

CONSIDERATION OF METRONIDAZOLE TOXICITY ON DEVELOPMENT AND REPRODUCTION

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Abstract

Metronidazole is one of the most used drugs in medical practice, due to its large antimicrobial specter, as well as its antiparasitic actions, being the drug chosen for genital trichomoniasis in men, as well as in women. This is not a nontoxic drug. There is a correlation between dose, duration of treatment and the moment of clinical severe manifestations associated to toxicity. Metronidazole and its derivatives have an action against protozoa, as well as bacterial microorganisms.

Metronidazole is an antibiotic also used in veterinary medicine, to treat various infections: anaerobic bacterial infections, protozoa infections, gastritis associated with helicobacter, hepatic encephalopathy. In addition, towards the anti protozoa and bacterial proprieties, metronidazole is considered to have immunomodulatory effects, being frequently used in treating intestine inflammatory diseases in dogs, as well as in cats.

Metronidazole is a drug with acceptable toxicity on reproduction; new studies are necessary in order to determine and deepen its implications to embryo-fetal development. As a rule, it is not administrated during the first pregnancy trimester when the embryogenesis process takes place, neither the women who breastfeed because it gets through milk, to fetus. When administrated during the third trimester to pregnant women with bacterial vaginosis, it prevents various pregnancy complications: preterm birth, premature and early membrane rupture and intra-amniotic infection.

Keywords: Metronidazole, toxicity, treatment, reproduction, pregnancy.

ASPECTE PRIVIND TOXICITATEA METRONIDAZOLULUI ASUPRA DEZVOLTĂRII ȘI REPRODUCERII

Rezumat

Metronidazolul este unul dintre cele mai folosite medicamente în practica medicală datorită spectrului său larg antimicrobian, cât și datorită acțiunii sale antiparazitare, el fiind medicamentul de elecție pentru trichomonioza genitală, atât la bărbat, cât și la femeie. Acesta nu este un drog lipsit de toxicitate. Există o strânsă corelație între doză, durata tratamentului și momentul manifestărilor semnelor clinice severe, asociate cu toxicitatea. Metronidazolul și derivații săi au atât o acțiune împotriva protozoarelor, cât și asupra microorganismelor bacteriene.

Metronidazolul este un antibiotic utilizat și în medicina veterinară pentru tratarea unei mari varietăți de infecții: infecții bacteriene anaerobe, infecții protozoare, gastrite asociate cu helicobacter, hepatoencefalopatii. În plus față de proprietățile antiprotozoare și bactericide, metronidazolul este considerat a avea efecte imunomodulatoare, el fiind frecvent utilizat în tratarea bolilor inflamatorii ale intestinului, atât în cazul câinilor, cât și a pisicilor.

Metronidazolul este un drog cu o toxicitate acceptabilă asupra reproducerii; sunt necesare noi studii care să precizeze și să aprofundeze care sunt implicațiile sale în dezvoltarea embriofetală. De regulă, nu se administrează în cursul primului trimestru de sarcină când are loc procesul de embriogeneză, dar nici la femeile care alăptează, deoarece trece prin lapte la făt. Administrat în cursul trimestrului trei la gravide cu vaginoză bacteriană, previne o serie de complicații ale sarcinii: nașterea

prematură, ruptura prematură a membranelor și infecția amniotică.

Cuvinte cheie: Metronidazol, toxicitate, tratament, reproducere, sarcină.

Metronidazole is one of the most used drugs in medical practice, due to its large antimicrobial specter (anaerobic cocci and bacilli), as well as its antiparasitic actions, being the drug chosen for genital trichomoniasis in men, as well as in women. However, metronidazole is not a nontoxic drug [1]. For this reason, in the following data, I will present a series of data on metronidazole toxicity, especially during its use in pregnant woman. There is a correlation between dose, duration of treatment and the moment of clinical severe manifestations associated to toxicity [2]. In dog, the dose is 60 mg/kg body weight and causes neurotoxicity after use between 3 to 14 days. The 250 mg/kg body weight dose causes signs of acute toxicity. In cats, acute toxicity is manifested after daily use, during 9 weeks or 58 mg/kg body weight.

