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Testicular damage in rats after co-administration of anti-tuberculosis drugs in different combinations

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Key words: antituberculosis drugs, fertility, testes, rat

In 2004, the WHO Assembly announced protection of reproductive health as a world-wide priority and approved the first international strategy on this problem [1]. On the assumption of the potential risks for reproductive health, special concern was given to the ability of a great number of xenobiotics (including medicines) to affect the function of reproductive system [2].

The epidemiological situation of tuberculosis in Central and Eastern Europe keeps worsening [3]. In general, all patients from countries with a known high incidence of resistant *M. tuberculosis* strains, all patients who had been treated previously, and all patients with life-threatening tuberculosis received as initial anti-tuberculosis therapy a combination of isoniazid, rifampin and pyrazinamide, together with at least one additional drug (ethambutol and/or streptomycin) [4]. The antifertility effect of antituberculosis drugs in combination, which contains ethambutol, in male rats has been reported earlier [5]. We suppose that for young men who have tuberculosis infection, the success of treatment with regimens that are toxic to testicular function could made reproductive disorders an important problem. After recovery, the quality of life, which often includes the ability to have a normal child, could become a major issue. Analysis of potential effects of different antituberculosis drugs combinations on the male gonads is urgently required for the development of more effective and safe regimens for the prevention and treatment of tuberculosis infection.

The aim of the study was comparative investigation of the two anti-tuberculosis drugs combinations, which contained ethambutol or streptomycin, effects on male rats' fertility and spermatogenesis parameters, as well as antenatal development of their offspring.

Materials and methods. Substances of ethambutol, isoniazid, pyrazinamide and rifampicin were supplied by the SIC «Borzhagovsky Chemical-Pharmaceutical Plant» CJSC, Ukraine. Streptomycin (powder for injection) was supplied by «Arterium», Ukraine.

Wistar albino male and female rats, body weight (b. w.) 150–170 g were purchased from Biomodel Service (Kyiv, Ukraine). The animals were kept at standard conditions of nutrition, water and light regimens. The study was carried out according to the national and international guidelines and the law on animal protection. All animal studies were performed in accordance with the recommendations of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes and approved by the Institutional Animal Care and Use Committee.

The male rats were divided into 3 groups: 1-control (n = 22); 2 – 1st combination (ethambutol, rifampicin, isoniazid, and pyrazinamide) administration (n = 22); 3 – 2nd combination (streptomycin, rifampicin, isoniazid, and pyrazinamide) administration (n = 16). Antituberculosis drugs were given in DOTS (directly observed treatment, short-course) regimen at maximal doses used in clinic [6]: ethambutol – 155 mg/kg b. w./day or streptomycin 14 mg/kg b. w./day, rifampicin – 74,4 mg/kg b. w./day, isoniazid – 62 mg/kg b. w./day, and pyrazinamide – 217 mg/kg b. w./day for 60 days (duration of spermatogene-

sis process and time of germ cell maturation in epididymis). Streptomycin was administered intramuscularly in 0,5 % novocaine solution. The other substances were suspended in 1% starch gel and administered intragastrically by gavage, and in this case the coefficient for conversion of human doses to animal equivalent doses based on body surface area was taken into account [7]. The control group received only starch gel in corresponding volumes (5 ml/kg b. w.). After 46 days of repeated administrations, the males from all groups were mated with intact females at the ratio 1 male: 2 females during 14 days (approximately 2–3 oestrous cycles). During this period the administration of antituberculosis drugs to male rats was continued. Effects of antituberculosis drugs on fertilizing capacity were determined by the index:

$$\frac{\text{number of pregnant females}}{\text{number of females mated with males}} \cdot 100\ \%$$

The females were sacrificed under mild ether anesthesia via cervical dislocation on day 20 of pregnancy. The numbers of corpora lutea in ovaries, of implantation sites and of live and dead fetuses in each uterine horn were counted after laparotomy of pregnant females. Indices of embryonic death at pre- and postimplantation periods of development were calculated according to standard procedures [8].

Males were sacrificed under mild diethyl ether anesthesia by decapitation after 60 days (duration of spermatogenesis and time of germ cell maturation in epididymis) of experiment.

In all cases the right testicle was used for the evaluation of morphologic and morphometric parameters and spermatogenesis indices. It was fixed in a 10 % solution of neutral formalin, dehydrated in ethanol solutions, and embedded in paraffin. Histologic sections (6 μm) were stained by haematoxylin and eosin. Histological examination was performed under a light microscope (100× and 400×).

