

PHARMACOTHERAPY OF NEONATES AND PREGNANT ANIMALS

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Evidence Tables

Category: anthelmintic

Drug:
albendazole

Species:
dogs

Citation:
Meyer, K. E. (1998). Adverse events associated with albendazole and other products used for the treatment of giardiasis in dogs. Vet Med Today 213. 44-46

Type of control:
not specified

Damage To:
dam

Age of Neonate:
n/a

Dosage:
single 10-20 mg/kg oral dose

Number of animals:
tx= 40

Trimester or stage of Pg studied:
n/a

Results
Teratogenic effects have been documented in sheep given albendazole at a single 10 to 20 mg/kg oral dose.(page 45)

Category: anthelmintic

Drug:
albendazole

Species:
cattle

Citation:
Theodorides, V.J. Carakostas, M.C. Colaianne, J.J. Et al... (1993) Safety of albendazole in developing bovine fetuses. Am J Vet Res 54, 12. 2171-2174

Type of control:
negative

Damage To:
fetus

Age of Neonate:
n/a

Dosage:
-exp 1-(early treated cows-25mg/kg albendazole drench at 7 and 14 days after mating, late treated cows-25 mg/kg drench on post service days 21,31, 41, and 51)
-exp 2 (25 mg/kg drench on day 7 and 14 of gestation)
-exp 3 (25 mg/kg drench on either postbreeding day 7 or 14)
-exp 4 (10 mg/kg oral dose on gestation days 7,14, 28, and 42)

Number of animals:
exp1 (tx=90), exp2 (tx=142), exp 3 (tx=300) exp 4 (tx=164)

Trimester or stage of Pg studied:
1, (1,2 for late-treated cows of Exp 1), 3

Results

Differences in conception rate among the control and the late-treated cows of experiment 1 were not significant. Albendazole, administered orally at a dose rate of 25 mg/kg of body weight to presumed pregnant cows on days 21, 31, 41, 51, and 61 of gestation, did not induce toxicosis in embryos or fetuses, and all calves born were structurally normal. Albendazole administration at a rate of 25 mg/kg to cows at 7 and/or 14 days of gestation decreased the apparent conception rate (ie, embryoletality), but did not have a teratogenic effect. Apparent embryoletality was greater in cows administered 25 mg/kg only on day 14, compared with those administered the drug only on day 7. Single dosage of 25 mg/kg given in the final 3 months of gestation did not induce abortion. There were no adverse effects of albendazole at a dosage of 10 of 15 mg/kg on developing embryos or fetuses when administered to presumed pregnant cows at various times in early gestation.

Category: anthelmintic

Drug:
albendazole and oxfendazole

Species:
rats

Citation:
Delatour, PF. Garnier, R. Benoit, E. et al... (1984). A correlation of toxicity of albendazole and oxfendazole with their free metabolites and bound residues. J. Vet. Pharmacol. Therap. 7, 139-145.

Type of control:
positive

Damage To:
fetus

Age of Neonate:
n/a

Dosage:
daily oral administration of SKF-525A (120 mg/kg 1 h before and 60 mg/kg 3-4 h after the benzimidazole

Number of animals:
not specified

Trimester or stage of Pg studied:
2

Results

The possible correlations between embryotoxicity, plasma kinetics of toxic metabolites and covalent binding of metabolites to fetal tissues were studied using two drugs, albendazole and oxfendazole. In the rat, the metabolic inhibitor, SKF-525A, induced changes in embryotoxicity which were well correlated with plasma levels of identified embryotoxic metabolites, but not with the levels of fetal tissue bound drug metabolites. It is strongly suggested that unchanged OFZ and the sulfoxide metabolite of ABZ are responsible for the observed teratogenic effects through a mechanism through which probably does not involve covalent binding of metabolites to tissues. The toxicity of these anthelmintics appear to be related to pharmacokinetics of their free metabolites. Bound residues for these compounds do not appear to have toxicological significance for the target animal with respect to teratogenic effect. OFZ has also been shown to be the ultimate embryotoxin of febantel, so these conclusions are also applicable to this anthelmintic.

Category: anthelmintic

Drug:
albendazole sulfoxide

Species:
cattle
rat

Citation:
Piscopo, S. E. Smoak, I. W. (1997) Comparison of effects of albendazole sulfoxide on in vitro produced bovine embryos and rat embryos. AJVR 58,9. 1038-1042

Type of control:
negative

Damage To:
fetus

Age of Neonate:
n/a

Dosage:
1M soln of purified ABZSO was prepared in dimethyl sulfoxide(1.10 g/ml) and diluted to produce stock solns in a volume of 10 microl: 10, 100, 250, and 500 ng, and 1 and 10 micro- grams

Number of animals:
not specified

Trimester or stage of Pg studied:
not specified

Results

44% of bovine embryos divided in culture (≥ 16 -cell stage). Fifteen percent of the controls had morphologic abnormalities, including disparity in blastomere size and cytoplasmic vacuoles and stippling. Treated (≥ 1 microgram of ABZSO/ml) bovine embryos differed ($P < 0.0001$) from controls, with 4 % development and 93% abnormal morphology. 45% of control rat embryos divided in culture. Treated (≥ 500 ng of ABZSO/ml) rat embryos differed ($P < 0.0003$) from controls with regard to ability to divide. There were no consistent morphologic abnormalities in rat embryos. In vitro produced bovine embryos were susceptible to ABZSO at a concentration ≥ 1 microgram/ml, resulting in decreased ability to divide and presence of gross morphologic abnormalities. Rat embryos produced in vivo and exposed in vitro to ABZSO at a concentration ≥ 500 ng/ml had decreased ability to divide in culture.

Category: anthelmintic

Drug:
ivermectin

Species:
rats

Citation:
Poul, JM. (1988). Effects of perinatal ivermectin exposure on behavioral development of rats. Neurotoxicology and teratology 10. 267-272.

Type of control:
negative

Damage To:
fetus

Age of Neonate:
n/a

Dosage:
females(1 mg/kg, 2 mg/kg, and 4 mg/kg depending on group assigned in peanut oil via stomach tube)

Number of animals:
not specified

Trimester or stage of Pg studied:
2/G

Results

Ivermectin had no effect on reproductive performance and dam's growth. The higher dose induced 100% pup mortality. Later on, ivermectin at 4 mg/kg was administered only during gestation. At that dose, the drug induced 22% mortality and affected temporary cliff avoidance, locomotion, negative geotaxis, and swimming development. At 2 mg/kg, the drug induced offspring mortality (31%), retarded growth and delayed eye opening, cliff avoidance and surface righting reflex, negative geotaxis, locomotion and swimming development. Ivermectin at 1 mg/kg had no effect on mortality and growth but cliff avoidance and locomotion were retarded. Data suggest that new born rats were highly susceptible to the neurotoxic action of ivermectin.

Category: anthelmintic

Drug:
ivermectin

Species:
horses

Citation:
McKissick, G. E. et al (1987) Safety of ivermectin in pregnant mares. Body conditioning and LH levels. J Equine Vet Sci 7. 357-367.

Type of control:
negative

Damage To:
none

Age of Neonate:
n/a

Dosage:
6 oral doses of at 600 mcg/kg at 2-wk intervals

Number of animals:
tx=58

Trimester or stage of Pg studied:
1

Results

In 58 mares given ivermectin during the first 3 mo of gestation, no teratogenic anatomic defects were noted in the progeny nor was there an effect on the mares/ fertility. The incidence of conception failures, abortion, neonatal deaths and cryptorchidism of progeny in control mares was equal to or greater than that in treatment mares. Poor body condition affected postpartum cyclicity. Mean gestation length was greater in 6 thin mares (condition score \leq 4.5) fed 85% of the NRC protein and energy recommendations the last 90 days of gestation than in 6 control mares (condition score \geq 6) fed 100% NRC recommendations (352 vs 343 days).

Category: anticholinergic

Drug:
belladonna (atropine)

Species:
humans

Citation:
Briggs, G.G.; Freeman, R.K. & Sumner, Y.J. (No year given) Drugs in Pregnancy and Lactation-A Reference Guide to Fetal and Neonatal Risks. Fourth Edition. P77-682

Type of control: none **Damage To:** fetus **Age of Neonate:** n/a

Dosage:
not specified

Number of animals:
tx=554
control=50,282

Trimester or stage of Pg studied:
1

Results

Belladonna is an anticholinergic agent. 50, 282 mother-child pairs were monitored, 554 of which used belladonna in the first trimester of pregnancy. The drug was found to be associated with malformations in general and with minor malformations. Specifically, increased risks were observed for respiratory tract anomalies, hypospadias and eye/ear malformations. The association between belladonna and eye/ear malformations was statistically significant. Interpretation of these data is difficult, however, since the authors of this study emphasized that even though some of these agents had elevated risks and significant associations did occur, a cause and effect relationship could not be inferred.

Category: anticonvulsant

Drug:
phenobarbital

Species:
mixed

Citation:
Briggs, G.G.; Freeman, R.K. & Sumner, Y.J. (No year given) Drugs in Pregnancy and Lactation-A Reference Guide to Fetal and Neonatal Risks. Fourth Edition. P77-682

Type of control: none **Damage To:** fetus
dam **Age of Neonate:** n/a

Dosage:
not specified

Number of animals:
not specified

Trimester or stage of Pg studied:
all

Results

Phenobarbital therapy in the epileptic pregnant woman presents a risk to the fetus in terms of minor congenital defects, hemorrhage at birth and addiction. The risk to the mother, however, is greater if the drug is withheld and the seizure control is lost. The benefit:risk ratio, in this case, favors continued use during pregnancy at the lowest dose possible to control seizures. In addition, the long term consequences of gestational phenobarbital exposure have only been investigated in one study, but in light of the findings revealing adverse effects on cognitive functioning combined with data from animal studies indicating significant toxicity on neural development and sexual function, further investigations are warranted.

