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Teratogenicity in dogs and cats - a review for practitioners and toxicologists[1]

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Keywords: teratogenicity, dog, cat, experimental, clinical observations.

Summary

After a short description of teratological principles, the dog and the cat are introduced as experimental animals by means of several drugs (including vitamin A) tested in the years 1959 - 2003.

Recommendations for drugs which should not be applied during pregnancy - as far as can be found in the literature - are given for the practitioner. These recommendations, however, are often extrapolated from data obtained in other species. Malformations seen after griseofulvin treatment or parvovirus vaccination in cats and hermaphroditism observed after testosterone treatment in dogs seem to be the only firm clinical observations.

Our knowledge about drug treatment in pregnancy is not satisfying at all. It is recommended to avoid any drug administration to pregnant pets unless absolutely necessary.

Schlüsselwörter: Teratogenität, Hund, Katze, experimentell, klinische Beobachtung.

Zusammenfassung

Teratogenität bei Hunden und Katzen - eine Übersicht für Praktiker und Toxikologen

Anhand 6 entscheidender Kriterien (WILSON, 1973) wird das Wesen der Teratogenität rekapituliert.

Auf der Suche nach Versuchstieren, die dem Menschen phylogenetisch näher stehen als Nagetiere, hat man vor allem in den 70er und 80er-Jahren des vorigen Jahrhunderts auch Hunde und Katzen als Versuchstiere im Rahmen der Teratogenitätsforschung herangezogen. Entsprechende Ergebnisse werden referiert. Eine direkte Übertragbarkeit der Ergebnisse auf den Menschen ist nicht in allen Fällen gegeben.

Für die Praxis gibt es wenig gesicherte Daten, welche Substanzen an trächtigen Hunden und Katzen vermieden werden sollen. Empfehlungen orientieren sich eher an den (experimentellen) Ergebnissen, die an anderen Tierarten erhoben wurden oder an einzelnen klinischen Beobachtungen. Konkret wurden an der Katze Mißbildungen nach Griseofulvinbehandlung bzw. nach Impfung mit einem Panleukopenie-Lebendimpfstoff beschrieben, am Hund Hermaphroditismus nach Testosteronbehandlung.

Alles gipfelt in der altbekannten Empfehlung, trächtige Tiere nur im äußersten Notfall medikamentell zu behandeln. Die Situation wird dadurch kompliziert, daß in vielen Fällen eine frühe Trächtigkeit nicht bekannt ist.

Introduction

Teratology (as part of feto/embryotoxicity) is the study of abnormal prenatal development leading to congenital malformations.

Interestingly enough, teratology as a science started in the 1930s with a “veterinary accident”: malformed piglets were born from a sow fed an experimental diet deficient in vitamin A. All these piglets suffered from a lack of eye balls (HALE, 1933).

The thalidomide catastrophe (in the late 1950s) is widely believed to be the catalyst that prompted regulatory authorities to investigate requirements for new drugs to be thoroughly tested in animals prior to approval for marketing, especially to investigate the effects on the reproductive system.

Physical (irradiation, elevated temperature [fever]), chemical (environmental [e.g. methyl mercury]), biological factors (infections [e.g. rubella], modified live virus vaccines) and medications (even vitamines) are able to elicit teratogenic effects. This review will cover experimental teratogenicity (chemicals, vitamin A) and teratogenicity induced by veterinary measures (medications, vaccination).

Exposure to teratogenic drugs can affect prenatal development directly (without or after metabolisation by the mother) by altering gene expression of the conceptus, by altering apoptosis, cell migration or proliferation, histiogenesis, synthesis or function of proteins or nucleic acids, or the supply of energy sources (POLIFKA and FRIEDMAN, 2002). Other factors might influence the development indirectly via the mother: e.g. in diabetes, the glucose produced during episodes of maternal hyperglycemia crosses the placenta, causing the fetus to produce insuline that cannot be cleared (McELHATTON, 2003). Also, fetal development can be impaired when as little as 10 per cent of the placenta (in humans) is adversely affected by infarction or

[1] Dedicated to Univ. Prof. Dr. Walter Kobinger on the occasion of his 80th birthday

fibrosis (McELHATTON, 2003). Although the endpoint is not malformation (= "classical" teratogenesis) it should be mentioned here, that in rabbits given human granulocyte colony-stimulating factor neutrophils accumulate in the vessels of the placenta leading to placental embolism with fetal death and abortion (KATO et al., 2001).

