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EVALUATION OF THE EFFECT OF TYLOSIN (MACROLIDE ANTIBIOTICS) ON MURINE TOXOPLASMOSIS

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ABSTRACT: Toxoplasmosis is a parasitic disease with global prevalence that is caused by a unicellular organism called *Toxoplasma gondii*. Given the high prevalence of the disease in the country, particularly in pregnant women, and severe complications of the disease for the fetus, congenital type, the disease consequences for patients taking medications that suppress the immune system as well as side effects caused by common treatment methods, discovery of new drugs with minimal side effects seems to be necessary. In this study was an attempt to investigate the effect of tylosin on *toxoplasma in-vivo* environment. 200000 parasites (tachyzoite form) were subcutaneously injected to 60 Balb/C mice that were divided into 6 groups (each consisting of 10 samples). Tylosin with four different concentration levels (10-80 mg/kg) was intraperitoneally injected. One of the groups was tested without injection of medicine and another group was tested with sulfadiazine and the disease process was carefully investigated in these groups. Comparison of treatment groups with the control group and statistical analysis of data showed a significant difference in the results obtained from the use of tylosin in the groups and it was observed that the effect of tylosin on the *T. gondii* is dose dependent. Also any increase in the drug dose up to 80 mg/kg prolonged the survival time in the mice. The results showed that there was a significant difference between the drug dosage and the average survival time in the mice infected with *T. gondii*. Therefore, this drug has proved to be effective in treatment of infected mice.

INTRODUCTION: *T. gondii* is an intracellular parasitic organism with worldwide prevalence. Warm-blooded animals such as mammals and birds are known as intermediate hosts and the family of cats serves as the final hosts of this parasite [1]. The symptoms of this infection in people with normal immune system are usually mild and include fever, lymph node involvement, lethargy, and muscle pain.

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In its congenital form, the parasite may cause adverse reactions such as abortion, chorioretinitis, hydrocephaly, microcephaly and jaundice in newborns. Infection is more severe in AIDS patients and mostly leads to fatal encephalitis [2]. This parasite is life threatening in patients receiving drugs that suppress the immune system such as organ transplant recipients and patients with various cancers and autoimmune diseases.

One of the complications of the infection isocular involvement leading to blindness that can be caused by parasite transmission in congenital and acquired ways. In addition, some acquired and chronic side effects such as schizophrenia and epilepsy have also been reported for this infection. The damage caused by toxoplasmosis is very high

and annually it imposes high costs paid the Ministry of Health. Selective treatment is a combination of pyrimethamine and sulfadiazine. These compounds are inhibitors of enzymes involved in pyrimidine biosynthesis in *toxoplasma*.

Pyrimethamine is known as an anti-malaria agent that is used, alone or along with sulfadiazine or quinine, for treating *Plasmodium species* resistant to treatment. The drug is also used to prevent and treat toxoplasmosis. This drug actually inhibits the dihydrofolate reductase enzyme [3]. Therefore, it prevents the synthesis of tetrahydrofolic acid in the parasite and the host. Tetrahydrofolic acid is a vital material and shortage or lack of it eventually reduces the production of red blood cells in the host. Thus, the important complications of the drug include blood complications such as megaloblastic anemia, leukopenia and thrombocytopenia. Another important side effect of this drug includes arrhythmia, insomnia, seizures, depression and Steven-Johnson syndrome. Extensive studies have also been conducted on teratogenese and the adverse effects of this drug during pregnancy and women are suggested not to take the drug during pregnancy [4].

Sulfadiazine is an antibiotic of sulfonamide family that is used in adjunctive therapy for the treatment of malaria and toxoplasmosis disease. The drug's mechanism of action includes disorder in the synthesis of folic acid due to competition with PABA [5]. The complications of this drug include Steven-Johnson syndrome, thyroid dysfunction, aplastic anemia, granulocytopenia, hemolytic anemia, leukopenia, thrombocytopenia, hepatitis, jaundice and acute nephropathy.

Dangerous and potentially harmful side effects of this drug have provoked the therapist to closely monitor different factors, including kidney and liver function before and after prescribing sulfadiazine. Few studies have been conducted on the effects of drugs on the fetus. Considering the above-mentioned complications, this drug is assigned to class C in terms of use during pregnancy. According to the above-mentioned points, preparing a highly efficient drug with the least side effects seems to be reasonable. Macrolide antibiotics are one of the antibiotics used to treat infections with gram-positive bacteria, including *Staphylococcus aureus*, *Streptococcus pneumonia*, and *Streptococcus pyogenes*. Macrolide is formed of a lactone ring and has different chemical names depending on the chemical groups attached to the ring. These groups include erythromycin, azithromycin, clarithromycin and tylosin.