The determination of the spermatogenic index in testicles was carried out according to four points system. It was based on the estimation of number of cell layers, types of cells, and the presence of late spermatids in the seminiferous tubules. The criteria were as follows: 1 – only spermatogonia present; 2 – spermatogonia and spermatocytes present; 3 – spermatogonia, spermatocytes and round (early) spermatids present with < 5 late spermatids per tubule; 4 – spermatogonia, spermatocytes, and round spermatids present with up to 25 late spermatids per tubule [21]. Simultaneously qualitative changes of spermatogenic epithelium: cells exfoliation (shedding of epithelial elements), desquamation epithelium (detachment) from tubule basal membrane, and presence of cell-free regions («windows») were taken into account.

The contents of reduced glutathione and proteins SH-groups in testes homogenates were determined with Ellman's reagent [9], lipid peroxidation was investigated as the rate of ascorbate-induced thio-barbituric acid reactive substances (TBARS) formation [10], protein contents by Lowry's method [11].

The obtained data were calculated by one-way analysis of variance (ANOVA) and compared using the Tukey test. Differences were considered statistically significant at $p < 0,05$.

Results and discussions. Almost regardless of the cellular target of toxicity within reproductive system, the most common morphological consequence of injury is a disturbance in spermatogenesis. In our experiment administration of both antituberculosis drugs combination in rats was accompanied by a development of destructive changes in spermatogenic epithelium. According to the data of Table 1, the spermatogenic indexes in the both experimental groups were decreased in comparison with control (simultaneously with mitotic activity and number of spermatogonia). At the same time number of cells at XII stage of spermatogenesis (characterizing primary spermatocytes meiotic division processes), demonstrated only tendency to lowering in 1st combination-treated group and statistically significant decrease in 2nd combination-treated group.

Beside the above mentioned quantitative changes, qualitative changes of sper-

Table 1

Spermatogenic epithelium indices after different anti-tuberculosis drugs combinations administration (M ± S. E. M.)

Parameters	Group of males		
	control	1st combination	2nd combination
Spermatogenic index (stages of spermatogenesis total/number of examined tubules)	3,615 ± 0,011	3,535 ± 0,014*	3,533 ± 0,011*
Number of spermatogonia (per tubular cross section)	69,393 ± 0,742	59,573 ± 0,861*	54,56 ± 2,398*
Cells at XII stage of spermatogenesis, %	3,563 ± 0,365	2,412 ± 0,508	2,455 ± 0,366*
Desquamated epithelium, %	1,063 ± 0,249	2,882 ± 0,283*	1,818 ± 0,444
Exfoliation of epithelium, %	0,313 ± 0,120	1,882 ± 0,363*	1,545 ± 0,390*
«Windows», %	0,500 ± 0,158	1,765 ± 0,265*	2,270 ± 0,070

**P < 0,05 in comparison with control.*

matogenic epithelium were also presented in the seminiferous tubules of both groups of rats. Increased level (2,7 times) of epithelial cells desquamation was observed after 1st combination administration (table 1). Great degenerative changes in testes such as epithelium exfoliation into the lumen of seminiferous tubules and presence of cell-free regions («windows») were also presented in great quantity in the experimental groups (table 1).

Thus, our results indicate great spermatogenesis impairment, which could cause lowering of sperm quantitative and qualitative parameters [12].

Parameters, which reflect the energy potential of sperm (time of motility) and it resilience to changes of the environment (osmotic resistance) are shown in the Figure 1. It was indicated that total time of sperm motility after administration of 1st and 2nd combination reduced 77 and 34 % respectively as compared with control. The viability of spermatozoids in KCl solutions of rising concentrations, decreased 65 % in 1st combination-treated rats, while in 2nd combination-treated animals this parameter revealed only clear tendency to decrease.

It is known that antituberculosis drugs administration produces the overproduction of reactive oxygen species (ROS) and activation of lipid peroxidation [13]. In our experiments we demonstrated an increase of TBARS formation in rat testis (15 %) and epididymal suspension of spermatozoids (38 %) in the group with 1st combination administration in comparison with the control group (table 2).

Following 2nd combination treatment only intensification of lipid peroxidation in testes was detected (table 2).