Category: anticonvulsant

Drug:

phenytoin

Species:

mice

Citation:

Lee, Jae-kwan, et al. (1994) Teratogenicity of phenytoin in ICR mouse and antiteratogenic effect of dimethyl sulfoxide

Type of control:

negative

Damage To:

fetus

Age of Neonate:

n/a

Dosage:

75 mg/kg IP

Number of animals:

tx = 532 (table 2)

control = 141 (table 2)

Trimester or stage of Pg studied:

2/M

Results

Major malformation of fetuses treated with PHT on day 10, 10-11, and 10-12 of gestation was cleft palate, and the percentages of fetus with cleft palate were 14.5%, 31.7%, and 51.7%, respectively. DMSO cut cleft palate rate from 51.7% to 30.8%.

Category: antifungal

Drug:

fluconazole

Species:

mice

Citation:

Tinoni, G.M., Iammarrone, E., Giampietro, F., et al. (1999) Teratological interaction between the Bis-triazole antifungal agent fluconazole and the anticonvulsant drug phenytoin. *Teratology* 59:81-87

Type of control:

negative

Damage To:

fetus

Age of Neonate:

n/a

Dosage:

0, 10, and 50 mg/kg IP as single dose on day 12

Number of animals:

tx = 31

control = 14

Trimester or stage of Pg studied:

2/M

Results

Administration of fluconazole (FCZ) at 10 or 50 mg/kg neither induced appreciable effects on maternal well-being, nor affected the maternal body weight. Mean fetal weight in both groups were comparable to the negative control group. Treatment with 10 mg/kg did not reveal embryocidal effects. However, at FCZ at 50 mg/kg significantly reduced embryo viability, with increases of resorption incidence. Fetuses exposed to 50 mg/kg FCZ had an increased incidence of rib abnormalities (supernumerary ribs), and a low but measurable incidence of dilated renal pelvis.

Category: antifungal

Drug:
fluconazole

Species:
humans

Citation:
Mastroiacovo, Pierpolo; Mazzone, Teresa; Botto, Lorenzo; et al. (1996) Prospective assessment of pregnancy outcomes after first-trimester exposure to fluconazole. Am J Obstet Gynecol 175:1645-50

Type of control: negative **Damage To:** fetus **Age of Neonate:** n/a

Dosage:
150 mg PO as single dose within first 12 weeks of gestation

Number of animals:
tx = 226
control = 452

Trimester or stage of Pg studied:
1

Results
Among the 226 pregnancies exposed to fluconazole there were 22 miscarriages, 1 stillbirth, and 7 infants with congenital anomalies. The prevalence of these outcomes and of neonatal growth parameters and the rate of neonatal complications were similar to those in the reference group. Women in the fluconazole group had a fivefold increased occurrence of induced abortions. First-trimester exposure to fluconazole does not appear to increase the prevalence of miscarriages, congenital anomalies, and low birth weight.

Category: antifungal

Drug:
fluconazole

Species:
humans

Citation:
Sanchez, Jose Maria; Moya, Graciela (1998) Fluconazole Teratogenicity Prenat. Diagn. 18: 862-869

Type of control: none **Damage To:** fetus **Age of Neonate:** 1 day

Dosage:
150 mg PO around time of conception

Number of animals:
tx = 1

Trimester or stage of Pg studied:
1/E

Results
The male infant had an occipital encephalocele, severe hypoplasia of cervical vertebrae, and a large cisterna magna. Conclusions cannot be drawn from such a small number of subjects, but this case is consistent with findings of another study (Aleck and Bartley (1997).

Category: antifungal

Drug:
griseofulvin

Species:
horses

Citation:
Schutte, J. & van den Ingh, T. (1997) Microphthalmia, brachygnathia superior, and palatocheiloschisis in a foal associated with griseofulvin administered to the mare during early pregnancy. Vet Quart 19, 58-60.

Type of control:
none

Damage To:
fetus

Age of Neonate:
n/a

Dosage:
100 g as a single oral dose for five consecutive days

Number of animals:
tx=2

Trimester or stage of Pg studied:
1/M

Results
Griseofulvin administered during pregnancy seems to have a teratogenic effect on the fetus, particularly on the development of the craniofacial bones and the eyes in various animal species. A citation referenced in the discussion (Hiddleston WA. The use of griseofulvin mycelium in equine animals. Vet Rec 1970; 87: 119) points out that for two pregnant mares given griseofulvin at 10 mg/kg po daily at alternate 30 day periods no birth defects were noted in the foals. Most probably this was due to avoiding the critical 40-60 day postconception period where the facial bones and eyes form in the foal.

Category: antimicrobial

Drug:
aminoglycosides

Species:
humans, rats,
mice, rabbits,
guinea pigs

Citation:
Czeizel, AE. Rockenbauer, M. Olsen, J. et al (2000). A teratological study of aminoglycosides antibiotic treatment during pregnancy. Scand J Infect Dis 32. 309-313.

Type of control:
negative

Damage To:
dam
fetus

Age of Neonate:
n/a

Dosage:
based on stage of gestation

Number of animals:
tx=60016 (humans)

Trimester or stage of Pg studied:
all

Results
The aim of this study was to investigate the teratogenicity of aminoglycoside antibiotics, such as parenteral gentamicin, streptomycin, tobramycin, and oral neomycin, during pregnancy. A teratogenic potential of gentamicin and neomycin was not indicated by a comparison of the occurrence of aminoglycoside antibiotic treatments in the total control group as referent with the figures of different congenital abnormality groups. In addition, the case-control pair analysis during the second -third months of pregnancy did not show a teratogenic risk of gentamicin and neomycin. Animal experiments showed a higher frequency of fetal death, CAs, hearing loss and nephrotoxicity after high doses of gentamicin (16-24), but the relevance of these findings to the use of clinical doses of gentamicin in human pregnancy is unknown. The frequency of CAs and auditory-vestibular lesions did not increase among the offspring of mice, rats, and guinea pigs treated during pregnancy with streptomycin in doses 2-10 times those used in humans. The exception was a mouse study, because the histological evidence of inner ear damage was detected among offspring of pregnant mice treated with 3 times the human dose of streptomycin. Teratogenicity was not found in rats and rabbits after doses of 100 mg and 20 or 40 mg/kg of tobramycin, respectively. Of 30 guinea pig newborns, 4 had hearing loss at 20,000Hz after daily treatment with 100 mg/kg tobramycin during the last 4 weeks of pregnancy. Animal studies in pregnant mice and rats did not indicate a teratogenic effect of neomycin, but hearing loss was found among the offspring of pregnant rats given IM injections of neomycin

in a dose similar to that used orally in humans. The conclusion of this study is that treatment with parenteral gentamicin and oral neomycin during pregnancy presents no detectable teratogenic risk to the fetus, when restricted to structural developmental disturbances.

Category: antimicrobial

Drug:
aminoglycosides (gentamicin, amikacin)

Species:
humans

Citation:
Schwarz, R.H.(1981) Considerations of Antibiotic Therapy During Pregnancy. Department of Obstetrics and Gynecology, Downstate Medical Center College of Medicine 58(5), 95s-99s.

Type of control:
none

Damage To:
dam,
fetus

Age of Neonate:
n/a

Dosage:
not specified

Number of animals:
not specified

Trimester or stage of Pg studied:
not specified

Results
Aminoglycosides have the same potential for ototoxicity and nephrotoxicity in the fetus as they do in the adult. While indications for use are few during pregnancy, there are situations, such as a resistant urinary tract infection, in which an aminoglycoside is mandatory and should be used. Duration of use should be limited to avoid the above mentioned toxicities.

Category: antimicrobial

Drug:
ampicillin

Species:
humans

Citation:
Kubacka, RT. Johnstone, HE. Henry, SIT, et al (1983). Intravenous ampicillin pharmacokinetics in the third trimester of pregnancy. Therapeutic Drug Monitoring. 5. 55-60

Type of control:
none

Damage To:
dam

Age of Neonate:
n/a

Dosage:
single dose of either 500 mg or 1 g sodium ampicillin IV

Number of animals:
tx=9

Trimester or stage of Pg studied:
3/G

Results
Women in the 3rd trimester of pregnancy appear to clear ampicillin from their bodies at a rate similar to nonpregnant adults when apparent total body clearance is expressed in per minute per kilogram body weight. There were no observed correlations between the week of gestation in our third trimester volunteers and the pharmacokinetic parameters calculated for them. The mean $t_{1/2\beta}$ for ampicillin in our volunteers was 1.60 +/- 0.51 h. One patient who delivered a stillborn child eliminated the drug more rapidly. Consistent with this observation was her clearance time of 11.9 ml/min/kg. Another patient suffered from acute pyelonephritis and appeared to eliminate ampicillin from her bloodstream much more slowly than the other subjects.

Category: antimicrobial

Drug:
ceftiofur sodium

Species:
cattle

Citation:
Brown, S.A. Chester, S.T. Robb, E.J. (1996) Effects of age on the pharmacokinetics of single dose ceftiofur sodium administered intramuscularly or intravenously to cattle. J. Vet. Pharmacol. Therap. 19.