1. Fertility and early infant development

Metronidazole and its derivatives have an action against protozoa, as well as bacterial microorganisms. Metronidazole toxicity on reproduction was studied in detail in the study: "Metronidazole effects on spermatogenesis, plasma gonadotrophin and testosterone in rats" by Davood Sohrabi, Mohsen Alipur and Ali Awsat Mellati [3]. For this study were used 18 Wistar rats on 70-90 days of gestation which were divided into three groups. Group I was the control group which was allowed only water; the animals in Groups II and III received metronidazole, the dose containing 200 to 400 mg/kg/day, for 60 days. The spermatogenesis quantitative analysis was made by assessing the number of each type of germinal cell in maturation phase into seminiferous tubules; for example, spermatogonia type A, spermatocytes type I and II and spermatids.

Radio immunological methods were used in order to determine pituitary gonadotrophins (FSH and LH) and testosterone. In groups II and III could be observed a significant decrease of these tests: decreasing the weight of genital glands, plasma concentration of FSH and LH, testosterone and a big degeneration of all germinal cells. The above mentioned data show that metronidazole has suppressive action on spermatogenesis and sexual hormones in rats.

2. Embryo fetal development

Metronidazole crosses the placenta and enters rapidly the fetal circulation. Appropriate and controlled laboratory studies on human were not made. Laboratory

studies on rats, which received doses 5 times bigger than the human, showed no fact that metronidazole causes insufficient fertility or development disorder. When administrated intraperitoneally to pregnant rat female, in a dose appropriate to human, metronidazole demonstrated that can cause fetotoxicity. No fetotoxicity was observed when metronidazole was administrated orally to pregnant rats. However, the use of metronidazole in trichomoniasis treatment is not recommended during the first trimester of pregnancy [4]. If metronidazole is used during the second and third trimesters, is recommended limited use in the patients whose symptoms are not controlled by local treatments. Laboratory studies on rats that received doses 5 times bigger than the ones administrated to human, showed no fact that metronidazole causes insufficient fertility or birth defects in fetus. When administrated intraperitoneally to pregnant rat female, in a dose appropriate to human, metronidazole demonstrated that can cause fetotoxicity. No fetotoxicity was observed when metronidazole was administrated orally to pregnant rats.

Metronidazole and pregnancy

A high risk of obstetric complications (including intra-amniotic infections, premature and early membrane rupture, preterm birth) and newborns with tiny weight in birth is associated to the presence of bacterial vaginosis, in pregnant women. Microorganisms found in high concentrations in women genital flora with bacterial vaginosis are frequently found in the patients diagnosed with postpartum or post caesarean endometriosis [5]. Random studies evidence show that the treatment for bacterial vaginosis reduces the rate of preterm birth, in women with high risk of complications during pregnancy.

3. Prenatal and postnatal development, including maternal function

Metronidazole is delivered into mother's milk, the concentrations being similar to the ones in mother's plasma. It is not recommended to use it during breastfeeding, as long as some studies on rats and mice demonstrated that metronidazole is carcinogenetic and can cause side effects in infants. During metronidazole treatment, mother's milk should be squeezed and thrown away. Breastfeeding should be continued 24-48 hours after finishing the treatment [6].

4. Studies where the descendents (young animals) are treated and/or evaluated subsequently

Metronidazole crosses the fetal placental barrier and enters the fetal circulation rapidly. No fetotoxicity was observed when metronidazole was administrated orally to mice. Due to the fact that studies on reproduction are not predictive towards the human answer, metronidazole

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should be used in human only if necessary [7].