As to the mechanism of action, macrolides attach to the large ribosomal subunit near the peptidyl-transferase enzymes, to prevent the activity of this enzyme and bind amino acids, consequently leading to prevention of protein synthesis [6]. Macrolides are antibiotics with relatively broad effect spectrum that is used to treat infections caused by gram-positive bacteria, mycoplasma, some gram-negative and anaerobic bacteria. These antibiotics are available at bacteriostatic therapeutic concentration levels, but can have significant bactericidal effects against streptococcal infections. The bactericidal effect of these antibiotics is time-dependent and the antimicrobial effect of these drugs increases at high pH levels and declines at low pH levels. Therefore, they are of limited use in treatment of abscesses, infectious necrotic tissue, and acidic urine [7].

Tylozin is an antibiotic from the macrolide family that mainly affects gram-positive organisms and mycoplasma. The salt of the drug in combination with tartrate and phosphate can be used in the treatment of infectious diseases such as lung infection and gastrointestinal infections in animals such as cattle, sheep, pigs *etc* [8]. This drug is usually injected in 10 - 50 mg/kg dosages and in most cases, the maximum plasma concentration 1 to 2 h is reached after drug administration. The toxic dose of the drug in mice and dogs is 5000 mg/ kg and 800 mg/kg respectively and its toxicity symptoms include increased salivation and diarrhoea [9].

Considering such problems as high prevalence of toxoplasmosis in the country, rarity of drugs, dangerous side effects of drugs commonly used in the treatment of this disease and their severe side effects in immuno compromised patients, as well as the inhibitory effect of macrolide antibiotics on protein synthesis in the parasite and high efficacy of these drugs in controlling the disease in various studies, in the present study attempts were made to investigate the effect of tylozin in treatment of toxoplasmosis in mice.

MATERIALS AND METHODS:

Parasite Preparation and Passage: *Toxoplasma* (RH strain) was intraperitoneally injected to 10 Balb/C mice (at 106). After 72 h, they were killed and prorogated in compliance with ethical rules. A longitudinal incision was created in the abdomen of the mice' body and its skin was removed. The incision area was disinfected using cotton and alcohol (70%) and the peritoneal cavity was flushed using physiological serum and cc syringe. By doing so, most of the parasites were collected from the peritoneal area and then rinsed with PBS.

The aspirated fluid was passed through high-gauge needle so that the parasites can be mechanically released from the host cells [10]. Then, the liquid was centrifuged for 10 min (at 200 g round) until cellular residues were removed. After that, the supernatant was removed and centrifuged at 800 g and the resulting precipitate was washed three times using a PBS with pH = 7.2 and finally tachyzoite parasite was prepared [11].

How to Prepare Animals: The Institutional Animal Ethics Committee, registered with the Government of Iran (registration no. IR.SUMS. REC.1393.01.01.7598), approved all animal experimental protocols and animal use. Ethical practices recommend the use of equal numbers of animals of both sexes wherever possible. A total of 60 Balb / C mice (aged 6 weeks and weighing 25 ± 2 g) were purchased from Medical Center of Shiraz University of Medical Sciences and Laboratory Animals Breeding Center. The mice were kept at temperature of 20 °C and humidity of 67% in the same place and provided with food and water in sufficient quantities.

Drug Grouping and Administration: A total of 60 mice were divided into 6 groups (each consisting of 10 mice). To investigate the effect of tylozin in the treatment of acute toxoplasmosis, two hundred thousand parasites (in the form of tachyzoites) were subcutaneously injected to all rat groups. After 24 h, tylozin was intraperitoneally injected in the four groups at doses of 10 mg/kg, 20 mg/kg, 40 mg/kg and 80 mg/kg based on body weight every 24 h for 5 days. The fifth group was considered a positive control group and sulfadiazine at a dose of 10 mg/ kg was administered to the mice on the basis of their body weight every 24 h for 5 days. The sixth group was considered a negative control group and only received the parasite.

All the groups were kept in separate cages and received injections with brand new needles. After injection of the parasite, all groups were monitored on a daily basis for one month and the number of deaths was recorded. Then, the data were analyzed by a statistician.

Statistical Methods: The data were analyzed through SPSS software and Kaplan meier statistical software.

RESULTS: A total of 60 Balb/C mice (aged 6 weeks and weighing 25 ± 2 g) were purchased from Medical Center of Shiraz University of Medical Sciences and Laboratory Animals Breeding Center. The mice were kept at a temperature of 20 °C and humidity of 67% in the same place and were provided with food and water in sufficient quantities. Control groups included a positive control group (the group infected with parasite that received a specific dosage of sulfadiazine on a daily basis) and a negative control group (the parasite-infected group that received no drug).