Type of control:
none

Damage To:
neonate

Age of Neonate:
1 day
6 months

Dosage:

-group 1(50 mg ceftiofur sodium equivalent activity/ml administered at 2.2 mg/kg IV at day 7 of age, repeated on day 30 and 1 and 3 months of age)
-group 2 (2.2 mg/kg IM at same intervals as above)

Number of animals:

tx=16 (1day old bull Holsteins) tx=14 (6month old Holstein steers)

Trimester or stage of Pg studied:

n/a

Results

The doses for ceftiofur sodium of 1.1-2.2 mg/kg will provide plasma concentrations above the MIC for bovine respiratory disease pathogens for a longer period of time in neonatal calves than in older calves. Peak plasma concentrations are no higher in neonatal calves than in more mature cattle, highly suggestive that tissue concentrations are no higher in neonatal calves than in more mature cattle.32-38.

Category: antimicrobial

Drug:
chloramphenicol

Species:
humans

Citation:
Schwarz, R.H.(1981) Considerations of Antibiotic Therapy During Pregnancy. Department of Obstetrics and Gynecology, Downstate Medical Center College of Medicine 58(5), 95s-99s.

Type of control:
none

Damage To:
neonate

Age of Neonate:
n/a

Dosage:
not specified

Number of animals:

not specified

Trimester or stage of Pg studied:

n/a

Results

High levels of free chloramphenicol in the neonate causes a marked prolongation of serum half life. While there are no characteristic pathological changes related to this syndrome, clinical characteristics include an ashen gray color and cardiovascular collapse 24 to 48 hours after delivery.

Category: antimicrobial

Drug:
ciprofloxacin

Species:
humans

Citation:
Bomford, J.A.L., Ledger, J.C., O'Keefe, B.J. & Reiter, Ch.(1993)Ciprofloxacin Use During Pregnancy. Drugs 45(suppl 3)461-462

Type of control:
none

Damage To:
fetus

Age of Neonate:
n/a

Dosage:
not specified

Number of animals:
tx=103

Trimester or stage of Pg studied:
all

Results

Ciprofloxacin was administered at different times to 103 different women. Of these women, 63 had normal, healthy babies, 18 had therapeutic abortions and 10 were reported to have spontaneous abortions. Four cases of fetal death in utero occurred, and 8 babies were born with congenital defects. In conclusion, ciprofloxacin has been used frequently in pregnancy without causing adverse effects, and no conclusive evidence has been found to implicate this drug in the fetal death or congenital abnormality reports.

Category: antimicrobial

Drug:
ciprofloxacin, norfloxacin, ofloxacin

Species:
humans

Citation:
Loebstein,R.; Addis,A.; Ho,E.;Andreou, R.; Sage,S.; Donnefeld, A.E.; Schick, B.; Bonati, M.; Moretti, M.; Lalkin, A.; Pastiszak, A. & Koren, G. (1998) Pregnancy Outcome Following Gestational Exposure to Fluoroquinolones: a Multicenter Prospective Controlled Study. Antimicrobial Agents and Chemotherapy (Vol.

Type of control:
none

Damage To:
fetus

Age of Neonate:
n/a

Dosage:
not specified

Number of animals:
tx=200
control=200

Trimester or stage of Pg studied:
all

Results

Concerns regarding the teratogenicity of fluoroquinolones have resulted in their restricted use during gestation. This is despite an increasing need for their use in emerging bacterial resistance. The objectives of the present investigation were to evaluate pregnancy and fetal outcomes following the maternal exposure to fluoroquinolones and to examine whether in utero exposure to quinolones is associated with clinically significant musculoskeletal dysfunctions. We prospectively enrolled and followed up 200 women exposed to fluoroquinolones (norfloxacin, ciprofloxacin, ofloxacin) during gestation. Pregnancy outcome was compared with that for 200 controls matched for age and for smoking and alcohol consumption habits. Controls were exposed to nonteratogenic, nonembryotoxic antimicrobial agents matched by indication, duration of therapy and trimester of exposure. Rates of spontaneous abortions, fetal maturity, prematurity and birth weight did not differ between the groups. It was concluded that the use of fluoroquinolones during embryogenesis is not associated with an increased risk of major malformations. 4, No. 6) 1336-1339

Category: antimicrobial

Drug:
clindamycin

Species:
rats
mice

Citation:
Bollert, J.A. Gray, J.E. Highstreete, J.D. Et al... (1974). Teratogenicity and neonatal toxicity of clindamycin 2-phosphate in laboratory animals. Toxicology and Applied Pharmacology 27. 322-329

Type of control:
positive

Damage To:
dam
fetus

Age of Neonate:
n/a

Dosage:
SQ injections of 100 and 180mg/kg (on gestation days 6-15) and SQ injections of 120 mg/kg (in nearly mature and recently weaned Gunn rats)

Number of animals:
not specified

Trimester or stage of Pg studied:
2/E

Results
Subcutaneous injections of clindamycin 2-phosphate at 100 and 180 mg/kg on gestation days 6-15 in Upjohn Sprague-Dawley rats, Upjohn ICR and CF1 mice had no detrimental effect on reproductive performance. Teratogenic effects were not observed. A concurrent low incidence of spontaneous cleft palate was confirmed in the Upjohn ICR strain of mouse. The sc LD50 of clindamycin 2-phosphate has been shown to be 179 mg/kg in the neonatal rat and >2000 mg/kg in the adult rat. Subcutaneous injections of clindamycin 2-phosphate at 120 mg/kg in nearly mature and recently weaned Gunn rats did not alter the partially impaired bilirubin metabolism in this neonatal model. Simultaneous treatment of immature Gunn rats with 120 mg/kg of clindamycin 2-phosphate and therapeutic levels of sulfadiazine and sulfamerazine did not produce sufficient displacement of bilirubin from albumin binding in the serum to produce clinical signs of kernicterus.

Category: antimicrobial

Drug:
clindamycin and gentamicin

Species:
humans

Citation:
Weinstein, AJ, Gibbs, RS, Gallagher, M. (1976) Placental transfer of clindamycin and gentamicin in term pregnancy. Am. J. Obstet. Gynecol. 124, 7, 689-691.

Type of control:
none

Damage To:
neonate

Age of Neonate:
n/a

Dosage:
600 mg clindamycin IV and 80 mg gentamicin IM given 30minutes before and 8 hours after surgery

Number of animals:
tx=54

Trimester or stage of Pg studied:
3/G

Results
Maternal clindamycin levels were within the normal range and cord levels were within the therapeutic range for this antibiotic. For gentamicin, however, maternal levels were depressed, with a concurrent depression of cord levels. Gentamicin and clindamycin were not detectable in the amniotic fluid during the first hour after injection. However, it has been demonstrated with other antibiotics that therapeutics levels may not be achieved in the amniotic fluid for at least 4 to 6 hours.

Category: antimicrobial

Drug:
doxycycline

Species:
rabbits

Citation:
Claussen, U. Breuer, H.W. (1975) The teratogenic effects in rabbits of doxycycline dissolved in polyvinylpyrrolidone, injected into the yolk sac.

Type of control:
negative

Damage To:
fetus

Age of Neonate:
n/a

Dosage:
0.01 ml soln of saline, water, and 500 microgram PVP injected into one uterine horn; a 0.01 ml soln containing 50 micrograms doxycycline and 500 micrograms PVP was injected into each yolk sac

Number of animals:
not specified

Trimester or stage of Pg studied:
3

Results
Tables 1 and 2 show the results of the 3 series of tests. Significant differences were only found in the malformations and resorption rates in series III. In the experimental horn, there were 53.3% resorptions and 68.8% malformations; in the control horn 29.9% resorptions and 16.7% malformations. The fetal weight and length did not significantly differ. DIP produced no specific pattern of malformations (table 2), but in general there was an increase in multiple malformations and a decrease in single malformations compared with the control. Tetracyclines directly applied to embryos (chicken and rabbit), but probably to other species, too, have teratogenic effects. As the placental barrier is transversable by all tetracyclines, these results, the basis of which must be looked for in the maternal organism, may perhaps be explained by the binding of tetracyclines to serum protein. It is imaginable that this factor is influenced by maternal illness. That is why the quantity of substance reaching the embryo may vary which may be the reason for the contradictory results concerning the teratogenicity of tetracyclines.

Category: antimicrobial

Drug:
erythromycin

Species:
humans

Citation:
Schwarz, R.H.(1981) Considerations of Antibiotic Therapy During Pregnancy. Department of Obstetrics and Gynecology, Downstate Medical Center College of Medicine 58(5), 95s-99s.

Type of control:
none

Damage To:
dam
fetus

Age of Neonate:
n/a

Dosage:
not specified

Number of animals:
not specified

Trimester or stage of Pg studied:
2 and 3

Results
The estolate salt of erythromycin is one of the two antibiotics contraindicated during pregnancy. The frequency of cholestatic jaundice due to use of this drug is higher when it is used during the latter half of pregnancy; also reported was an incidence of subclinical but reversible hepatotoxicity.

Category: antimicrobial

Drug:
florfenicol

Species:
cattle

Citation:

Adams, P. E. Varma, K. J. Powers, T. E. Lamendola, J.F. (1987). Tissue concentrations and pharmacokinetics of florfenicol in male veal calves given repeated doses. Am J Vet Res, 48,12. 1725-1732.