Principles of teratogenesis

The (direct) teratogenesis follows certain principles (WILSON, 1973):

- "Susceptibility to teratogenesis depends on the genotype of the conceptus and how it interacts with the environment." This principle will be important for the present review as far as different species of animals respond differently to a developmental toxicant.
- "Susceptibility to a teratogenic agent varies with the developmental stage at which the exposure occurs." The period of maximum sensitivity to a teratogen corresponds to the critical period of organogenesis. The following values are given by SCHARDEIN (1985) regarding this critical period: dog = day 14 to 30, cat = day 14 to 26 of pregnancy. Prior to these periods the embryo will either continue to develop normally or spontaneously abort; after organogenesis the embryo (fetus) becomes less susceptible to teratogenic effects.
- "Teratogenic agents act through specific mechanisms on developing cells and tissues to initiate abnormal embryogenesis (pathogenesis)". A short overview on these different mechanisms was given above (POLIFKA and FRIEDMAN, 2002).
- "The final manifestation of abnormal development are death, malformation, growth retardation and/or functional disorder." This principle points out that structural malformations are not the only possible outcome after the conceptus is exposed to a developmental toxicant. For endpoints like "death", however, today the term "embryotoxicity" instead of teratogenicity is used.
- "The access of an adverse environmental agent to developing tissues depends on the nature of the agent (influences)." This point addresses the questions of teratogenic action without or after metabolic activation, the placental transfer etc. However, it seems inappropriate to classify some agents as more potent teratogens than others because teratogenicity depends not only on the nature of the agent itself , but also on the gestational timing and on the dose and route of exposure. These considerations culminate in the so-called Karnofsky´s law stating that "any drug administered at the proper dosage and at the proper stage of development to embryos of the proper species ….. will be effective in causing disturbances in embryonic development" (KARNOFSKY, 1965).
- "Manifestations of deviant development increase in degree as dosage increases from no-effect to the lethal level." This sentence is valid as long as we omit the "lethal level" (see above). Teratogenic effects (malformations) are mostly dose-dependent (after exceeding a threshold dose), but not necessarily in a linear manner. The most important point is, that maternal and embryonic susceptibility to a drug can be entirely different and, therefore, it is possible for a given dose which is harmless to the mother to cause severe damage to the embryo.

Experimental teratogenicity

Most embryotoxic studies in animals are performed in the course of the development of drugs for human use (LORKE, 1987). However, there is no animal species which meets the human situation exactly. Not only the placental structure and the placental transport/barrier function should be comparable but also the metabolism and the kinetics of the study drug. It is important to note that even non-human primates (with an identical placenta) can differ kinetically from humans as much as other species (ICH S5 [R2], 2005).

Today rats (as a rodent species) and rabbits (as a non-rodent species) are used routinely for teratologic studies (ICH S5 [R2], 2005). Although both species have a hemochorial placenta as humans, mature placentas show certain morphological differences (PICHLER, 2006). Furthermore, placental tranfer functions in relation to teratogenicity are of doubtful significance for man because the atypical yolk sac placenta, on which these 2 species depend during early organogenesis, is thought to transfer many chemicals differently from that seen in humans (see WILSON, 1974).

It was therefore the goal of many scientists in the past to broaden the spectrum of animal species, to include experimental animals with closer phylogenetic relationship to man than do rodents (KHERA, 1979a). Dogs and cats were also considered.

The usefulness of the dog is controversially discussed. ROBERTSON et al. (1979) considered the dog as an acceptable alternative species in teratogenic screening and justified this statement by the sensitivity of the dog to several teratogens including thalidomide, trypan blue, hypervitaminosis A, and antiestrogens. ESAKI et al. (1980) admit that dogs respond differently to potential teratogens than other laboratory animals, but were found to be a useful animal species for comparative studies in teratology. EARL et al. (1975) concluded that the dog has not the required index of sensitivity to become an efficient indicator of teratogenicity. Costs of conducting studies involving large numbers of dogs, needed for significant results, are almost prohibitive in addition to an extended time lapse (4 to 8 month) before results can be obtained.

Cats (almost exclusively used by KHERA [1973, 1975, 1976, 1979 a,b]) are suggested as a useful species for screening drugs and chemicals for their teratogenic potential, and this is justified by the positive response to the teratogenic effects of methyl mercury, thalidomide, and griseofulvin. Neurological signs associated with cerebral and cerebellar lesions in offspring of cats poisoned with methyl mercury are especially pointed out (KHERA, 1973).

Dogs

The malformation rate in a very small number of litters treated with placebo via gastric intubation ranged between 0 and 18.2 % (ROBERTSON et al., 1979).