TABLE 1: THE RELATIONSHIP BETWEEN THE DAYS AFTER THE INJECTION OF THE PARASITE AND NUMBER OF DEATHS RECORDED DURING ONE MONTH

Days after the injection of the parasite and on registered deaths															
27	17	16	13	10	9	8	7	6	5	4	3	2	1	Concentration	Group number
					***	*	****	*		*				(10)	1
						****	***	***						(20)	2
					***	**	******	*						(40)	3
	*	*			****	*		*						(80)	4
*			*	*	****	*	**							Positive control	5
						***	****	**	*					Negative control	6

The number in parentheses indicates the concentration of the drug prescribed for each group per mg/kg is
Any sign *indicates a death.

Preparation of infectious mice by injecting tachyzoites form of the parasite is one of the standard techniques for development of acute toxoplasmosis that was used in the present study. In this technique, the animal samples developed symptoms such as weight loss, blindness and unkempt hair; they huddled up during the first three days and finally die in 6 - 8 days. As the following Table shows, the groups were studied separately for one month and the number of deaths in each group was carefully recorded.

TABLE 2: COMPARISION OF ANTI-*TOXOPLASMA* EFFECT TYLOSIN BY INCREASING THE DOSE OF POSITIVE AND NEGATIVE CONTROL GROUPS BASED ON THE AVERAGE SURVIVAL TIME OF MICE IN DAYS

Positive control	Negative control	(80)[4]	(40)[3]	(20)[2]	(10)[1]	Group
10.8	6.9	10.3	7.7	7.1	7.3	Mean of date
		0	0.085	0.668	0.213	P-value

P-value of pair wise comparison group taking the drug tylosin obtained with the negative control group

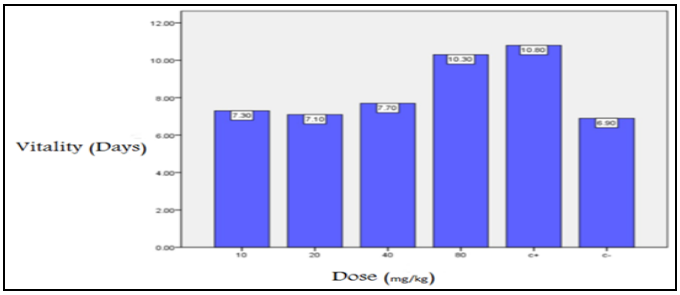

FIG. 1: COMPARISION GROUPS RECEIVING TYLOSIN WITH TOXOPLASMOSIS BY INCREASING THE DOSE OF POSITIVE AND NEGATIVE CONTROL GROUPS BASED ON THE AVERAGE SURVIVAL TIME OF MICE IN DAYS

According to **Fig. 1** and **Table 2**, the average survival time of the mice in the group receiving tylosin increased compared to the negative control, and this is indicative of the influence of the drug which increased the survival of the mice infected with *toxoplasma*. The study time in the tylozin group (80 mg/kg) was almost equal to the study time in the positive control group receiving standard drugs.

DISCUSSION: Toxoplasmosis is created by an obligate intracellular parasite called *T. gondi i*n and is one of the most common parasitic diseases in man and animals so that at least one-third of the world population are infected with this disease [12]. *T. gondii* has an organelle with prokaryotic origin that is known as Apicoplast. In fact, it is a cyanobacteria that has found its way into eukaryotic cells through evolution. This organelle has essential metabolic pathways, and, therefore, plays an important role in the life of the parasite and in the synthesis of fatty acids, proteins, and isopentenyldiphosphate. Due to its prokaryotic origin, this organelle is affected by antibiotics and is considered a drug target in the treatment of toxoplasmosis infection [1]. A limited number of drugs are effective in the treatment of toxoplasmosis. The treatment of choice for this disease is administration of a combination of pyrimethamine-sulfadiazine drugs that inhibit the synthesis of pyrimidine enzymes in *toxoplasma* [13].

In addition to bone marrow suppression, these drugs cause congenital abnormalities and kidney failure, particularly in patients with AIDS [14 - 16]. Spiramycin drug is used for treatment of toxoplasmosis infection in pregnant women to prevent transmission of the infection to the fetus [17]. This drug, however, is associated with side effects such as rash, urticaria and gastrointestinal bleeding [18]. Common macrolide antibiotics, such as erythromycin, azithromycin and roxithromycin had a significant effect on toxoplasmosis parasite in the cell culture medium [19]. Tylosin is a drug from the macrolide antibiotics family that is mostly used to treat infectious diseases in animals. Depending on the type of the sub-groups participating in its chemical structure, this drug is divided into four types A, B, C, D with type A being the most commonly used type [20]. Spiramycin and metronidazole had synergistic effect in recovery of brain cysts caused by chronic toxoplasmosis. This is due to the influence of metronidazole on increased permeability of the brain to spiramycin; thus, the combination of these two drugs is prescribed to treat cerebral cysts in patients with chronic toxoplasmosis [21, 22].