Type of control:
none

Damage To:
dam

Age of Neonate:
n/a

Dosage:

11mg/kg IV and 11 mg/kg PO every 12 hours for 7 doses

Number of animals:

tx= 7

Trimester or stage of Pg studied:

n/a

Results

After florfenicol administration, PO, there was a wide variation in the calculated half-life, which was attributed to variation in the rate of florfenicol absorption. The half-life was 167.4 to 534.9 minutes after the first oral dose and 190 to 808.8 minutes after the 7th dose. The median bioavailability after the 1st oral dose was 0.8888. Peak and trough concentrations of florfenicol were increased after subsequent doses were administered, compared with those after the 1st oral dose. The percentage of protein binding in serum from one adult cow was 22% to 26%. Florfenicol concentrations in tissues and body fluids of male veal calves were studied after the 7th dose of 11 mg/kg of florfenicol. High concentrations of florfenicol were measured in the urine, kidney, and bile. Low concentrations were measured in the brain, CSF, and aqueous humor. Concentrations in all other tissues and fluids were similar to the concurrent serum concentration.

Category: antimicrobial

Drug:
florfenicol

Species:
cattle

Citation:

Bretzlaff, K. N. Neff-Davis, C. A. Ott, R. S. etc... (1987).Florfenicol in non-lactating dairy cows: pharmacokinetics, binding to plasma proteins, and effects on phagocytosis by blood neutrophils. J Vet Pharmacol. Therap. 10, 233-240.

Type of control:
none

Damage To:
dam

Age of Neonate:
n/a

Dosage:

50 mg/ml of FLO given IV

Number of animals:

tx=5

Trimester or stage of Pg studied:

1/E

Results

Serial blood samples were collected and plasma concentrations of florfenicol were measured following the administration of an intravenous bolus of 50 mg/kg FLO to 5 healthy non-lactating dairy cows. A triexponential equation provided the best fit of the data for 4 of the 5 cows. The mean value for beta corresponded to a half-life of 3.2 h. The mean apparent distribution was 0.67 L/kg, and the mean body clearance was determined in vitro at concentrations of 5 micrograms/ml and 50 micrograms/ml by equilibrium dialysis and ultrafiltration. The drug was 18% and 19% bound by equilibrium dialysis and 23% and 19% bound by ultrafiltration, at 5 micrograms/ml and 50 micrograms/ml, respectively. Phagocytosis of 32 phosphorus-labelled Staph aureus by bovine blood neutrophils was compared in vitro between neutrophils incubated in phosphate-buffered saline alone or in combination with 5, 125, or 1000 micrograms/ml chloramphenicol or FLO. There was no significant effect of chloramphenicol at any concentration. Florfenicol significantly inhibited phagocytosis at all concentrations, but the percentage inhibited was small. The clinical significance, if any, or this effect of FLO remains to be demonstrated.

Category: antimicrobial

Drug:

florfenicol

Species:

cattle

Citation:

Lobell, R. D. Varma, K. J. Johnson, J. C. etc... (1994). Pharmacokinetics of florfenicol following intravenous and intramuscular doses to cattle. J. Vet. Pharmacol. Therap, 17. 253-258

Type of control:

none

Damage To:

neonate

Age of Neonate:

2 to 6 weeks

Dosage:

single 20 mg/kg IV or IM dose

Number of animals:

tx=10

Trimester or stage of Pg studied:

n/a

Results

The disposition of florfenicol after single intravenous and intramuscular doses of 20 mg/kg of florfenicol to feeder calves was investigated. Serum florfenicol concentrations were determined by a sensitive high performance liquid chromatographic method with a limit of quantitation of 0.025 micrograms/ml. The extent of serum protein binding of florfenicol was only 13.2% at a serum florfenicol concentration of 3.0 micrograms/ml. Serum concentration-time data after intravenous administration were best described by a triexponential equation. Total body clearance and steady state volume of distribution were 3.75 ml/min/kg b.w. and 761 ml/kg b.w., respectively. The terminal half-life after intravenous administration was 159 min. The absolute systemic availability after IM administration was 78.5% and the harmonic mean of the terminal half-life was 1098 minutes, indicating slow release of the florfenicol from the formulation of the IM injection site.

Category: antimicrobial

Drug:

florfenicol

Species:

cattle

Citation:

Varma, K. J. Adams, P. E. Powers, T. E. etc..(1995) Pharmacokinetics of florfenicol in veal calves

Type of control:

none

Damage To:

neonate (female)

Age of Neonate:

2 to 4 weeks

Dosage:

22 mg/kg I.V.

Number of animals:

tx=6

Trimester or stage of Pg studied:

n/a

Results

The pharmacokinetic disposition of florfenicol was described in veal calves after administration of a single 22-mg/kg dose IV, orally after a 12 h fast and orally 5 min post feeding. Both serum concentrations and urinary excretion were studied. After intravenous administration, the median elimination half-life was 171.9 min while the half-life of the distribution phase was 5.9 min. The median body clearance and apparent volume of distribution were median bio-availability was 0.88 for calves dosed after a 12-h fast and 0.65 for calves dosed 5 min post feeding. Calves given the oral doses had a complex absorption pattern with delayed absorption. Slightly more than 50% of the administered dose both orally and intravenously was recovered unchanged florfenicol in the urine by 30 h.

Category: antimicrobial

Drug:

metronidazole

Species:

humans

Citation:

Schwarz, R.H.(1981) Considerations of Antibiotic Therapy During Pregnancy. Department of Obstetrics and Gynecology, Downstate Medical Center College of Medicine 58(5), 95s-99s.

Type of control:

none

Damage To:

fetus

Age of Neonate:

n/a

Dosage:

not specified

Number of animals:

not specified

Trimester or stage of Pg studied:

1

Results

The use of metronidazole has been abandoned by most obstetricians because of reports of mutagenesis in animals, especially when administered during the first trimester of gestation. While this has not been documented in humans, the decision to abandon use of this drug was influenced by the fact that it was used to treat a non-life-threatening infection (*Trichomonas vaginalis*).

Category: antimicrobial

Drug:

metronidazole and ethyl alcohol

Species:

mice

Citation:

Damjanov, I. (1983) Metronidazole and alcohol in pregnancy. JAMA 256, 4,472.

Type of control:

none

Damage To:

fetus

Age of Neonate:

n/a

Dosage:

not specified

Number of animals:

not specified

Trimester or stage of Pg studied:

all

Results

For all practical purposes metronidazole is not teratogenic in experimental animals, unless administered in extremely high doses. However, if metronidazole together with ethyl alcohol is given to pregnant mice, fetotoxicity and teratogenicity occur far in excess of that noted in animals exposed to each of these drugs administered separately. It seems, that in mice, metronidazole potentiates the teratogenicity of alcohol. Since metronidazole may cause intolerance to alcohol as well as dizziness and nausea if taken together with alcohol, a warning against the simultaneous use of two drugs in pregnancy may be warranted.

Category: antimicrobial

Drug:
nitrofurantoin

Species:
humans

Citation:
Schwarz, R.H.(1981) Considerations of Antibiotic Therapy During Pregnancy. Department of Obstetrics and Gynecology, Downstate Medical Center College of Medicine 58(5), 95s-99s.

Type of control:
none

Damage To:
dam

Age of Neonate:
n/a

Dosage:
not specified

Number of animals:
not specified

Trimester or stage of Pg studied:
all

Results
The nitrofurantoin are among several agents that can precipitate hemolytic anemia in patients who are deficient in glucose 6-phosphate dehydrogenase. This presents at least a theoretical risk to the fetus of a mother with this deficiency.

Category: antimicrobial

Drug:
norfloxacin, ciprofloxacin

Species:
humans

Citation:
Berkovitch, M.;Pastuszak, A.;Gazarian, M.;Lewis, M. & Koren, G.(1994) Safety of the New Quinolones in Pregnancy. Pediatric Res (Vol. 84, No. 4, Part 1) 535-538

Type of control:
none

Damage To:
fetus

Age of Neonate:
n/a

Dosage:
not specified

Number of animals:
tx= 38

Trimester or stage of Pg studied:
1

Results
Thirty-five women treated with ciprofloxacin or norfloxacin received therapy during their first trimester. The most common indication for therapy was urinary tract infections. More pregnancies in the quinolone group resulted in caesarian section delivery due to reported fetal stress as compared to the controls. No malformations were found in the quinolone group, whereas one child in the control group had ventricular septal defect. No differences were detected between the groups in achievement of developmental milestones or in the musculoskeletal system. In conclusion, the use of the new quinolones during the first trimester of pregnancy does not appear to be associated with an increased risk of malformations or musculoskeletal problems; however, longer follow up and magnetic resonance imaging of the joints may be warranted to exclude subtle cartilage and bone damage.

Category: antimicrobial

Drug:
pyrimethamine

Species:
rats

Citation:
Raynaud, F & Horvath, C. (1994) Folate deficiency and congenital malformations induced by pyrimethamine in the rat. *Reprod Nutr Dev* 34, 461-471.

Type of control:
negative

Damage To:
fetus

Age of Neonate:
n/a

Dosage:
12.5, 15.63, 18.75, and 25 mg/kg IP as single dose on day 12

Number of animals:
tx = 150
control = 43

Trimester or stage of Pg studied:
2/E

Results
Despite depressed folate concentrations, little effect was seen at the lower 2 doses. However significant teratology occurred at the upper two doses with incidences of 52.9 and 58.3%, respectively. A dose-dependent decrease in fetal weight occurred.

Category: antimicrobial

Drug:
pyrimethamine

Species:
humans

Citation:
Schwarz, R.H.(1981) Considerations of Antibiotic Therapy During Pregnancy. *Department of Obstetrics and Gynecology, Downstate Medical Center College of Medicine* 58(5), 95s-99s.