Beagle bitches were administered acetylsalicylic acid (Aspirin) as aqueous suspension via gastric intubation at either 100 or 400 mg/kg/day between days 15 and 22 or days 23 and 30 post mating. Maternal toxicity was evident in all dogs with 400 mg/kg/day. The malformation rate was 0 % in the 100 mg/kg group (days 15-22, 3 litters), 20 % in the second 100 mg/kg group (days 23-30, 1 litter), 14.3 %

in the 400 mg/kg group (days 15-22, 2 litters), and 50 % in the group treated with 400 mg/kg on pregnancy days 23-30 (3 litters). Observed malformations included, but were not limited to cleft palate, micrognathia, anasarca, cardiovascular malformations, and tail anomalies. Authors (ROBERTSON et al., 1979) consider only 400 mg/kg/day of Aspirin given during days 23 to 30 (i.e. the second half of development of the major organ systems in the dog) as clearly teratogenic.

ESAKI et al. (1980) did not observe drug-related malformations with Aspirin given at 100 and 200 mg/kg during pregnancy days 20-34.

Cortisone acetate was administered during pregnancy days 20 to 34 at 2.5, 10 and 25 mg/kg. Malformations (mainly umbilical hernia and ventricular septal defects) were observed in the 10 and 25 mg/kg groups (ESAKI et al., 1980).

No drug-related malformations were observed after treatment of dogs with diphenylhydantoin at 100, 200, 400, or 800 mg/kg during pregnancy days 20-34 (ESAKI et al., 1980).

SCHARDEIN et al. (1973) tested an estrogen antagonist (CI-628) given orally by capsule once daily for 15 days beginning on the day of the first mating at 0.075, 0.125, 0.25, 0.5, 1, 2, and 5 mg/kg in groups of 1 to 4 females. No malformations were seen at 0.075 mg/kg, 5.3 % at 0.125 mg/kg, and 60 % at 0.25 mg/kg. None of the dogs receiving 0.5, 1, 2, or 5 mg/kg became pregnant.

Studies in dogs have shown that griseofulvin may cause adverse effect in pups (USP CONVENTION, 1994).

No drug-related malformations were observed for methotrexate (0.05 or 0.2 mg/kg at pregnancy days 20-24 or 25-29) by ESAKI et al. (1980).

SHANE et al. (1969) fed female dogs with methyl testosterone (150 µg/kg/day) from the day of first mating through pregnancy, parturition, lactation and for 9 month thereafter. They compared 14 litters of treated bitches and 14 control litters. In the treatment group 45 males, no females but 42 intersex puppies were born, whereas this ratio was 51 males, 33 females and no intersex in the control group. According to their karyotype, the intersex puppies were genetic females.

No drug-related malformations were observed with tetracycline given at 1,000 or 2,000 mg/kg during gestational days 20-34 (ESAKI et al., 1980).

All pups of bitches treated orally with 60 mg/kg of thalidomide died in utero. In 6 dogs treated analogously with 30 mg/kg during days 8 to 20 of pregnancy, 46 nidationes and 9 resorptions were observed. 37 pups could be examined, 14 of which showed anomalies : celosomia, exencephaly, scoliosis, harelip, malposition of tail and limbs , hypoplasia and amelia of hind limbs, and agenesia of the pelvic girdle (DELATOUR et al., 1965).

ESAKI et al. (1980) tested thalidomide at 50 to 800 mg/kg during pregnancy days 15-19, 20-24, or 25-29. Malformations were observed in groups administered with dosages over 100 mg/kg during pregnancy days 20-24. The malformations mainly observed were hooked- and screwtails, missing kidneys and cardiovascular anomalies including coarctation of the aorta, truncus arteriosus, and double outlet right ventricle. Other malformations such as hairlip, cleft palate, and umbilical hernia were observed at low frequency.

CONN and HARDY (1959) tried to produce cardiovascular anomalies in dogs (for diagnostic and operative studies) by trypan blue. 0.5 ml of an 1 % aqueous solution was injected (no route given) per pound of body mass on day 10 of pregnancy. However, “only” 8 cardiovascular anomalies were produced in 106 puppies.

Missing kidneys were observed at low frequency in urethane treated dogs by ESAKI et al. (1980). Doses used were 500 or 1,000 mg/kg at gestational days 20 or 30, and 1,000 mg/kg at gestational day 30.

Vitamin A was given by WIERSIG and SWENSON (1967) to mated Beagle bitches to investigate a teratogenic effect. Daily oral administration of vitamin A in doses of 50,000 to 125,000 IU/kg of body mass and at varying periods from day 9 through day 31 of pregnancy was used. Cleft palate was produced when daily treatment with 125,000 IU/kg included day 17 through 22. Other abnormalities observed were deformed and accessory auricles and kinked tails.

