11 mg/kg, PO, q12h). During lithium treatment, serum or plasma lithium concentrations should be measured weekly in order to see if the drug reaches optimum therapeutic levels (0.5 to 1.8 mmol/L, in the dog) (32). Renal function should also be evaluated during treatment since nephrotoxicosis may be easily induced. One should be aware that the efficacy of lithium or anabolic steroids such as nandrolone decanoate and methyltestosterone in EIM has not been established other than by case reports.

In untreated cases, the prognosis of dogs with EIM is always considered to be unfavorable, despite early diagnosis. Death from estrogen toxicity frequently occurs from complications of hemorrhage and infection (11,14). Necropsy findings include swollen spleen with hypoplastic germinal centers, reduction in size of the ovaries or testes, enlarged prostate or uterus, inguinal hernia, general depletion of lymphocytes, amyloidosis, and fatty degeneration of the liver (6,15).

In conclusion, whenever using estrogens in dogs, the risk of stimulating the development of pyometra and the potential for inducing aplastic anemia should be discussed with the owner and weighed against the potential benefits. Alternative treatments with progesterone-receptor blockers, dopamine agonists, phenylpropanolamine or GnRH analogs for mismating, pseudopregnancy, or hormonal urinary incontinence should be considered. CVJ

References

1. Eilts BE. Pregnancy termination in the bitch and queen. Clin Tech Small Anim Pract 2002;17:116–123.
2. Angioletti A, De Francesco I, Vergottini M, Battocchio ML. Urinary incontinence after spaying in the bitch: Incidence and oestrogen-therapy. Vet Res Commun 2004;28:153–155.
3. Kutzler MA. Estrus induction and synchronization in canids and felids. Theriogenology 2007;68:354–74.
4. Gobello C, de la Sota RL, Goya RG. A review of canine pseudocyesis. Reprod Dom Anim 2001;36:283–288.
5. McDonald LE. Estrogens. In: Booth NH, McDonald LE, eds. Veterinary Pharmacology and Therapeutics. 6th ed. Ames, Iowa: Iowa State Univ Pr, 1988:598–604.
6. Lowenstein LJ, Ling GV, Schalm OW. Exogenous estrogen toxicity in the dog. Calif Vet 1972;26:14–19.
7. Mills JN, Slatter DH. Stilboestrol toxicity in a dog. Aust Vet J 1981;57:39–42.
8. Weiss DJ, Klausner JS. Drug-associated aplastic anemia in dogs: Eight cases (1984–1988). J Am Vet Med Assoc 1990;196:472–475.
9. Van Kruiningen HJ, Friedland TB. Responsive estrogen-induced aplastic anemia in a dog. J Am Vet Med Assoc 1987;191:91–92.
10. Hall EJ. Use of lithium for treatment of estrogen-induced bone marrow hypoplasia in a dog. J Am Vet Med Assoc 1992;200:814–816.
11. Acke E, Money CT, Jones BR. Estrogen toxicity in a dog. Ir Vet J 2003;56:465–468.
12. Castrodale D, Bierbaum O, Halwig EB, MacBryde CM. Comparative studies of the effects of estradiol and stilbestrol upon the blood, liver and bone marrow. Endocrinology 1941;29:363–372.
13. Crafts RC. The effects of estrogens on the bone marrow of adult female dogs. Blood 1948;3:276–285.
14. DeVita J. Hyperestrogenism. In: Progress in Canine Practice. Catcott EJ, Smithcors JF, eds. California: American Veterinary Publications, 1967:419–420.
15. Schwartz E, Tornaben JA, Boxill GC. Effects of chronic oral administration of a long-acting estrogen, quinestrol, to dogs. Toxicol Appl Pharmacol 1969;14:487–494.
16. Bowen RA, Olson PN, Behrendt MD, Wheeler SL, Husted PW, Nett TM. Efficacy and toxicity of estrogens commonly used to terminate canine pregnancy. J Am Vet Med Assoc 1985;186:783–788.
17. Suess RP, Barr SC, Sacre BJ, French TW. Bone marrow hypoplasia in a feminized dog with interstitial cell tumor. J Am Vet Med Assoc 1992;200:1346–1348.
18. Sanpera N, Masot N, Janer M, Romeo C, De Pedro R. Estrogen-induced bone marrow aplasia in a dog with a sertoli cell tumour. J Small Anim Pract 2002;43:365–369.
19. McCandlish IA, Munro CD, Breeze RG, Nash AS. Hormone producing ovarian tumours in the dog. Vet Rec 1979;105:9–11.
20. Maddux JM, Shaw SE. Possible beneficial effect of lithium therapy in a case of estrogen-induced bone marrow hypoplasia in a dog: A case report. J Am Anim Hosp Assoc 1983;19:242–245.
21. Roberts SJ. The estrogens. In: Roberts SJ, ed. Veterinary Obstetrics and Genital Diseases. Woodstock, Vermont: Roberts SJ, 1986:403–405.
22. Wanke MM, Romagnoli S, Verstegen J, Concannon PW. Pharmacological approaches to pregnancy termination in dogs and cats, including the use of prostaglandins, dopamine agonists and dexamethasone. In: Concannon PW, England G, Verstegen J, Linde-Forsberg C, eds. Recent Advances in Small Animal Reproduction. Available from www.ivis.org Document No. A1223.0802. Last accessed July 28, 2009.

