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ANTACIDS AS ALUMINUM HYDROXIDE AND MAGNESIUM HYDROXIDE EFFECT ON TRICHINOSIS: EXPERIMENTAL STUDY

By

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Abstract

Trichinellosis is a resurgent parasite that affects people globally. Acid suppressing drugs (ASDs) are among the most frequently prescribed and generally safe medications in many distinct processes (changes defense mechanisms as gut microbiota and immunology). The study evaluated the antacids effect of aluminium hydroxide and magnesium hydroxide in treating *Trichinella spiralis* in experimental infected mice. Mice (128) were divided into four groups GI: negative control (non-infected untreated), GII: positive control (infected untreated), GIII: mice were infected and treated with albendazole and GIV: mice were infected and treated with antacids. Half of them were sacrificed on 7th day post infection (PI) for intestinal phase and second half were sacrificed on 35th day PI for muscular phase. Treatment efficiency was assessed by parasitological, biochemical and histopathological examinations.

The results showed that antacids treated mice gave highest number of *T. spiralis* adult count in intestine and larval count in muscle. Antacids increased the infection (30.5%, 32.5%) respectively compared to infected control. Biochemically showed higher level of IL4, IL10, MDA and lower level of GSH than infected control.

Keywords: Antacids, *Trichinella spiralis*, albendazole, MDA, IL4, IL10, GSH

Introduction

Trichinellosis is a worldwide zoonotic parasitic infection of numerous mammals, including pigs and humans with nematodes of genus *Trichinella*, with signs & symptoms which appear mainly in humans (CDC, 2017), being reported in Egypt (Morsy *et al*, 2022). Zoonotic illness can be lethal associated with serious neurological, ophthalmic, and cardiovascular consequences (Othman and Shoheib, 2016). Infectious *T. spiralis* muscle larvae are released from the capsules in the stomach upon consumption of the contaminated meat, where they develop into intestinal infective larvae by gastric fluid digestion (Hu *et al*, 2020). Larvae then enter intestinal epithelium and moult four times into adults (Liu *et al*, 2013). A fertilized female releases about 1500 newborn larvae in the first two to three weeks following infection, which penetrate, and encapsulate in the host skeletal muscles (Wang *et al*, 2017). Tissue damage in trichinellosis is caused by a various mechanisms other than the direct harm caused by the parasite itself. The increased production of various stress markers, such as the omega class glutathione S-transferases or GSTO-1, hemeoxygenase 1 or HO-1 (Bruschi *et al*, 2003), superoxide dismutase (SOD), and malondialdehyde (MDA) demonstrated that *Trichinella* infection is one of the main causes of damage (Mido *et al*, 2012). Mebendazole and albendazole are the medications frequently used in therapy, but neither affected the encysted *T. spiralis* nor the newborn larvae (Saad *et al*, 2016).

Antacids are used in treating mild intermittent gastroesophageal reflux disease accompanied with heartburn (Sontag, 1990). Antacids consist of chemicals as calcium, magnesium, and aluminium salts acting as active ingredients reducing gastric acidity by blocking the proteolytic enzyme pepsin action (Maton and Burton, 1999). Al(OH)3 breaks into Al3+ and OH- in the stomach, and the liberated hydroxide groups eventually mix with free protons to form water and insoluble aluminium compounds, mai-

nly Al(Cl)3. The proton binding raises the stomach's total pH, making it less acidic, Owing of aluminum hydroxide's capacity to bind phosphate decreasing, its level led to negative effect on parasitic cycle (Li *et al*, 2015). Together with its ability to bind acids, the aluminum antacid compound displayed cytoprotection, significantly raising tissue prostaglandin-2 levels. Magnesium antacids bind free radicals preventing intracellular calcium increase. The aluminum-magnesium antacid has a cytoprotective effect by acid binding, prostaglandins formation of free radical scavenging (Jávor *et al*, 1989).

Pyrophosphatases (PPases) in *Plasmodium falciparum, Toxoplasma gondii, Schistosoma,* and *Ascaris* were associated to parasitic development (Islam *et al*, 2005). Also, antacids were effective in amoebiasis (Jaisen *et al*, 2007), as well as the ASDs may be helpful since having antileishmanial and antimalarial properties (Fisher and Fisher, 2017).

This study aimed to evaluate antacids (aluminium hydroxide and magnesium hydroxide) versus Albendazole® in treating *Trichinella spiralis* infected murine model.

Materials and Methods

One hundred and twenty eight Swiss albino mice were purchased from Theodor Bilharz Research Institute. Strain of *T. spiralis* was isolated at the laboratory of Tanta University's Medical Parasitology Department from infected albino mice. The used mice were kept in the experimental lab of Tanta Medical Parasitology Department to preserve the strain of *T. spiralis.* Strain of *T. spiralis* was obtained from infected Albino mice in the Medical Parasitology Department Laboratory, Tanta University.

Ethical approval code was 36029/11/22 allowed by Tanta University, Faculty of Medicine Research Committee. Mice were kept on a standard commercial pelleted diet with free accessible water all over the study period. *Trichinella spiralis* L1 larvae were given to each mouse orally in a dose of 200 larvae.