Zonisamide, an anti-epileptic agent, was administered to pregnant dams during the period of fetal organogenesis at doses of 10, 30, and 60 mg/kg/day (TERADA et al., 1987). At 30 and 60 mg/kg various kinds of visceral abnormalities, mainly ventricular septal defects (6.7 and 45.0 %, respectively), and an increased incidence of 8 lumbar vertebrae (20.7 and 31.6 %, respectively) occurred. Kinky, short or rudimentary tails due to fusion and deformity of the caudal vertebrae was frequently observed at 60 mg/kg (50 %).

Further examples for the use of dogs in teratogenicity studies are the papers of TAYLOR and MAYS (1978, testing Ca-DTPA, a chelating vehicle used in nuclear medicine), of NISHIMURA et al. (1985, testing alacepril, an angiotensin converting enzyme inhibitor), of BAILIE et al. (1986, testing acetohydroxamic acid, a potent urease inhibitor, used in urinary infections), and of CLARK et al. (1992, testing ivermectin and pyrantel pamoate).

Cats

KHERA (1975,1979b) reported an 8 % incidence of fetal cardiovascular anomalies and 7.7 % of visceral and skeletal anomalies in control groups of cats which were given empty capsules on pregnancy days 10-20/22.

Acetylsalicylic acid (Aspirin) was administered orally in gelatine capsules at 25 mg/kg (10 cats, pregnancy days 15-20) and 50 mg/kg (pregnancy days 10-15, n=12; pregnancy days 15-20, n=8). In both 50 mg/kg groups an increased frequency of anomalies was observed. The anomalies involved various organs and appeared to be non-specific (KHERA, 1976).

Aminopterin (a folic acid antagonist) was also given in capsules at 0.1 mg/kg on pregnancy day 12 (n=3), 14 (n=5), or 16 (n=6). An increased incidence of abortion and adverse effects on fetal development was observed, both effects, however, were not significant (KHERA, 1976).

Diphenylhydantoin (phenytoin, an anticonvulsive drug and teratogen in mouse and rat) was given orally in gelatine capsules at 1 or 2 mg/kg on gestational days 10 to 22 to 13 cats each. The number of resorptions in the 2 mg/kg group was higher than in the control; the occurrence of anomalies and their types in the live fetuses, however, suggested no treatment-related effect (KHERA, 1979b).

SCOTT et al. (1975) treated in their experimental study 4 queens with griseofulvin : 3 of them received 4 oral dos-

es of 500 mg at weekly intervals starting at day 22, 29 and 35 of gestation, respectively. The fourth queen received 4 times 1,000 mg weekly starting 1 day after breeding.

The latter cat gave birth to 3 kittens: 1 was normal, 1 stillborn with an exencephaly, the third died at 18 days from a heart defect. No kittens were obtained from the queen with the first treatment on day 22 : kittens were probably stillborn and eaten by the mother. The cat starting with treatment on day 29 delivered 4 normal kittens. 2 of them died 6 and 10 days later and were eaten by the queen. The last cat (start of treatment on day 35) gave birth to 6 normal kittens.

Authors conclude from their limited study that treatment during the last half of pregnancy was not detrimental, whereas treatment starting the third or fourth week can result in weak or stillborn fetuses and during the first week may result in malformations.

Hydroxyurea (an antitumor drug and known teratogen in rat, miniature swine and dog [Tab.3]) was tested by KHERA (1979b). 50 or 100 mg/kg were given orally in gelatine capsules at pregnancy days 10 to 22 to 17 cats each. The higher dose decreased maternal body mass and increased incidence of non-pregnancy. This dose also caused a significant reduction in mean fetal body mass and an increase in resorptions. Only 2 kittens were gained in the 100 mg/kg group, one of which was malformed. From the 38 kittens in the 50 mg/kg group, 11 showed malformations. Cleft palate and microphthalmia were most frequent.

Methotrexate (a folic acid antagonist) was administered orally in gelatine capsules at 0.5 mg/kg on pregnancy days 11-14 (n=20), 14-17 (n=17), or 17-20 (n=18). With this dose maternal toxicity, maternal mortality and abortions were observed. There was a high frequency of several fetal anomalies. Umbilical hernia appeared to be methotrexate-specific (KHERA, 1976).