5. Toxicity after repeated doses

Cosar and Julou (quoted by Ciuca, in his work, *Vulvovaginitis, 1986, Bucharest*), administered 0.10g/mg/kg metronidazole for 40-60 days to rats (male and female), starting 10 days before breeding. Studies on 14 animals showed no fecundity mutation, gestation duration, number of newborns, neither the mortality during the first weeks of life compared to 12 untreated witnesses. No malformation was observed. Daily treatment with very high doses of metronidazole in hamsters during whole life, showed no actions. No mutation in weight, neither the hematological, biological and histological examinations was observed in dogs that received at the same time 25.50 and 100 mg/day metronidazole per bone (Cosar and Julou).

Most authors consider that the treatment should be postponed until the second half of pregnancy in pregnant women, though the literature data show no malformations published, in human, after using the drug.

6. Genotoxicity

The study published in 2001 by PanGeo Quebec Pharma Inc. Montreal, Quebec, H2P 2R9, Canada, after long term administration of metronidazole, showed increased chromosome mutation in peripheral lymphocyte's blood, in patients diagnosed with Crohn disease, treated with 200-1200 mg of metronidazole for 1-2 months. However, another study on patients with Crohn disease, treated with metronidazole for 8 months highlighted no chromosome mutation in leucocytes in the peripheral blood.

Anti trichomonas nitroimidazoles have mutagenic action on microorganisms that possess nitroreductases. For example, in *Klebsiella pneumoniae*, raised in an environment with metronidazole, the number of mutations increased 3-7 times towards spontaneous mutation rate. Transposing these data to human is controversial. Existing evidence show that metronidazole presents mutagenic activity in vitro on study bacterial systems. In addition, related to dose, the frequency of micronucleus in mice increases after intraperitoneally injections.

7. Carcinogenicity. Long term, short and medium studies

Such studies are illustrated in the same report accomplished in 2001, by PanGeo Quebec Pharma Inc. Montreal, Quebec, H2P 2R9, Canada, after long cutaneous administration of metronidazole. Hereby, it is considered that metronidazole presents carcinogenetic action to a number of species after orally and chronic administration in mice, rats but not in hamsters.

In few long term studies, mice received orally doses of 225 mg/m²/day or stronger (almost 37 times more than the dose for human in mg/m²) that ended with lung and lymphoma tumors. Other long term studies [8] in rats, also

showed a significant increase of breast and hepatic tumors, bigger than 885 mg/m²/day (144 times more than human dose). Olson E.J et al. made a study in which metronidazole was suspected of neurotoxicity in cat [9].

8. Other studies

Metronidazole is an antibiotic also used in veterinary medicine, to treat various infections: anaerobic bacterial infections, protozoa infections, gastritis associated with helicobacter, hepatic encephalopathy. In addition, towards the anti protozoa and bacterial proprieties, metronidazole is considered to have immunomodulatory effects, being frequently used in treating intestine inflammatory diseases in dogs, as well as in cats. The medicine is lipophilic and has a large tissue distribution with bioavailability that varies between 50 and 100%. Metronidazole is mainly metabolized in liver and it was proved that crosses rapidly the hemato-encephalic barrier.

Another study uses ¹⁴C metronidazole for detecting the drug's accumulation unconverted in cerebellum and hippocampus in mice, after intravenous administration. Side effects on central nervous system were observed in human, as well as in various animal species, including rats, dogs and cats, being associated with metronidazole toxicity [10].

Often, in case of human, was reported peripheral neuropathy, due to metronidazole toxicity; sickness, nausea, tremor, ataxia and convulsions were also reported. In cats and dogs, brain dysfunctions manifested by ataxia, nystagmus, head inclination, tremor and convulsions, were frequently reported in case of metronidazole toxicity.

In conclusion, metronidazole is a drug with acceptable toxicity on reproduction; new studies are necessary in order to determine and deepen its implications to embryo-fetal development. As a rule, it is not administered during the first pregnancy trimester when the embryogenesis process takes place, neither the women who breastfeed because it gets through milk, to fetus. When administered during the third trimester to pregnant women with bacterial vaginosis, it prevents various pregnancy complications: preterm birth, premature and early membrane rupture and intra-amniotic infection.

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