Type of control:
none

Damage To:
fetus

Age of Neonate:
n/a

Dosage:
not specified

Number of animals:
not specified

Trimester or stage of Pg studied:
n/a

Results
No adverse effects with limited use of pyrimethamine have been reported when administered in early gestation. However, pyrimethamine is a folic acid antagonist and consequently should be avoided during early gestation. This agent is recommended for the treatment of toxoplasmosis.

Category: antimicrobial

Drug:

quinolones

Species:

mixed

Citation:

Burkhardt, J.E.;Walterspiel, J.N.;Schaad, U.B.(1997) Quinolone Arthropathy in Animals Versus Children. Clinical Infectious Diseases (25) 1196-1204

Type of control:

none

Damage To:

fetus

Age of Neonate:

n/a

Dosage:

not specified

Number of animals:

not specified

Trimester or stage of Pg studied:

not specified

Results

The comprehensive review of the published data compiled for this study leads to the conclusion that quinolone arthropathy, as described in juvenile animals, is to date not convincingly correlated with the use of these compounds in children and adolescents. The clinical observations temporally related to quinolone use are reversible episodes of arthralgia, with and without effusions, that do not lead to long term sequelae when treatment with the agents is discontinued. It is also concluded that it is ethically justifiable to perform prospective studies of selected quinolone agents on children.

Category: antimicrobial

Drug:

tetracycline

Species:

humans

Citation:

Davis, JS. Kaufman, RH. (1966). Tetracycline toxicity. Am. J. Obst. And Gynec. 95, 4. 523-529.

Type of control:

none

Damage To:

dam

Age of Neonate:

n/a

Dosage:

not specified

Number of animals:

tx=6 (4pregnant)

Trimester or stage of Pg studied:

2

Results

Two of the pregnant women were treated for acute pyelonephritis associated with pregnancy; one pregnant woman was treated for severe bronchopneumonia, and one for septic abortion with pelvic thrombophlebitis. Clinically the women manifested nausea and vomiting, icterus, lethargy, and coma, mild to moderate hemorrhagic phenomena, mild abdominal pain, hypotension, azotemia, acidosis, elevated white blood cell counts, mild to moderate elevation of serum amylase levels.

Category: antimicrobial

Drug:
tetracycline

Species:
humans

Citation:
Schwarz, R.H.(1981) Considerations of Antibiotic Therapy During Pregnancy. Department of Obstetrics and Gynecology, Downstate Medical Center College of Medicine 58(5), 95s-99s.

Type of control:
none

Damage To:
dam
Fetus

Age of Neonate :
n/a

Dosage:
not specified

Number of animals:
not specified

Trimester or stage of Pg studied:
all

Results

Tetracycline has been shown to cause a well defined syndrome of fulminating hepatic decompensation in pregnant patients treated with large intravenous doses for pyelonephritis. This is further complicated by the nephrotoxicity of tetracycline itself, thus making it one of the two antibiotics specifically contraindicated during pregnancy.

Category: antimicrobial

Drug:
trimethoprim

Species:
humans

Citation:
Schwarz, R.H.(1981) Considerations of Antibiotic Therapy During Pregnancy. Department of Obstetrics and Gynecology, Downstate Medical Center College of Medicine 58(5), 95s-99s.

Type of control:
none

Damage To:
fetus
dam

Age of Neonate:
n/a

Dosage:
not specified

Number of animals:
not specified

Trimester or stage of Pg studied:
1

Results

No adverse effects with limited use of trimethoprim have been reported when administered in early gestation. However, trimethoprim is a folic acid antagonist and consequently should be avoided during early

Category: bronchodilator

Drug:
clenbuterol

Species:
mixed

Citation:
Menard, L. (1984) Tocolytic Drugs for Use in Veterinary Obstetrics. Can Veterinary Journal (25) 389-393

Type of control: none
Damage To: dam
Age of Neonate: n/a

Dosage:
not specified

Number of animals:
not specified

Trimester or stage of Pg studied:
n/a

Results

Clenbuterol has not to date been widely used in human patients for tocolytic effects but rather for it's bronchodilatory effects. It has, however, been developed as a tocolytic agent for veterinary use in farm animals to provide either a zootechnical or a therapeutical interruption of parturition. Good results have been recorded in cases of dystocia due to fetal oversize, uterine torsion and cervical spasm corrected by fetotomy or caesarian operation.

Category: bronchodilator

Drug:
theophylline

Species:
dogs

Citation:
Alberola, Jordi; Perez, Yolanda; Puigdemont, Ana; Arboix, Margarita (1993) Effect of age on theophylline pharmacokinetics in dogs. Am J Vet Res (54) 7:1112-1115

Type of control: none
Damage To: neonate
Age of Neonate: 1, 2, 3, 4, 8, 12, 16, 24, 52, and 104 weeks of age (six dogs per group)

Dosage:
5 mg/kg IV as single dose

Number of animals:
tx = 60

Trimester or stage of Pg studied:
n/a

Results

It was noticed that young dogs have a slower elimination half-life than do older animals. These findings may have relevance with regard to the therapeutic range of theophylline. For this reason, dosage should be carefully adjusted in younger animals. T_{1/2} and CI near adult values at 3-4 weeks. V_d not affected by age. (From Figures 2-4 and text.)

Category: cardiovascular

Drug:
benazepril

Species:
not specified

Citation:
Briggs, G.G.; Freeman, R.K. & Sumner, Y.J. (No year given) Drugs in Pregnancy and Lactation-A Reference Guide to Fetal and Neonatal Risks. Fourth Edition. P77-682

Type of control:
none

Damage To:
fetus
neonate

Age of Neonate:
12 to 36 hours

Dosage:
not specified

Number of animals:
not specified

Trimester or stage of Pg studied:
1

Results

Benazepril is an angiotensin-converting enzyme inhibitor. No reports of the use of this agent in human pregnancy have been located, but this class of drugs should be used with caution, if at all, during gestation. Use of the angiotensin-converting enzyme inhibitors limited to the first trimester does not appear to present a significant risk to the fetus, but fetal exposure during this time has been associated with teratogenicity and severe toxicity in the fetus and newborn, including death.

Category: cardiovascular

Drug:
digoxin

Species:
sheep

Citation:
Hernandez, Antonio, et al. (1975) The effects of long-term administration of H-digoxin to the pregnant ewe upon the cardiovascular hemodynamics of the fetal lamb. Am. J. Obstet. Gynecol. April 15, 1975

Type of control:
none

Damage To:
fetus

Age of Neonate:
n/a

Dosage:
6 microgram/kg/day of tritiated drug (0.03 mcg/kg/day of total digoxin) for 130-140 days

Number of animals:
tx =7

Trimester or stage of Pg studied:
all/G

Results

Fetal blood concentration approximately the same as maternal blood but tissue concentrations less. Would be hard to produce therapeutic fetal tissue concentrations without causing maternal toxicity.

Category: cardiovascular

Drug:
isoxsuprine

Species:
cattle

Citation:
Gilbert, R.O. & Schwark, W.S. (1992) Pharmacologic Considerations in the Management of Peripartum Conditions in the Cow. Veterinary Clinics of North America: Food Animal Practice 8(1) 29-56

Type of control:
none

Damage To:
dam

Age of Neonate:
n/a

Dosage:
not specified

Number of animals:
not specified

Trimester or stage of Pg studied:
n/a

Results
Isoxsuprine has a lack of discrimination between beta1 and beta2 adrenoreceptors, which probably accounts for the tachycardia that may accompany use of this drug. Isoxsuprine also bears a structural similarity with epinephrine and papaverine; the resemblance to the latter compound may account for the spasmolytic effect on smooth muscle.

Category: cardiovascular

Drug:
isoxsuprine

Species:
mixed

Citation:
Menard, L. (1984) Tocolytic Drugs for Use in Veterinary Obstetrics. Can Veterinary Journal (25) 389-393

Type of control:
none

Damage To:
dam

Age of Neonate:
n/a

Dosage:
0.4 - 2.0 mg/kg (recommended dose)

Number of animals:
not specified

Trimester or stage of Pg studied:
G (parturition)

Results
Isoxsuprine has a tocolytic effect predominately in ruminants. It has been used extensively at parturition, specifically when difficulties such as uterine torsion and dystocia occur. This article is more of a review dealing with the tocolytic effects of isoxsuprine than a specific study of the drug.

Category: diuretic

Drug:
furosemide

Species:
cattle

Citation:
Gilbert, R.O. & Schwark, W.S. (1992) Pharmacologic Considerations in the Management of Peripartum Conditions in the Cow. Veterinary Clinics of North America: Food Animal Practice 8(1) 29-56

Type of control:
none

Damage To:
dam

Age of Neonate:
n/a

Dosage:
500 mg IM or IV or 2.2 to 4.4 mg/kg orally

Number of animals:
not specified

Trimester or stage of Pg studied:
n/a

Results

Excessive use of furosemide in the pregnant cow can cause extensive calcium loss in the urine, and this could lead to postparturient hypocalcaemia.

Category: gastrointestinal

Drug:
metaclopramide

Species:
humans

Citation:
Briggs, G.G.; Freeman, R.K. & Sumner, Y.J. (No year given) Drugs in Pregnancy and Lactation-A Reference Guide to Fetal and Neonatal Risks. Fourth Edition. P77-682

Type of control:
none

Damage To:
fetus

Age of Neonate:
n/a

Dosage:
not specified

Number of animals:
not specified

Trimester or stage of Pg studied:
all

Results

Metaclopramide has been used for the treatment of nausea and vomiting in pregnant women. Ten out of one hundred and ninety two babies exposed to the drug during the first trimester had major birth defects; half of them had cardiovascular defects and the other half were polydactylic. In addition, metaclopramide apparently does not present a risk to the nursing infant with maternal doses of less than 45 mg/kg per day.