The anti-*toxoplasma* effect of roxithromycin (from the macrolide antibiotics family) *in-vitro* and *in-vivo* as well as its synergistic effect in combination with pyrimethamine and sulfadiazine has been studied in another study. It is also pointed out that this drug can also be used as an alternative therapy for toxoplasmosis in human [23, 24]. Avelino *et al*., (2014) studied 246 newborns at risk for congenital toxoplasmosis in Goiânia (Brazil), and failed to

prove the usefulness of pyrimethamine-sulfadiazine in the treatment of mothers during pregnancy as well as the usefulness of spiramycin in reducing the ocular and intracranial complications in children [25].

Druin *et al*., (1988) investigated the effect of macrolide antibiotics including erythromycin, roxithromycin, spiramycin, josamycin, clindamycin *in-vitro* and it was shown that the effect of these drugs is dose-dependent, and due to the extensive circulation of these drugs in body tissues, especially the lungs and placenta, they can be used to treat toxoplasmosis [26]. And in a new study Ayachit *et al*., reported a case of ocular toxoplasmosis in a 12-year-old female child. The child was clinically diagnosed as having ocular Toxoplasmosis involving the whole posterior pole of the left eye and few parafoveal lesions in the right eye. Follow-up visit revealed new chorioretinitis lesions in the left eye. The patient was treated with oral spiramycin 1500 mg/day in two divided doses with prednisolone tablet (1 mg/kg body weight) for a period of 6 weeks; it was shown that the effect of these drugs is dose dependent [27].

In a study conducted by Montazeri *et al*., (2015), it was pointed out that propranolol in combination with azithromycin, pyrimethamine and sulfadiazine *in-vivo* and *in-vitro* can have a synergistic effect in the treatment of acute toxoplasmosis, (especially in the blood and lung involvement). The inhibitory effect of the azithromycin on intracystic bradyzoites of this parasite *in-vitro* was also confirmed [28]. In another study conducted by Antczak *et al*., (2016), it was noted that a combination of roxithromycin with dapsone and sulfamethoxazole can be used in the prevention and control of opportunistic infections such as *T. gondii*, *Pneumocystis carinii* and *Mycobacterium avium* complex in persons with impaired immune systems [29].

Chang *et al*., (1988), Neville *et al*., (2015) and Lashay *et al*., (2017) showed the inhibitory effect of roxithromycin, azithromycin and spiramycin on *T. gondii in-vitro* [24, 30, 31]. The effect of macrolide antibiotics on *T. gondii in-vivo* and *in-vitro* has been investigated by researchers in numerous studies and the beneficial effect of these antibiotics in the treatment of toxoplasmosis has been proved in them. Since almost no domestic or foreign study has been conducted to evaluate the effects of tylozin on *T. gondii*, it can be argued that the present study, compared to other studies, provides new insights into the important role of macrolide antibiotics in the treatment of this disease, but as mentioned before, spiramycin as a member of this family plays an important role in preventing the transmission of *toxoplasma* to the fetus; thus, the role of other drugs in this group should not be overlooked.

In the present study, the drug was administered for the mice through intraperitoneal injection. The rat's peritoneum provides a vast drug absorption range, and due to proximity to the gastrointestinal mucosa capillaries and simple release of substances into the capillaries, this injection is the most qualified and appropriate method compared to a variety of other methods such as intravenous injection and oral administration. On the other hand, considering the habitat of mice and the possibility of hitting the container of drinking water, the oral administration method does not seem to be reliable, because the mice may fail to receive the quantity of drug prescribed based on their body weights and this may, in turn, increase the risk of error.

CONCLUSION: The present study was an attempt to investigate the effect of tylozin 9 from the macrolide antibiotics family) on *T. gondii* tachyzoites *in-vivo* environment and evaluate the effects of different doses of the drug on the treatment of acute toxoplasmosis. In this study, it was shown that intraperitoneal injection of tylozin can increase the survival time of the mice and the effect of this drug is dose dependent. In other words, the drug's effect is more visible in higher doses (*i.e*. 80 mg/kg). On the other hand, in the one month period, the average number of deaths in each group receiving tylozin (80 mg/kg) and in the positive control group receiving sulfadiazine was fairly the same, and this shows the significant impact of high dosage of tylozin on the survival of the mice. Due to the increased survival time in the mice receiving high doses of tylozin, the author suggests other researchers to re-evaluate the effect of higher doses of tylozin on the mice as well as the effects of the drug on a larger group of mice and pregnant mice in particular.

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