Cats were administered orally 0.03, 0.083, 0.25, or 0.75 mg/kg Hg (as methylmercury chloride, CH_3HgCl) from day 10-58 of pregnancy. 0.75 mg/kg caused maternal toxicity: vomiting, ataxia, and death within 32 days of commencement of treatment. At 0.25 mg/kg there was an increased incidence of abortion and (non-specific) fetal anomalies. In surviving fetuses a reduced neuronal population in the external granular layer of the cerebellum was noticed. Minimal or no embryopathic effects were noted at lower doses (KHERA, 1973).

The overall incidence of thalidomide-induced anomalies in cats appeared related to dose and treatment period (10 mg/kg orally on days 10-20 of pregnancy, 240 mg/kg on days 10-14, and 120, 240, and 480 mg/kg on days 15-17 or 18-20 of pregnancy). Cardiovascular anomalies were observed including ventricular septal defects, right atrial distension primarily involving the coronary sinus, malpositioned great vessels, and narrowed left ventricular chamber with hypertrophic walls (KHERA, 1975).

FREYTAG and MORRIS (1997) evaluated the teratogenic potential of vitamin A by feeding 3 groups of cats with 20,000 IU retinyl acetate/kg diet (controls), with 1 million, or 2 million IU/kg for 2 years. Malformation rates were 0.8 % in the control group (121 kittens), 2.9 % in the 1 million group (173 kittens), and 8.6 % in the 2 million group (81 kittens).

The same group (FREYTAG et al., 2003) investigated the incidence of birth defects in kittens of queens given diets with retinyl acetate concentrations of 6,000 (control), 306,000 (low), or 606,000 (high) retinol equivalents/kg diet for 3 years (1 retinol equivalent = 1 µg retinol = 3.3 IU). A total of 396 kittens were born in 97 litters; there was no difference among treatment groups. 2, 5 and 11 malformed kittens were found in the control, the low and the high treatment group, respectively. Malformations included cleft palate, cranioschisis, foreshortened mandible, stenotic colon, enlarged heart and agenesis of the spinal cord and small intestine. Authors conclude, that the minimum teratogenic dose for cats is greater than 6,000 and less than 306,000 retinol equivalents/kg diet.

Further examples for the use of cats in teratogenicity studies present the papers of KHERA et al. (1976, testing amaranth, a food coloring, E 123) and of KHERA (1979a, testing dimethoate, an acetylcholinesterase-inhibiting systemic insecticide).

Iatrogenic teratogenicity

General

DAVIES (1983) specifies in 3 tables drugs for dogs and cats which were (i) found to be save for the use during pregnancy, (ii) not proven to be safe for use during pregnancy but not necessarily contraindicated, and (iii) contraindicated during pregnancy. From this latter table all drugs causing anomalies are summarized in Tab. 1.

KUSTRITZ (2003, 2006) reports that effects of drugs during pregnancy in dogs and cats are often extrapolated from data obtained in other species. She, however, lists the following substances as teratogenic and cites the related malformations:

- anti-convulsants: primidone (cardiac defects, cleft palate, skeletal anomalies)
- anti-infectives: griseofulvin (microphthalmos in kittens, cleft palate in puppies),
ketoconazole (stillbirth in dogs),
tetracycline (bone and teeth malformations),
aminoglycoside antibiotics (deafness and renal disease) and metronidazole (described only as being teratogenic in laboratory animals, no specific disorders)
- anti-inflammatories: Aspirin (embryonic death),
dimethyl sulfoxide (DMSO; described as being teratogenic in laboratory animals) and
glucocorticoids (anasarca in brachycephalic breeds)
- antineoplastic agents: all (embryotoxic and can produce a variety of malformations in offspring that survive)
- hormones: diethylstilbestrol and estradiol cypionate (feminization of males),
testosterone and mibolerone (masculinization of females; see SHANE et al.,1969) and
progesterone (masculinization of females)
- sedatives: diazepam, midazolam (congenital defects in laboratory animals and human beings; not recommended for use during early pregnancy in dogs and cats)
- vitamin excess: vitamin A (cleft palate, kinked tails, cardiac defect in kittens) and
vitamin D (tissue calcinosis, enamel hypoplasia, cardiac defects)

Dogs

The spontaneous malformation rate for dogs is reported by SCHARDEIN (1985) in the range of 0.2-1.9 %. Common

Tab. 1: Drugs contraindicated during pregnancy in dogs and cats because of causing anomalies (DAVIES, 1983)