23. Tsutsui T, Mizutani W, Hori T, Oishi K, Sugi Y, Kawakami E. Estradiol benzoate for preventing pregnancy in mismated dogs. Theriogenology 2006;66:1568–1572.
24. Gaunt SD, Pierce KR. Effect of estradiol on hematopoietic and marrow adherent cells of dogs. Am J Vet Res 1986;47:906–909.
25. Chiu T. Studies on estrogen-induced proliferative disorders of hemopoietic tissue in dogs, [Thesis] St. Paul, University of Minnesota, USA. 1974:1–270.
26. Farris GM, Benjamin SA. Inhibition of myelopoiesis by conditioned medium from cultured canine thymic cells exposed to estrogens. Am J Vet Res 1993;54:1366–1373.
27. Farris GM, Benjamin SA. Inhibition of myelopoiesis by serum from dogs exposed to estrogen. Am J Vet Res 1993;54:1374–1379.
28. Mylonakis ME, Saridomichelakis MN, Lazaridis V, Leontides LS, Kostoulas P, Koutinas AF. A retrospective study of 61 cases of spontaneous canine epistaxis (1998 to 2001). J Small Anim Pract 2008;49:191–196.
29. Sarrafzadeh-Rezai F, Saifzadeh S, Mazaheri R, Behfar M. First report of vaginal prolapse in a bitch treated with oestrogen. Anim Reprod Sci 2008;106:194–199.
30. Smith FO. Canine pyometra. Theriogenology 2006;66:610–612.
31. Tilley LP, Smith FWK. Estrogen toxicity. In: Tilley LP, Smith FWK, eds. The 5-Minute Veterinary Consult: Canine and Feline. 3rd ed. Philadelphia: Lippincott Williams and Wilkins, 2004:430–431.
32. Shabidi NT, Diamond LK. Testosterone-induced remission in aplastic anemia of both acquired and congenital types: Further observations in 24 cases. N Engl J Med 1961;264:953–967.
33. Daiber A, Herve L, Con I, Donoso A. Treatment of aplastic anemia with nandrolone decanoate. Blood 1970;36:748–753.
34. Legendre AM. Estrogen-induced bone marrow hypoplasia in a dog. J Am Anim Hosp Assoc 1976;12:525–527.
35. Hammond WP, Dale DC. Lithium therapy of canine cyclic hematopoiesis. Blood 1980;55:26–28.