Category: gastrointestinal

Drug:
metoclopramide

Species:
humans

Citation:
Kearns, G., van den Anker, J., Reed, M., & Blumer, J. (1998) Pharmacokinetics of metoclopramide in neonates. J Clin Pharmacol 38, 122-128

Type of control: none **Damage To:** neonate **Age of Neonate:** up to 31 weeks

Dosage:
0.1 to 0.15 mg/kg single oral dose

Number of animals:
tx =10

Trimester or stage of Pg studied:
3/E

Results

A prolonged apparent plasma clearance of metoclopramide was observed in 30% of the infants studied, and the mean Cl/F and apparent steady-state volume of distribution were approximately 1.4- and 2.1-fold higher, respectively, than values reported in previous studies of metoclopramide disposition in adults. These data suggest that metoclopramide pharmacokinetics may exhibit a developmental dependency; thus, a metoclopramide dose of 0.15 mg/kg given orally every six hours is recommended for the initiation of prokinetic therapy with this agent in infants who are ≤ 31 weeks postconceptional age.

Category: hormone

Drug:
oxytocin

Species:
humans

Citation:
Davis, L.E. & Stanton, H.C. (No other reference title given)

Type of control: none **Damage To:** fetus **Age of Neonate:** n/a

Dosage:
not specified

Number of animals:
not specified

Trimester or stage of Pg studied:
G

Results

Oxytocin is usually employed to correct uterine inertia, and the extensive use of this drug in veterinary obstetrics would indicate that it does not produce adverse effect on the newborn. However, oxytocin will cause constriction of the umbilical vessels, and this could compromise an already hypoxic fetus.

Category: NSAID

Drug:
acetylsalicylic acid

Species:
rabbits

Citation:
Ueno, K.; Masumura, H.; Kawamoto, H.; Kitagawa, H. (1988) Effects of Ketoprofen and Other Drugs on Release of Prostaglandins from Uterus of Rabbits in Prenatal Period. Research Communications in Chemical Pathology and Pharmacology (Vol. 59, No. 1) 141-144

Type of control:
none

Damage To:
fetus

Age of Neonate:
n/a

Dosage:
100 mg/kg

Number of animals:
not specified

Trimester or stage of Pg studied:
all

Results

It has been proven in previous studies that some NSAIDs can prolong parturition due to the inhibition of both contractions and prostaglandin release from the uterus in rats. Due to species differences, it is of interest to study the effects of PGF2 alpha and prostaglandin E release from the isolated rabbit uterus. Administration of the drug in rabbits did indeed have an inhibitory effect on the release of prostaglandins from the uterus of the rabbit in late gestation. Results in this study were similar to those of the rat study, all of which have been noted in this article.

Category: NSAID

Drug:
aspirin

Species:
humans

Citation:
Welsch, F.(1982) Placental Transfer and Fetal Uptake of Drugs. Journal of Veterinary Pharmacologic Therapy 5, (91-104)

Type of control:
none

Damage To:
fetus

Age of Neonate:
n/a

Dosage:
not specified

Number of animals:
not specified

Trimester or stage of Pg studied:
all

Results

Analgesic drugs such as aspirin have received a lot of attention because it is so commonly used by pregnant women. While there have been no studies in humans, it has been shown to be teratogenic in lab animals. Aspirin inhibits the biosynthesis of prostaglandins which seem to be involved in keeping the ductus arteriosus patent in the fetus while in utero.

Category: NSAID

Drug:
flurbiprofen

Species:
rats

Citation:
Ueno, K.; Masumura, H.; Kawamoto, H.; Kitagawa, H. (1987) Effects of Ketoprofen on Release of Prostaglandin F2 Alpha from Uterus of Rat in Prenatal Period. Research Communications in Chemical Pathology and Pharmacology (Vol. 58, No. 2) 173-182

Type of control: none **Damage To:** fetus **Age of Neonate:** n/a

Dosage:
0.1 and 1.0 mg/kg

Number of animals:
not specified

Trimester or stage of Pg studied:
2

Results
The results of this study suggest that deficiency of PGF2 alpha release from the uterus might result in the delay of spontaneous delivery, and also concomitant decrease of progesterone might be involved in the prolongation of gestation induced by treatment

Category: NSAID

Drug:
flurbiprofen

Species:
rabbits

Citation:
Ueno, K.; Masumura, H.; Kawamoto, H.; Kitagawa, H. (1988) Effects of Ketoprofen and Other Drugs on Release of Prostaglandins from Uterus of Rabbits in Prenatal Period. Research Communications in Chemical Pathology and Pharmacology (Vol. 59, No. 1) 141-144

Type of control: none **Damage To:** fetus **Age of Neonate:** n/a

Dosage:
1.0 mg/kg

Number of animals:
not specified

Trimester or stage of Pg studied:
all

Results
It has been proven in previous studies that some NSAIDS can prolong parturition due to the inhibition of both contractions and prostaglandin release from the uterus in rats. Due to species differences, it is of interest to study the effects of PGF2 alpha and prostaglandin E release from the isolated rabbit uterus. Administration of the drug in rabbits did indeed have an inhibitory effect on the release of prostaglandins from the uterus of the rabbit in late gestation. Results in this study were similar to those of the rat study, all of which have been noted in this article.

Category: NSAID

Drug:
indomethacin

Species:
rats

Citation:
Ueno, K.; Masumura, H.; Kawamoto, H.; Kitagawa, H. (1987) Effects of Ketoprofen on Release of Prostaglandin F2 Alpha from Uterus of Rat in Prenatal Period. Research Communications in Chemical Pathology and Pharmacology (Vol. 58, No. 2) 173-182

Type of control: none **Damage To:** fetus **Age of Neonate:** n/a

Dosage:
0.1, 1.0 and 3.0 mg/kg

Number of animals:
not specified

Trimester or stage of Pg studied:
2

Results

The results of this study suggest that deficiency of PGF2 alpha release from the uterus might result in the delay of spontaneous delivery, and also concomitant decrease of progesterone might be involved in the prolongation of gestation induced by treatment

Category: NSAID

Drug:
indomethacin

Species:
rabbits

Citation:
Ueno, K.; Masumura, H.; Kawamoto, H.; Kitagawa, H. (1988) Effects of Ketoprofen and Other Drugs on Release of Prostaglandins from Uterus of Rabbits in Prenatal Period. Research Communications in Chemical Pathology and Pharmacology (Vol. 59, No. 1) 141-144

Type of control: none **Damage To:** fetus **Age of Neonate:** n/a

Dosage:
1.0 and 3.0 mg/kg

Number of animals:
not specified

Trimester or stage of Pg studied:
all

Results

It has been proven in previous studies that some NSAIDS can prolong parturition due to the inhibition of both contractions and prostaglandin release from the uterus in rats. Due to species differences, it is of interest to study the effects of PGF2 alpha and prostaglandin E release from the isolated rabbit uterus. Administration of the drug in rabbits did indeed have an inhibitory effect on the release of prostaglandins from the uterus of the rabbit in late gestation. Results in this study were similar to those of the rat study, all of which have been noted in this article.

Category: NSAID

Drug:
ketoprofen

Species:
humans

Citation:
Bannwarth, B. (1999) (S)-Ketoprofen Accumulation in Premature Neonates Who Were Exposed to the Racemate During Pregnancy. (Letter to the Editor) Br J Clin Pharmacology (47) 459-461

Type of control:
none

Damage To:
fetus

Age of Neonate:
n/a

Dosage:
100 mg -200mg daily ranging from 1 day to 6 weeks before parturition

Number of animals:
tx=7

Trimester or stage of Pg studied:
3

Results
This study refers to plasma concentrations of ketoprofen in infants with renal failure who were exposed to racemic ketoprofen in the last few days or weeks before delivery. NSAIDS have been used as tocolytic agents to prevent premature labor in patients who did not respond to conventional therapy. All babies in the study were born with normal hepatic and renal functions, although NSAIDS have been proven to cause fetal damage such as premature closing of the ductus arteriosus, renal insufficiency and necrotizing enterocolitis. In conclusion, the data collected indicates that ketoprofen cutomer tends to accumulate in plasma of premature neonates in varying stages of renal function. The underlying mechanism awaits, however, further classification.

Category: NSAID

Drug:
ketoprofen

Species:
rabbits

Citation:
Ueno, K.; Masumura, H.; Kawamoto, H.; Kitagawa, H. (1988) Effects of Ketoprofen and Other Drugs on Release of Prostaglandins from Uterus of Rabbits in Prenatal Period. Research Communications in Chemical Pathology and Pharmacology (Vol. 59, No. 1) 141-144

Type of control:
none

Damage To:
fetus

Age of Neonate:
n/a

Dosage:
1.0 mg/kg

Number of animals:
not specified

Trimester or stage of Pg studied:
all

Results
It has been proven in previous studies that some NSAIDS can prolong parturition due to the inhibition of both contractions and prostaglandin release from the uterus in rats. Due to species differences, it is of interest to study the effects of PGF2 alpha and prostaglandin E release from the isolated rabbit uterus. Administration of the drug in rabbits did indeed have an inhibitory effect on the release of prostaglandins from the uterus of the rabbit in late gestation. Results in this study were similar to those of the rat study, all of which have been noted in this article.