Drug	Effect
acetazolamide	fetal anomalies
androgens	masculinization of fetus
antineoplastics	fetal death and anomalies
amphotericin B	congenital anomalies
corticosteroids	cleft palate
dimethylsulfoxide	congenital anomalies
EDTA	congenital anomalies
estrogens	feminization of fetus
ethoxyzolamide	congenital anomalies
fluocytosine	congenital anomalies
gold salts	congenital anomalies
griseofulvin	congenital anomalies
iododeoxyuridine	congenital anomalies
meclizine	congenital anomalies
phenytoin (cats)	congenital anomalies[1]
prochlorperazine	congenital anomalies
streptomycin	hearing loss and congenital anomalies
tetracyclines	impaired bone and tooth development
vitamin A (large doses)	multiple anomalies

[1] although declared as "negative" in Tab. 3

Tab. 2 : Drugs which should not be given during pregnancy in dogs

To be avoided (FRESHMAN, 1999)	Contraindicated (LANDSBERGEN et al., 2001)
aminoglycosides	carprofen
chloramphenicol	clindamycine
diethylstilbestrol	doxycycline
enalapril	fenylbutazon
fluoroquinolones	ketoprofen
griseofulvin	meloxicam
metronidazole	oxytetracycline
misoprostol	sulfadiazine
mitotane	sulfadoxine
omeprazole	sulfamethoxazol
organophosphates	sulfatroxazole
tetracyclines	tolfenamzur
theophylline	trimethoprim
trimethoprim	

spontaneous anomalies are: cleft palate, tail defects, eye defects, closure defects, and persistent cloaca (see SCHARDEIN et al., 1973).

In the paper on adverse reactions to veterinary drugs of TJÄLVE (1997) a total of 318 reports are concerning dogs. 8 reports concern benzimidazole anthelmintics. In one case 5 malformed pups were born by a bitch which was treated with fenbendazole on days 18-20 of pregnancy. Teratogenic effects, however, have hitherto not been reported for fenbendazole (DELATOUR, 1983). In one of 2 reports on nitroscanate, 3 dead pups and 3 pups without tails were born by a bitch treated with nitroscanate on the 5th week of pregnancy. It remains uncertain whether this effect was drug-related.

In Tab. 2 drugs are compiled which are "to be avoided" (FRESHMAN, 1999) or are "contraindicated" (LANDSBERGEN et al., 2001) in pregnancy. Drugs are listed irrespective of the harm they could elicite (embryotoxic, teratogenic etc.); e.g. non-steroidal anti-inflammatory drugs should better not be used during the last stage of pregnancy as they might cause delay of the delivery.

True hermaphroditism was reported in 6 female pups of a bitch which was treated approximately on day 40 with a synthetic testosterone mixture (ROOSTER et al., 2006). Female pseudohermaphroditism was observed in 3 greyhounds. The dam had been treated with testosterone proprionate for estrus prevention (OLSON et al., 1989).

Retinoids - strongly teratogenic in humans - are used in the dog without major concern (WERNER and POWER, 1994). Etretinate is used to treat "seborrheic" dermatoses,

isotretinoin to treat acne, etretinate and isotretinoin in the treatment of the Schnauzer comedo syndrome, the canine ichthyosis, flank alopecia, and sebaceous adenitis (WERNER and POWER, 1994).

Excess vitamin C may interfere with normal processes of bone development, and because dogs produce sufficient amounts of this vitamin, supplementation with vitamin C is simply unnecessary (DAVOL, 2000).

It is generally accepted that modified live vaccines should not be given to a pregnant bitch (FRESHMAN, 1999). PERCHMAN et al. (1977), on the other hand, concluded from their limited survey that a live rabies vaccine (low egg passage, Flury strain) administered to the pregnant bitch apparently had no significant effect on the litter.

Cats

The spontaneous malformation rate for cats is given by SCHARDEIN (1985) as 1.2 %. The following incidence (in percent) of congenital malformations is given by NODEN (1986): musculoskeletal 0.24, urogenital 0.13, cardiovascular 0.08, gastrointestinal 0.04, sensory 0.13, neurologic 0.17, and others 0.43.

SCOTT et al. (1975) reported teratogenesis associated with griseofulvin (a fungistatic agent) from 2 clinical cases and from an experimental study (see above). The clinical cases comprise 2 ringworm epizootics (*Microsporum canis*). More than 50 cats were treated at weekly intervals orally with 500-1,000 mg griseofulvin. 4 kittens of 2 queens with multiple congenital malformations are described showing severe malformations of the brain, the skeleton, and the eyes (cyclopia, anophthalmia). Furthermore, atresia ani, atresia coli, lack of atrioventricular valves of the heart, and absence of external nares and soft palate were present.

Systemic isotretinoin is used in the treatment of acne, obviously without major concern, although retinoids are strongly teratogenic in humans (WERNER and POWER, 1994).