Administration of 1st combination also resulted in some decrease of reduced glutathione testicular pool (23 %) due to peroxidation processes activation (fig. 2).

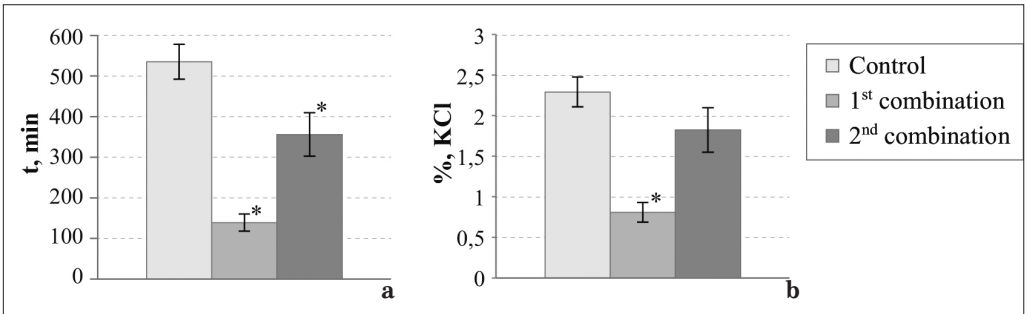

Fig. 1. Qualitative parameters of rats' sperm after different anti-tuberculosis drugs combinations administration: a) time of motility; b) osmotic resistance

**P < 0,05 in comparison with control*

Table 2

The rate of ascorbate-induced formation of TBARS in male rats testes and epididymal suspension of spermatozoids, nmoles · min^{-1} · mg of protein^{-1}

Group of males	Tissues	
	testes	epididymal suspension of spermatozoids
Control	0,250 ± 0,020	0,100 ± 0,006
1st combination	0,317 ± 0,010*	0,162 ± 0,006*
2nd combination	0,302 ± 0,031*	0,104 ± 0,006

**P < 0,05 in comparison with control.*

It should be noted that ROS play a central role for sperm physiology, such as sperm maturation and capacity [14]. On the other hand, abnormal ROS production is associated with defective sperm function. The delicate balance between ROS production and recycling is essential for spermatogenesis. Excessive generation of seminal ROS can cause male infertility [14]. In our experiment the increase of testicular and epididymal lipid peroxidation may be a result of *in situ* formation of ROS due to antituberculous agents metabolism. It is important to emphasize the presence of high-inducible CYP2E1 in male gonads [15]. At least isoniazid and rifampicin may act as CYP2E1 inducers [16]. Previously we have reported the possibility of 1st combination to increase CYP2E1 mRNA content in testes of rats [17]. CYP2E1 generates ROS, such as superoxide radicals, which in turn could rapidly react with organic molecules generating secondary free radicals.

Less pronounced intensity of peroxidation processes in the testes of 2nd combination-treated rats at list partially could be associated with the inhibition of CYP2E1 protein synthesis by streptomycin. The *in vitro* activities of many aminoglycoside antibiotics in eucaryotic model systems derived from yeasts and mammalian cells were studied. The ability of aminoglycoside antibiotics to inhibit protein synthesis via inhibition the

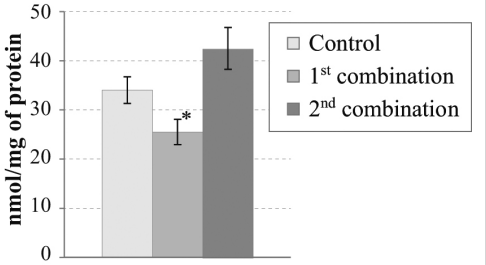

Fig. 2. Content of reduced gluthatione in rats' testes after different anti-tuberculosis drugs combinations administration

**P < 0,05 in comparison with control*

polypeptide chain elongation phase was demonstrated [18].

Our data on sperm quality were in good accordance with results concerning fertilizing capacity of experimental animals (table 3). The smaller number of pregnant females in the experimental groups could be evidence of decreased male fertility after antituberculosis drugs administration (table 3). But it is obvious, that the fertility index in 2nd combination – treated group decreased insignificantly, while 1st combination caused fatal decrease of this parameter.