Category: NSAID

Drug:
ketoprofen

Species:
rats

Citation:
Ueno, K.; Masumura, H.; Kawamoto, H.; Kitagawa, H. (1987) Effects of Ketoprofen on Release of Prostaglandin F2 Alpha from Uterus of Rat in Prenatal Period. Research Communications in Chemical Pathology and Pharmacology (Vol. 58, No. 2) 173-182

Type of control:
none

Damage To:
fetus

Age of Neonate:
n/a

Dosage:
0.1, 1.0 and 3.0 mg/kg

Number of animals:
not specified

Trimester or stage of Pg studied:
2

Results

The results of this study suggest that deficiency of PGF2 alpha release from the uterus might result in the delay of spontaneous delivery, and also concomitant decrease of progesterone might be involved in the prolongation of gestation induced by treatment with these anti-inflammatory drugs.

Category: NSAID

Drug:
ketoprofen

Species:
rats

Citation:
Ueno, K.; Masumura, H.; Kawamoto, H.; Kitagawa, H. (1987) Effects of Ketoprofen on Release of Prostaglandin F2 Alpha from Uterus of Rat in Prenatal Period. Research Communications in Chemical Pathology and Pharmacology (Vol. 58, No. 2) 173-182

Type of control:
none

Damage To:
fetus

Age of Neonate:
n/a

Dosage:
10 and 100 mg/kg

Number of animals:
not specified

Trimester or stage of Pg studied:
2

Results

The results of this study suggest that deficiency of PGF2 alpha release from the uterus might result in the delay of spontaneous delivery, and also concomitant decrease of progesterone might be involved in the prolongation of gestation induced by treatment.

Category: NSAID

Drug:
naproxen

Species:
rabbits

Citation:
Ueno, K.; Masumura, H.; Kawamoto, H.; Kitagawa, H. (1988) Effects of Ketoprofen and Other Drugs on Release of Prostaglandins from Uterus of Rabbits in Prenatal Period. Research Communications in Chemical Pathology and Pharmacology (Vol. 59, No. 1) 141-144

Type of control:
none

Damage To:
fetus

Age of Neonate:
n/a

Dosage:
1.0 mg/kg

Number of animals:
not specified

Trimester or stage of Pg studied:
all

Results

It has been proven in previous studies that some NSAIDS can prolong parturition due to the inhibition of both contractions and prostaglandin release from the uterus in rats. Due to species differences, it is of interest to study the effects of PGF2 alpha and prostaglandin E release from the isolated rabbit uterus. Administration of the drug in rabbits did indeed have an inhibitory effect on the release of prostaglandins from the uterus of the rabbit in late gestation. Results in this study were similar to those of the rat study, all of which have been noted in this article.

Category: NSAID

Drug:
naproxen

Species:
rats

Citation:
Ueno, K.; Masumura, H.; Kawamoto, H.; Kitagawa, H. (1987) Effects of Ketoprofen on Release of Prostaglandin F2 Alpha from Uterus of Rat in Prenatal Period. Research Communications in Chemical Pathology and Pharmacology (Vol. 58, No. 2) 173-182

Type of control:
none

Damage To:
fetus

Age of Neonate:
n/a

Dosage:
0.1 and 1.0 mg/kg

Number of animals:
not specified

Trimester or stage of Pg studied:
2

Results

The results of this study suggest that deficiency of PGF2 alpha release from the uterus might result in the delay of spontaneous delivery, and also concomitant decrease of progesterone might be involved in the prolongation of gestation induced by treatment.

Category: NSAID

Drug:

NSAIDs (aspirin, dipyron, ketoprofen, flunixin meglumine, phenylbutazone)

Species:

cattle, swine, sheep, human

Citation:

Damian, P. Craigmill, A. L. Riviere, J. E. (1997) Extralabel use of nonsteroidal anti-inflammatory drugs. JAVMA 211, 7. 860-861.

Type of control:

not specified

Damage To:

fetus

Age of Neonate:

n/a

Dosage:

not specified

Number of animals:

not specified

Trimester or stage of Pg studied:

n/a

Results

Despite the fact that aspirin is of low regulatory concern, some epidemiologic data suggest a link between salicylates and Reye's syndrome in children with chickenpox or influenza. For this reason, FARAD recommends minimum meat and milk WDI of 24 hours for typical uses of aspirin in food animals. Dipyron has been associated with toxic effects in human beings including bone marrow toxicosis, agranulocytic anemia, and teratogenicity.

Category: NSAID

Drug:

phenylbutazone

Species:

goats

Citation:

Eltom, S.E. Guard, C.L. Schwark, W.S. (1993) The effect of age on phenylbutazone pharmacokinetics, metabolism and plasma protein binding in goats. J Vet Pharmacol. Therap 16. 141-151.

Type of control:

none

Damage To:

neonate

Age of Neonate:

birth to 6 weeks

Dosage:

IV as a single dose (10 mg/kg) given

Number of animals:

tx=6 adults

tx=7 neonates

Trimester or stage of Pg studied:

n/a

Results

The elimination half-life of PBZ decreased from 120 h in the 1-day old to 16 h in the adult goats. Although the volume of distribution did not change significantly during the maturation, the total body clearance increased from 2ml.h⁻¹.kg⁻¹ in 1 day old to 13 ml.h⁻¹.kg⁻¹ in the adult goats; the increase was 2-fold in the first 10 days of life. Oxyphenbutazone was detectable in the plasma of adult and 6-wk old goats as early as 15 min after PBZ administration. Its peak concentration occurred at 1.5 h (1.6 microgram/ml) in adults and at 6 h (0.95 microgram/ml) and 12 h (0.36 microgram/ml) in 6- and 4-wk old goats respectively. The highest plasma concentration of gamma-OHPBZ was achieved in 4-wk old followed by 6-wk old and adult animals. In conclusion, drug disposition in neonatal goats differs markedly from adults and special considerations should be taken when treating neonates.

Category: sedative /
tranquilizer

Drug:
xylazine

Species:
cattle

Citation:
Gilbert, R.O. & Schwark, W.S. (1992) Pharmacologic Considerations in the Management of Peripartum Conditions in the Cow. Veterinary Clinics of North America: Food Animal Practice 8(1) 29-56

Type of control:
none

Damage To:
fetus

Age of Neonate:
n/a

Dosage:
not specified

Number of animals:
not specified

Trimester or stage of Pg studied:
3

Results

Xylazine is not an approved drug for use in food producing animals, but it is widely used as a sedative/analgesic in these species. It may also be used at the time of parturition for obstetrical manipulations. Xylazine is contraindicated in cattle because of the increase tendency of premature parturition. However, in one trial, all calves born prior to their delivery date did survive.

PHARMACOTHERAPY OF IMMUNOCOMPROMISED ANIMALS

Mark Papich, DVM, MS, DACVCP

INTRODUCTION

Treating infections in immunocompromised animals presents a special challenge. Because of the patient's incompetent immune system, the correct selection of antimicrobial drugs and the appropriate dosing regimen is especially important. The immunocompromised condition may be either primary or secondary. Secondary causes include: disease (cancer or viral disease for example), bone marrow failure, or drug therapy (immunosuppressive drugs, corticosteroids, anticancer drugs).

RISK FACTORS

The patient risk factors that increase the likelihood, or the severity of infection in these patients are, neutropenia, duration of neutropenia, cancer treatment, administration of immunosuppressive drugs (corticosteroids, azathioprine, cyclophosphamide, cyclosporine), intravenous catheters, and diseases that may compromise the integrity of the intestinal barrier (eg parvovirus). Cancer patients are particularly at risk because they are receiving immunosuppressive drugs, often aged, catheterized or subject to invasive surgery, their nutritional status may not be adequate, and the cytotoxic drugs may decrease the integrity of the intestinal barrier.

In human medicine, it has been shown that a neutropenia less than 500 cells/ μ l is the single most important risk factor for infection¹. In veterinary patients, neutropenia of less than 1,000 cells/ μ l is generally cited as an important threshold at which risk of infection becomes the greatest. A range of values have been published for what constitutes neutropenia severe enough to withhold cancer chemotherapy. Total white blood cell counts less than 2,500 cells/ μ l or granulocytes less than 2,000 cells/ μ l are often cited. Duration of neutropenia also is important. Patients that have neutropenia that persists for longer than 7 days are more vulnerable to infections caused by opportunistic pathogens.

ORGANISMS CAUSING INFECTION

The bacteria encountered in animals that present the most life-threatening problem are the gram-negative bacilli. In both large animals and small animals the most common bacteria is *Escherichia coli*. Other potential causes of infection are *Klebsiella pneumoniae*, *Enterobacter*, *Proteus*, and possibly *Pseudomonas aeruginosa*. Life-threatening gram-positive bacterial infections are less common, but also can be potentially serious. Bacteria of this group causing infection may include *Staphylococcus intermedius*, *Staph. aureus*, streptococci, and *Enterococcus* species. An important characteristic of *Enterococcus* is the degree of resistance that it can exhibit. In humans with neutropenia and cancer there has been a shift in the organisms causing infection. There has been an increase in infections caused by bacteria that were not accounted for in earlier antibacterial regimens². These include increased rate of infections caused by gram-positive bacteria such as streptococci and enterococci, and the emergence of gram-negative bacteria such as *Klebsiella pneumoniae*, *Enterobacter* species, and *E. coli*, that are resistant to broad-spectrum drugs.