In his paper on adverse reactions to veterinary drugs, TJÄLVE (1997) reported 61 cases concerning cats. 9 reports concern antimicrobial agents. In one case a cat which was treated at about day 20 of pregnancy with enrofloxacin and ampicillin gave birth to 4 malformed kittens. Enrofloxacin is the suspected drug.

The influence of so called endocrine disruptors (hormones or chemicals with hormone-like properties) on the developing genital system of the cat was excellently reviewed recently by HOLLER et al. (2007).

Both vitamin A deficiency and excess during pregnancy can cause fetal malformations. In response to the potential teratogenicity of vitamin A in cat foods (see above), the Association of American Feed Control Officials Committee set the maximum permissible concentration in cat foods at 225,000 retinol equivalents/kg of diet. This concentration, however, is over 100 times the vitamin A requirement for growing kittens (see FREYTAG et al., 2003).

It is generally accepted that administration of (live) vaccines to pregnant queens is contraindicated. 6 weeks after vaccination with a modified live feline parvovirus vaccine, a cat gave birth to 5 kittens, 3 of which died soon afterwards. The remaining 2 kittens showed hydrocephalus or hydranencephaly, combined with severe cerebellar hypoplasia or agenesis. Parvoviral DNA was amplified by the polymerase chain reaction from the brain of both kittens. The severe malformations observed presumably resulted from an in-utero parvovirus infection, possibly due to vaccination, that occurred late in the first, or early in the second, third of pregnancy (SHARP et al., 1999).

SIMONS et al. (1974) did not recommend the use of their vaccine (an attenuated feline panleukopenia virus grown in ferret cell culture) in pregnant queens although they could show that the vaccine was harmless for queens and their litter.

Discussion

Reproductive and developmental toxicity (including negative influence on fertility and early embryonic development, as well as embryo-fetal development, and pre- and postnatal toxicity) is an indispensable part within the development of drugs for human therapeutic use. The extrapolation of teratogenicity studies from experimental animals to man, however, remains problematic (ZBINDEN, 1985; NEUBERT, 1987). Not all species are equally susceptible or sensitive to teratogenic influences by a given drug. Furthermore, both the type of malformation produced as well as the teratogenic dose levels used may show drastic species differences. Metabolic peculiarities have to be considered: e.g. glucuronic acid conjugation is usually deficient in the cat; the dog is a poor acetylator; dogs are particularly efficient biliary excretors (NAU, 1986) .

Inspection of Tab. 3 confirms these statements. Aspirin for example is not teratogenic in humans but in dogs and cats; cortisone and dexamethasone are not teratogenic in humans but in dogs; diphenylhydantoin on the other hand is teratogenic in humans but not in dogs and cats.

The dose plays an important role in teratogenicity. In the dog Aspirin was clearly teratogenic at 400 mg/kg given during pregnancy days 23 to 30, the second half of the development of the major organ systems. Taking into account the allometric scaling factor of 1.8 for the dog (FDA, 2005) this dose would be equivalent to a human dose of 222 mg/kg. To mimic the animal experiment, a women of 60 kg body mass would have to take 13,320 mg (i.e. 26.6 Aspirin tablets of 500 mg each) every day during days 37 to 55 of pregnancy. (The critical period of organogenesis in humans are days 20-55 of pregnancy or days 35-70 after last menstrual period [SCHARDEIN,1985]).

Although the experimental results compiled in this paper might be of interest from a scientific point of view, dogs and cats do not play a role any longer in teratogenic routine testing which is performed nowadays in rats and rabbits.

For the practitioner, very little is known about the teratogenic potential of most drugs used in dogs and cats. As stated above, recommendations not to use a drug in pregnancy are often extrapolated from work in other species. The general recommendation is to avoid any drug in pregnant pets unless absolutely necessary.

Very often, however, the pet owner is not aware of the pregnancy and the possibility of a pregnancy is rarely taken into account by the veterinarian when prescribing medications.

There is one additional point which might be of interest for the practitioner. A single treatment (rather the norm in veterinary practice than the exemption) might be more ter-

Tab. 3: Comparison of the reproductive effects of drugs in humans, dogs, and cats