In general it was difficult to perform adequate statistic analysis of fetal antenatal development indices in 1st combination-treated group due to very low number of pregnant females, but the negative tendencies appeared to be evident (table 4). The number of living fetuses

Table 3

Male rats' fertility index after different anti-tuberculosis drugs combinations administration

Group of males	Number of mated females	Number of pregnant females	Fertility index, %
Control	44	38	86,36
1st combination	44	4	9,09
2nd combination	32	25	78,12

Table 4

Embryo- and fetogenesis parameters on day 20th of gestation of intact female rats sired by experimental male rats

Parameters	Group of males		
	Control	1st combination	2nd combination
Number of pregnant females	38	4	25
Total number of corpora lutea	403	50	259
Number of corpora lutea per one female, M ± S. E. M.	10,60 ± 0,28	12,5 ± 3,20	10,36 ± 0,38
Total number of implantation sites	380	30	228
Number of implantation sites per one female, M ± S. E. M.	10,0 ± 0,31	7,50 ± 3,43	9,12 ± 0,64
Preimplantational loss, abs/%	23/5,7	18/40,0	30/12,0
Preimplantational loss per one female, M ± S. E. M.	0,61 ± 0,21	4,50 ± 1,94	1,20 ± 0,41
Postimplantational loss, abs/%	10/2,63	19/63,33	18/12,0
Postimplantational loss per one female, M ± S. E. M.	0,26 ± 0,08	4,75 ± 3,81	0,72 ± 0,21*
Total number of living fetuses, abs/%	371	11	212
Number of living fetuses per one female, M ± S. E. M.	9,76 ± 0,32	2,75 ± 2,43	8,48 ± 0,66
Total mortality, %	7,94	78,0	18,15

per one female in this group was lowered, while 2nd combination didn't show negative effect (table 4).

The comparison of embriolethality levels in experimental and control groups at different terms of embryonal development demonstrated great negative effects of antituberculosis drugs in 1st combination. In this experimental group the levels of paternal mediated pre- and postimplantational lethality increased respectively 7 and 24 times as compared with control (table 4). The 2nd combination revealed more weak effect: pre- and postimplantational lethality levels were increased only 2 and 4 times (table 4).

In our experiments postimplantational lethality may have been caused by genotoxic action of substances [12].

This assumption could be confirmed by the data of experiments on mice demonstrating weak genotoxicity of pyrazinamide at doses of 125, 250 and 500 mg/kg b. w. [19]. Moreover, in vitro experiments showed that one isoniazid metabolite – mono acethylhydrazine – increased the number of *Salmonella typhimurium* TA100 and TA1535 revertant mutations and the number of micronuclei in polychromatophylic erythrocytes, which could be evidence of its mutagenic action [20]. The weak mutagenic effect of isoniazid and its ability to cause liver DNA injury was also demonstrated experimentally [21, 22]. Rifampicin genotoxicity investigation showed increased frequency of sister chromatids exchanges in bone marrow cells at doses of 160, 240 and 310 mg/kg b. w. and a number of chromosomal aberrations of spermatocytes at the dose of 80 mg/kg b. w. [23]. The most recent data suggest that isoniazid and rifampicin gave positive responses in both genotoxicity and carcinogenicity assays; pyrazinamide tested positive in one genotoxicity assays, but was noncarcinogenic; ethambutol gave positive response in micronucleus test with Swiss mice *in vivo* and streptomycin – positive response in Ames test [24].

As to preimplantation lethality, it must be stressed that mutagenic, as well as nonmutagenic effects could be involved. Particularly, abovementioned data of other authors allow us to assume the mutagenic events in germ cells, while results of our present study evidenced about spermatotoxic action (table 1) of both anti-tuberculosis drugs combinations.

The great part of paternal-mediated negative effects could be attributed to

ethambutol, which significant male-mediated developmental toxicity was demonstrated previously [25]. Presented results clearly indicated that, ethambutol replacement by streptomycin in certain manner alleviated such abnormalities.

Conclusions. In experiments with male rats we have shown a significant gonadal toxicity of co-administered rifampicin, isoniazid, pyrazinamide and ethambutol therapeutic doses. Ethambutol replacement by streptomycin allowed us in certain grade to avoid toxic action of anti-tuberculosis drugs on testes and alleviate some paternal-mediated negative effects in offspring.

