

## Embryo toxicity of pefloxacin in mice

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### Abstract

Fluoroquinolones are extremely useful agents and an important therapeutic advance. Each fluoroquinolones tends produce characteristic adverse effects. Different studies showed that there was evidence about adverse effects of some fluoroquinolones as levofloxacin, alatrofloxacin, trovafloxacin and moxifloxacin on the pregnant experimental lab. Animals when they were administered higher than the maximum recommended human doses , the current study was conducted to highlight the effects of different dosages of pefloxacin on the pregnant mice .The study revealed that the litter size and weight of birth were unaffected at the recommended oral human doses. Also reflects that there were little effects on body weight gain of dams when the dose exceeds the maximum recommended human dosage. No teratogenic effects were observed even at high oral doses. This project needs further investigation using different lab. Animals with large sample size.

### تأثير العلاج بالبفلوكساسين على الفئران الحوامل

رفاه هادي لطيف

#### المستخلص:

يعتبر الفلوروكينولون من الادويه المفيده وله فوائد علاجيه متقدمه . لكل مجموعه من الفلوروكينولون مردودات معاكسه. هنالك تقارير عديده اشارت بوجود اثار جانبيه لبعض من هذه المجموعات مثل ليفوفلوكساسين , الاترافلوكساسين , التروفلوكساسين والموكسوفلوكساسين على الحيوانات المختبريه الحوامل وذلك عند استخدام جرعات فمويه اعلى من تلك التي يوصى بها للانسان. اجريت الدراسه الحاليه لبيان تأثير الجرعات المختلفه من البفلوكساسين على الفئران الحوامل . بينت الدراسه بان حجم المواليد ووزن المواليد لم يتأثر عند اعطاء الدواء با لجرع التي يوصى بها عن طريق الفم للانسان. كذلك بينت الدراسه ان هنالك تأثيرات طفيفه قد طرأت بزيادة وزن الاناث الحوامل عند اعطاء جرعات أكبر من الجرعه التي أوصي بها للانسان. ولم تشاهد أي علامات للتشوهات الخلقية نتيجة اعطاء الجرعات العاليه من العلاج. توصي با جراء تجارب على حيوانات مختبريه مختلفه وبحجم عينه أكبر.

## **Introduction:**

Fluoroquinolones are considered to be safe and well tolerated. They are generally highly comparable with other classes of antibiotics in terms of overall frequency and severity of adverse effects. Each fluoroquinolone tends to produce characteristic adverse effects. The teratogenic effects of the fluoroquinolones are highly variable in animal models ;harmful fetal effects are appear specific to dose intensity, animal species, and sometimes route of administration.(1) No teratogenic embryo toxic effects were associated with high dosages of ciprofloxacin in rats, mice, and rabbits. Levofloxacin dosages equivalent to 81 times the maximum recommended human dosage (based on body weight) caused decreased fetal body weight and increased fetal mortality in rats, but no teratogenic effects were seen when similar dosages administered to rabbits.(2) Increased fetal skeletal variation occurred with both oral trovafloxacin and intravenous alatrofloxacin when administered to rats at approximately 4-15 times the highest recommended human dosage(based on body weight);increased prenatal mortality and decreased body weights also were observed with oral administer of these very high dosages. Fetal skeletal variations were not seen when oral trovafloxacin was administered to rabbits at approximately 9 times the highest recommended human dosage(based on body weight).(3,4)Gatifloxacin produced skeletal malformations, increased late post implantation fetal loss, and increased neonatal and prenatal mortality when administered to rats in dosages approximately equal to the highest recommended human oral dose . (5) Administration of moxifloxacin to pregnant rabbit in dosages approximately equal to maximum

recommended doses for humans resulted in decreased fetal body weight and delayed skeletal calcification; fetal birth weights were reduce when moxifloxacin was administered to Cynomolgus monkeys at dosages approximately 2.5 times higher than the maximum dosages recommended in humans (6,7).Fluoroquinolones caused fetal harm in animal studies, including decreased body weights and malformed bones as well as an increased risk of death (8). Because of the potential for serious adverse effects to the fetus, the current study was conducted to highlight the effects of different dosages of pefloxacin on the pregnant mice.

## **Materials and methods:**

Mature, virgin, female Swiss Webster Albino mice used in this study bred in the animal facilities of AL-Razi Center for research and diagnostics production. Their body weight ranged from 20-25gm.Maintained under environmental conditions controlled with respect to room temperature (20-25 C) .Animals were housed two per cage. Vaginal smears (Plate-1) were recorded daily and each mouse completed at least two consecutive estrous cycles before use. Females were placed with fertile males on the evening of proestrus; the presence of sperm in the vagina during estrus denoted Day 0 postcoitum. Animals were randomly assigned to control and experimental groups. Controls received saline. Each group of test animals and each group of controls consisted of at least 4mice chosen by random selection. The groups of presumed pregnant mice were given gavages doses of 200,250,500 or 750 mg/kg bw/day of pefloxacin on gestation days 6 to 13.Dams were killed on gestation day 18.All litters examined as soon as possible after

delivery. The following parameters were recorded: litter size, number of stillborn, and number of live births, and pup weights were recorded at birth, four days after birth, and at weaning. In reporting the results, the following reproductive indices were used; "gestation index" (the percentage of pregnancies resulting in the birth of live litters); "viability index" (the percentage of animal born that survive four days or longer). Statistical analysis of data sample means of pefloxacin treated groups were compared for significance of difference by the student's t test (two tailed). In this study p values of  $<0.05$  were regarded as statistically significant.