Drug	Teratogenic effects in humans	dogs	cats	References
acetylsalicylic acid (Aspirin)	negative[1]	positive[2]	positive[3]	[1] BAILEY et al. (2005) [2] ROBERTSON et al. (1979) [3] KHERA (1976)
alcohol (ethanol)	fetal alcohol syndrome[1]	positive[1,2]		[1] BAILEY et al. (2005) [2] SCHARDEIN (1985)
aminopterin	positive[1]	positive[1, 3]	increased fetal loss[1,2], negative [3]	[1] BAILEY et al. (2005) [2] KHERA (1976) [2] SCHARDEIN (1985)
cortisone	negative[1]	positive[1, 2]		[1] BAILEY et al. (2005) [2] ESAKI et al. (1980)
dexamethasone	negative[1]	positive[1, 2]		[1] BAILEY et al. (2005) [2] SCHARDEIN (1985)
diphenylhydantoin (phenytoin)	positive [1]	negative[2]	negative[3]	[1] CLS (2006) [2] ESAKI et al. (1980) [3] KHERA (1979b)
griseofulvin	no adequate studies available[1]	positive[2],[4]	positive[3]	[1] ANONYMOUS (2002) [2] USP CONVENTION (1994) [3] SCOTT et al. (1975) [4] SCHARDEIN (1985)
hydroxyurea	negative[1] (no report)	positive[2]	positive[3]	[1] BAILEY et al. (2005) [2] EARL et al. (1972) [3] KHERA (1979b)
methotrexate	positive[1]	negative[2]	positive[3]	[1] BAILEY et al. (2005) [2] ESAKI et al. (1980) [3] KHERA (1976)
methylmercury	positive[1]	negative[2]	positive[3]	[1] CLS (2006) [2] SCHARDEIN (1985) [3] KHERA (1973)
oxytetracycline	dental staining[1] (tetracycline)	positive[1, 2]		[1] BAILEY et al. (2005) [2] SCHARDEIN (1985)
quinine	positive[1]	negative[1,2]		[1] BAILEY et al. (2005) [2] SCHARDEIN (1985)
thalidomide	positive[1]	positive[2],[3]	positive[4]	[1] BAILEY et al. (2005) [2] DELATOUR et al. (1965) [3] ESAKI et al. (1980) [4] KHERA (1975)
vitamin A	positive[1]	positive[2]	positive[3,4]	[1] ROTHMAN et al. (1995) [2] WIERSIG and SWENSON (1967) [3] FREYTAG and MORRIS (1997) [4] FREYTAG et al. (2003)

atogenic than a chronic treatment. The possible explanation is that repeated treatment might induce metabolizing enzymes that are able to lower maternal plasma levels of the medication before the embryo´s most sensitive period is reached (WILSON, 1974).

In conclusion, further investigations will be necessary to understand all the mechanisms causing abnormal prenatal development which leads to congenital malformations.

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Die Verhaltensforschung hat in den letzten 4 Jahrzehnten einen enormen Aufschwung erfahren, der sich in zahlreichen Spezialisierungen, wie Verhaltensgenetik, Verhaltensphysiologie, Kognitionsforschung, um nur einige Fachrichtungen zu nennen, widerspiegelt.

Angesichts der Fülle an Literatur, die es mittlerweile auf diesen Fachgebiet gibt, ist es schwierig geworden, einen Überblick über die wichtigsten Forschungsergebnisse zu behalten. Außerdem fehlte Studenten im deutschsprachigen Raum bislang ein aktuelles Lehrbuch in deutscher Sprache, das Grundprinzipien und Zusammenhänge der Verhaltensbiologie komprimiert und leicht verständlich darstellt.

Das vorliegende Werk schließt diese Lücken. Da es den Rahmen eines Lehrbuches sprengen würde, allen Forschungsrichtungen der Verhaltensbiologie gerecht zu werden, setzt der Autor in seiner Themenauswahl einen Schwerpunkt und verdeutlicht die zentrale Bedeutung des Verhaltens von Tieren für das Verständnis ihrer Biologie und evolutionären Anpassung. Studierenden bietet das Werk ein theoretisches Grundgerüst zur Einordnung von Informationen aus den verschiedensten untergeordneten Fachrichtungen der Verhaltensbiologie.

Einleitend werden Grundlagen der Verhaltensbiologie beschrieben. Darauf folgt die Darstellung von verschiedenen Überlebensstrategien, gefolgt von den Themen Fortpflanzung, Jungenaufzucht und soziale Evolution.

Zahlreiche Farbschemata, farbige Fotos, Tabellen und Diagramme tragen zum besseren Textverständnis bei.

Am Ende jedes Kapitels findet der Leser eine Zusammenfassung sowie Literaturhinweise. Letztere sind in vielen Fällen on-line verfügbar und enthalten Verweise auf grundlegende „klassische“ Arbeiten.

Erfreulich für den interessierten Leser ist außerdem das günstige Preis-Leistungsverhältnis dieses Buches, dessen Erwerb jedem an Verhaltensbiologie interessierten Leser empfohlen werden kann.

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