It is clear that direct extrapolation of obtained results to humans cannot be done due to interspecies differences. Nevetherless, taking into account that compared to rats used routinely in toxicity testing, fertility of the human male is particularly susceptible to agents that reduce the number or quality of sperm produced [12], we consider to be reasonable supervise the sperm quality in patients treating with fixed-dose anti-tuberculosis drugs combinations. In our opinion a critical examination of the evidence, both epidemiological and laboratory animals' data, for effects of antituberculous drugs on human fertility should be done in order to reach a general conclusion.

The data obtained allow us to add new evidence to the theoretical base for understanding of male infertility mechanisms and paternal-mediated negative impacts in posterity.

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Г. М. Шаяхметова

Ушкодження сім'яників щурів після введення протитуберкульозних лікарських засобів у різних комбінаціях

Мета роботи – порівняльне дослідження фертильності, показників сперматогенезу та антенатального розвитку потомства щурів-самців за умов сумісного введення протитуберкульозних засобів у двох комбінаціях, які містили ізоніазид, піразинамід, рифампіцин та етамбутол або стрептоміцин (комбінація 1 та 2 відповідно).

Ступінь деструктивних змін у сперматогенному епітелії за введення протитуберкульозних препаратів в обох комбінаціях був майже на одному рівні, але час рухливості сперматозоїдів після введення комбінацій 1 та 2 знижувався порівняно з контролем на 77 та 34 % відповідно. Осмотична резистентність сперматозоїдів за введення комбінації 1 зменшувалась на 65 %, тоді як комбінація 2 не справляла значного впливу. При застосуванні комбінації 1 підвищувався рівень перекисного окиснення ліпідів (ПОЛ) у сім'яниках (15 %) та епідидимісах (38 %), тоді як після введення комбінації 2 було зафіксовано інтенсифікацію ПОЛ лише в сім'яниках. Індекс запліднювальної здатності щурів-самців після введення комбінацій 1 та 2 складав відповідно 9,09 та 78,12 %. У групі самиць, запліднених самцями, що отримували комбінацію 1, рівні до- та післяімплантаційної смертності зростали відповідно у 7 і 24 рази порівняно з контролем, а комбінацію 2 – лише в 2 і 4 рази.

Таким чином, заміна етамбутолу на стрептоміцин певною мірою знижувала токсичну дію протитуберкульозних препаратів на гонади та опосередковані батьком негативні ефекти на потомство. Результати дослідження розширюють теоретичну базу стосовно розуміння механізмів чоловічого безпліддя та розвитку, залежних від батька порушень у нащадків.

Ключові слова: протитуберкульозні засоби, фертильність, сім'яники, щури

А. М. Шаяхметова

Повреждение семенников крыс после введения противотуберкулезных лекарственных средств в различных комбинациях

Цель работы – сравнительное исследование фертильности, показателей сперматогенеза и антенатального развития потомства крыс-самцов при совместном введении противотуберкулезных средств в двух комбинациях, содержащих изониазид, пиразинамид, рифампицин и этамбутол или стрептомицин (комбинация 1 и 2 соответственно).

Степень деструктивных изменений в сперматогенном эпителии при введении обеих комбинаций противотуберкулезных препаратов была почти на одном уровне, но время подвижности сперматозоидов после введения комбинаций 1 и 2 снижалось по сравнению с контролем на 77 и 34 % соответственно. Осмотическая резистентность сперматозоидов при введении комбинации 1 снижалась на 65 %, тогда как комбинация 2 не оказывала значительного влияния. При применении комбинации 1 повышался уровень перекисного окисления липидов (ПОЛ) в семенниках (15 %) и эпидидимисах (38 %), тогда как после введения комбинации 2 была зафиксирована интенсификация ПОЛ только в семенниках. Индекс оплодотворяющей способности крыс-самцов после введения комбинаций 1 и 2 составил соответственно 9,09 и 78,12 %. В группе самок, оплодотворенных самцами, получавшими комбинацию 1, уровни до- и постимплантационной смертности возрастали соответственно в 7 и 24 раза по сравнению с контролем, а комбинацию 2 – только в 2 и 4 раза.

Таким образом, замена этамбутола на стрептомицин в определенной степени снижала токсическое действие противотуберкулезных препаратов на гонады и опосредованные отцом отрицательные эффекты на потомство. Результаты исследования расширяют теоретическую базу относительно понимания механизмов мужского бесплодия и развития, зависимых от отца нарушений у потомков.

Ключевые слова: противотуберкулезные средства, фертильность, семенники, крысы

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