MANAGEMENT

The management of immunocompromised human patients has evolved over the years and a review of past practices is helpful when considering treatment of, or prevention of infections in immunocompromised animals^{3,4}. The first widely used strategy consisted of injections of an antipseudomonas penicillin combined with an aminoglycoside. This combination was synergistic, more rapidly bactericidal, and more effective than either drug alone. With the availability of new drugs that were more active than the older β -lactam antibiotics, monotherapy with injections of either ceftazidime (a third-generation cephalosporin with antipseudomonas activity) or imipenem (a carbapenem with broad spectrum activity) were instituted⁵. Most recently, the practice of treating patients out of the hospital with oral drugs has gained interest³. Drugs given as oral therapy have been a fluoroquinolone (such as ciprofloxacin) in combination with an oral β -lactam and β -lactamase inhibitor (amoxicillin-clavulanate). One of the advantages of out-patient treatment with oral drugs compared to in-hospital treatment with IV medications is (1) no need for invasive IV catheters, (2) less stress to the patient, (3) usually less cost because overnight hospitalization is avoided, and (4) decreased risk of exposure to hospital nosocomial pathogens.

When treatment with antibiotics is initiated in the immunocompromised patient, the duration of treatment will vary on individual circumstances and risk factors. In the case of a neutropenic, febrile patient, one should administer antibiotics for 5

to 7 days after the temperature has returned to normal and neutrophil counts are at least above 1,000 cells/ μ l. If fever persists, addition of other drugs with a broader spectrum, such as doxycycline or an antifungal drug should be considered. The combinations discussed below do not include either clindamycin or metronidazole for the anaerobic spectrum. However, if anaerobic infections are identified, either of these drugs can be added to the regimen.

ANTIBIOTIC DRUG SELECTION

Treatment is often empirical. In practically every case, treatment should include an antimicrobial that has activity against the Enterobacteriaceae. Activity against *Escherichia coli*, and *Klebsiella pneumoniae* is particularly important. The clinician will have to make the decision of whether or not the drug should have activity against *Pseudomonas aeruginosa*, based on risk factors and the patient's history. In human medicine, it is known that infections caused by *Pseudomonas aeruginosa* are associated with a poorer prognosis and drugs with an antipseudomonas spectrum are often included. Some of the specific drugs are listed below under separate headings. More complete discussion about these drugs can also be found in a recent review⁶. Doses of these drugs have been published in current textbooks⁷.

MONOTHERAPY OR COMBINATION THERAPY

Combination antibiotic therapy in an immunocompromised patient has traditionally consisted of the use of an aminoglycoside (amikacin or gentamicin), in combination with a β -lactam antibiotic (a penicillin or cephalosporin). This combination broadens the spectrum of the aminoglycoside to include anaerobes and gram-positive bacteria, and is more active than either drug used alone. The choice of a β -lactam in this combination has been an antipseudomonas penicillin (ticarcillin or piperacillin), but if activity against *Pseudomonas aeruginosa* is not critical, another penicillin or cephalosporin would suit the purpose⁸. After the introduction of fluoroquinolones to therapy in the late 1980s, the combination choice has shifted somewhat to the use of a fluoroquinolone in combination with a β -lactam. In two studies reported simultaneously, it was shown that combination therapy in neutropenic human patients with an oral fluoroquinolone (ciprofloxacin) in combination with oral amoxicillin-clavulanate was as effective as IV ceftazidime or IV ceftriaxone and amikacin³. There is no evidence that fluoroquinolones and β -lactams are directly synergistic. But, the addition of the β -lactam broadens the spectrum to include anaerobes and gram-positive cocci.

Monotherapy is the use of a single agent to treat or prevent infections in immunocompromised patients. In order to achieve a high likelihood of activity against gram-negative bacteria, the selection of a single agent should consider a 3rd generation cephalosporin, a carbapenem (imipenem), or an antipseudomonas penicillin + β -lactamase inhibitor (for example, ticarcillin + clavulanate). The recent availability of a 4th generation cephalosporin (cefepime) offers another possibility, because it has an extended spectrum that includes gram-positive and gram-negative bacteria. However, the use of cefepime has not been reported in veterinary medicine except in experimental studies.

There are many instances in which it is justified to select a fluoroquinolone as single-agent therapy. In a meta-analysis in which fluoroquinolones were used as monotherapy in human patients with neutropenia, they alone were effective in preventing gram-negative bacteremia. If β -lactams were added to the regimen, it significantly decreased the occurrence of gram-positive bacteria.

NARROW SPECTRUM VS BROAD SPECTRUM

Many of the traditional guidelines for antibiotic drug therapy suggest that emergence of resistance is decreased when the antibiotic drug selection has an antimicrobial spectrum as narrow as possible. However, there is little evidence that this practice accomplishes this goal of decreasing resistance and it may lead to superinfection. When treating or preventing infections in neutropenic patients, the antimicrobial spectrum should be broad.

DECONTAMINATION

Administration of locally-active oral antimicrobials in an attempt to "sterilize" or decontaminate the intestine has been advocated in the past. The goal was not to actually sterilize the gut, but to selectively decrease the gram-negative bacteria, but retain the beneficial anaerobes. This has been called "colonization resistance"⁴. The rationale for this practice was to prevent translocation of gram-negative bacteria from the intestine to the blood stream in neutropenic patients. Drugs used for this purpose were usually poorly absorbed oral antimicrobials with a gram-negative spectrum. This practice has been mostly discontinued because it may lead to breakthrough resistance, superinfection with gram-positive bacteria, and has unproven efficacy. However, there is some evidence that oral administration of fluoroquinolones may result in fewer gram-negative bacteremia⁴.

DRUGS

Aminoglycosides

The aminoglycosides remain one of the most effective drugs for use in acute infections. Their rapid bactericidal activity and synergism with β -lactam antibiotics has contributed to their efficacy. The most common drugs used in veterinary medicine are gentamicin and amikacin. These drugs have been used once daily because of their concentration-dependent antibacterial action and long post-antibiotic effect. Amikacin is more active than gentamicin, because of less likelihood of resistance, but there is little evidence that it is less nephrotoxic. Once daily administration also decreases the risk of nephrotoxicosis. To guide safe treatment with aminoglycosides, therapeutic drug monitoring can be used to ensure that renal drug clearance is adequate.

Fluoroquinolones

The fluoroquinolones have the advantage of convenience of oral administration and potent gram-negative bactericidal activity. The drugs used in veterinary medicine include enrofloxacin, difloxacin, orbifloxacin, and marbofloxacin. If there is a strong suspicion that the bacteria causing infection is a gram-negative bacilli, one of the fluoroquinolones usually has high activity. However, resistance among *E.coli* to enrofloxacin has been observed in recent studies^{9,10}. Although ciprofloxacin is not registered for use in animals, it has been used by veterinarians when there is a documented *Pseudomonas* infection or risk of *Pseudomonas*. Ciprofloxacin is more active against this organism than the veterinary fluoroquinolones¹¹. If fluoroquinolones are used, one should be cognizant that anaerobic bacteria and gram-positive cocci may not be inhibited. There are new fluoroquinolones available in human medicine with extended spectrum that includes anaerobes and gram-positive cocci, (for example, moxifloxacin, gatifloxacin), but whether or not these will be effective for monotherapy still has to be evaluated.

Cephalosporins

The 1st generation cephalosporins such as cephalexin (oral) or cefazolin (injectable) are widely-used cephalosporins in veterinary medicine. However, against the gram-negative bacteria that are likely to cause serious infection in a neutropenic animal, the activity of these drugs is questionable. In a recent report, the % of *E. coli* susceptible, were lower for 1st generation cephalosporins (23%) than any other drug group¹⁰. Resistance caused by β -lactamase production or failure to penetrate the outer-membrane is common. Therefore, to ensure greater activity against these organisms, injectable drugs that are classified as 3rd-generation cephalosporins are more likely to be effective. The preferred 3rd generation cephalosporins are cefotaxime, ceftazidime, or cefoperazone. Cefotaxime has activity against most of the gram-negative bacilli, except *Pseudomonas aeruginosa*. It also has activity against streptococci, but not against staphylococci. If it is important for the spectrum of activity to include *Pseudomonas aeruginosa*, ceftazidime is the cephalosporin of choice because it has the highest activity against this organism. Ceftazidime was recently investigated in dogs and dosage regimens have been calculated¹². The 3rd generation cephalosporins are usually given IV, IM or subcutaneous (SC). A significant drawback of IM or SC administration is the pain that these drugs elicit. A drawback for all of these drugs, via any route, is the frequency with which they must be administered (often 3 or 4 times daily). Ceftiofur (or its active metabolite) shares the spectrum of activity as cefotaxime. However, this drug is approved in animals only for some narrow indications. If used for systemic infections at doses needed for broad-spectrum activity, the ceftiofur dose may have to be increased above the label recommendation, which may elicit a toxic reaction.

Carbapenems

The carbapenems are β -lactam antibiotics that have greater activity than any previously available β -lactam. Drugs in this class include imipenem and meropenem. Imipenem is combined with cilastatin to decrease renal metabolism. Imipenem is used more frequently than meropenem, because it has been available for a longer time and is less expensive than meropenem. A potential advantage of meropenem, however, is ease of administration (can be diluted in smaller fluid volume) and less risk of central nervous system toxicity. Imipenem has been used in many veterinary patients, delivered as an IV infusion or administered with SC fluids. The broad spectrum activity, bactericidal action, post-antibiotic effect, and low incidence of resistance makes this a valuable drug in severely immunocompromised patients. Because carbapenems have more selectivity for the penicillin-binding protein (PBP) 1 and 2, rather than PBP-3, they are less likely to cause release of endotoxin in animals compared to other β -lactam antibiotics. This may elicit less of a reaction in a bacteremic animal than other drugs.

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KEY WORDS

Immunosuppressive
Neutropenia
Antibiotic
Aminoglycoside
Cephalosporin
Carbapenem
Fluoroquinolone