## **Results**

The average number of litter and litter weights (table -1) reflect both male and female weights because offspring not sexed until 10 days of age. The litter size and weight at birth were unaffected at oral doses of (200,250,500 mg/kg b .w.). The fetal weight was lowered at 750 mg/kg b. w. /day, and single litter died. No teratogenic effects observed at this dose. Percent maternal weight gain from day 0 through day 18 of pregnancy was shown in (table-2). Groups treated with pefloxacin doses (200,250,500 mg/kg b. w.) had no effects on body weight gain of dam's .Embryo mortality and number of live fetuses was similar between groups. There were little effects on body weights gain of dams at 750 mg/kg b. w. Also there were effects on embryo mortality at the above dose of oral pefloxacin. No teratogenic effects observed at this dose.

**Plate-1: Vaginal smear showing luminal epithelium in estrus stage (stained by 1% methylene blue).**

**Table-1: The effects of pefloxacin during different schedules of administration on the embryo -development.**

Treatment condition	No of litters M +SE	Fetal length M +SE	Fetal body weight M +SE
Pefloxacin (200,250,500 mg/kg b.w.)	20.5+0.35	19.2+1.24	6.1 +0.4
Pefloxacin (750 mg/kg b.w.)	12.9+0.52	18.97+1.45	6.0+0.4
Control	10.8+0.02	19.3+1.13	6.7+0.5

- Sacrificed day=18 days after fertilization.

**Table-2: The effects of pefloxacin administration on embryo-mortality and maternal weight gain.**

Treatment condition	Litter size Pups/litters M+SE	Mortality %	Maternal weight Gain %
Pefloxacin (200,250,500 mg/kg b.w.)	10.4+2.4	9.6	76.37
Pefloxacin (750 mg/kg b.w.)	10.2+1.4	4.5	67.74
Control	8.9+0.5	10.7	75.56

\* Statistical significant (p<0.05)

## **Discussion**

Ideally every successful union of a male and female gamete would result in the birth of a normal healthy offspring who would live to maturity and in due course reproduce and give birth to further offspring. In reality, in addition to the loss of gametes prior to fertilization there is a surprising high rate of post fertilization and implantation mortality in all mammals in which reproduction has been adequately studied. (9) All pregnancy losses and birth defects are the result either of a genetic abnormality in the fetus or an adverse environment. The latter can be the result of suboptimal conditions for fetal growth and development as a consequence of inadequacy or abnormality of the maternal reproductive system, or the result of exposure of the mother and fetus to an environmental insult; such as an infectious agent, harmful drug...etc. (10)

Fluoroquinolones are extremely useful agents and an important therapeutic advance. They are relatively nontoxic, well tolerated and broad-spectrum agents. Their excellent oral bioavailability permits their use for treatment of a variety of serious bacterial infections. Serum half-lives rang from 3 hour (norfloxacin and ciprofloxacin) up to 10 hours (pefloxacin and fleroxacin). Serum concentrations of intravenously administered drug are similar to those of orally administered drug. (11) Mice have widely been employed in teratology studies because of their fertility rate, general suitability and high sensitivity to teratogens. (12) The pregnant mice receiving pefloxacin during the period of organogenesis or during the whole period of gestation did not show a significant differences in number of litters, fetal length and fetal body weight when they were administered the recommended oral

doses (200, 250, 500 mg/kg b.w.). Several investigators mentioned; that the teratogenic effects of the fluoroquinolones are highly variable in animal models; harmful fetal effects are appear specific to dose intensity, animal species, and sometimes route of administration. (2, 3, 5, 7) The results revealed little effects on number of litters, fetal length and fetal weight when they were administered pefloxacin over the recommended human dosage (750 mg/kg b. w.). Adam et al (13) mentioned that there were no teratogenic embryo toxic effects associated with high dosages of ciprofloxacin in rats, mice and rabbits. The effects of pefloxacin on mortality rate and maternal weight gain showed that there were no effects at doses 200, 250, 500 mg/kg b. w. on the other hand the dose 750 mg/kg b.w. gives little effects on mortality rate and maternal weight gain. The levofloxacin dosages equivalent to 81 times the maximum recommended dosage (based on body weight) caused decrease fetal body weight and increased fetal mortality in rats. (14) Also both oral trovafloxacin and alatrofloxacin when administered to rats at approximately 4-15 times highest recommended human dosage (based on body weight); increased perinatal mortality and decreased body weight (3,4). In the current study no teratogenic effects were observed at different doses and these results are in agreement with the results obtained when high doses of levofloxacin (81 times the recommended dosage) were administered to rabbits (15). The current investigation, support the hypothesis that high doses of pefloxacin may influence the fetal development and pregnancy in mice. Because the number of mice used in this study are small, the finding should be interpreted with caution and need to

be confirms with larger numbers of subjects.

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