Experimental design: Albendazole: Alzental suspension (EIPICO), a commercialized version of drug, with a 200mg/5ml. Each mouse was received drug via intra-esophageal gavage (50mg/kg/day). Antacids (aluminum hydroxide and magnesium hydroxide or Maalox 175/200mg suspension, Sanofi Co.) were instilled as 125mg/kg/day by an intra-gastrical to mice (Berstad *et al*, 1987).

Experimental animals: The128 laboratory-bred male Swiss albino mice were divided into 4 main groups; each main group was divided into two subgroups: acute (16 mice): sacrificed at 7th day post infection (PI), chronic (16 mice): sacrificed at 35th day PI. GI: 32 mice neither-infected nor treated (negative control). GII: 32 mice infected but non treated (positive control). GIII: 32 mice divided on two subgroups of 16 each, acute infected treated with albendazole on 3rd day PI, each one with 50mg/kg/day intra-esophageal gavage for three days and then sacrificed at 7th day PI. Chronic infected mice received albendazole 50mg/kg/day after 3rd week PI and continued for 10 successive days and then sacrificed at 35th day PI. GIV: 32 mice divided into two subgroups of 16 mice each. Acute infected treated with antacid on the 2nd day PI each with125 mg/kg/day orally. Chronic infected mice received Antacids starting after 3rd week PI and continued for ten successive days PI.

Drugs evaluation: a- Parasitological by counting adults in small intestine**.** Eight mice from acute sub group of the positive control group and other treatment groups were slaughtered on 7th day PI. Parts of intestine were cut into 2cm pieces, put in physiological saline at 37°C for 3-4 hours, and then thoroughly agitated in the solution and rinsed with saline. Fluid was centrifuged for five minutes at 1500 rpm, with a magnification of 40 and worms in reconstituted sediment were counted drop by drop (Issa *et al*, 1998). For larvae in muscles on the 35th day PI, eight mice from chronic subgroup were slaughtered, and their number in muscle was counted (Dunn and Wr-

ight, 1985). Each mouse was dissected and muscles were digested with 200ml of distilled water with 1% pepsin-hydrochloride in distilled water. By sedimentation technique, encysted larvae were recovered after incubated at 37°C for an hour with continuous stirred with an electric stirrer, and then carefully washed in distilled water.

b- Biochemical on 7th day PI, eight mice from each acute subgroups were dissected for intestinal samples, also another eight from each chronic sub-groups were dissected out for muscles samples on 35th day PI. To eliminate RBCs and clots, intestinal and muscles' tissues were perfused with PBS pH 7.4, with 0.16 mg/ml heparin. Tissues were dissected, dissolved in 5-10ml of cold buffer (50mM K_3PO_4, pH7.5.1mM EDTA)/gram tissue, using tissue homogenizer, and then centrifugation at 4,000rpm for 15min. at 4°C. Supernatant was tested for oxidative markers. MDA and reduced glutathione levels (Biodiagnostic Assays, Cairo. CAT. No. MD 25-29 and CAT. No. GR 25-11 respectively). Blood were taken at 7th day PI in acute subgroups, and at 35th day PI in chronic subgroups, left at room temperature for 15-30min, centrifuged at 3000x g, 4°C for 10min and sera were examined ELISA for quantitative detection of IL-4 & IL-10 in mice sera using mouse Interleukin 4, IL-4 ELISA Kit (Code no: E0051Mo; BT LAB, UK), mouse Interleukin 10, IL-10 ELISA Kit (Code no: E0022Mo; BT LAB, UK) respectively.

c- Histopathological mice from each subgroup were sacrificed at 7th day PI. One ml of intestinal samples was obtained. On the 35th day PI, mice from each group were sacrificed and muscle samples were processed for paraffin embedding, sectioning at 5µ thickness, hematoxylin and eosin stained and microscopically examined (Shalaby *et al*, 2010).

Statistical analysis: Data were collected, computerised and analysed using computer software SPSS (Statistical package for social science) version 25. Data were expressed as mean and standard deviation SD. Either Kruskal-Wallis or ANOVA was used to identify significant difference. If P value < 0.05 was considered significant.

Results

There was increase in adult *T. spiralis* count in intestine and larvae in muscle in antacids mice treated (30.5%, 32.5%) respectively, with P = 0.059 & 0.473 respectively. Antacids treated mice showed increased in IL-4 & IL-10 levels of acute and chronic infected mice compared to negative control and albendazole treated mice.

Antacid-treated mice compared to positive control without significant (P= 0.627). The antacids treated mice showed decrease in GSH level in acute and chronic compared to negative control and albendazole treated ones. Comparing antacid-treated mice to positive control ones was not significant (P= 0.839).

The antacids treated mice showed increase in MDA level in acute and chronic mice compared to negative control and albendazole treated ones. Comparing antacid-treated mice to positive control group was not significant (P= 0.545).

Small intestine sections of antacids treated mice showed broad inflammatory infiltration, mostly in villi core extended to submucosa. Lieberkuhn crypts elongated, an increase in goblet cells, reduction in villous height to crypt depth ratio, and extensive ulceration of mucosa. Also, larvae number increased surrounded by severe inflammatory reaction in skeletal muscles.

Details were given in tables (1, 2, 3, 4 & 5) and figures (1 to 14).

Table 1: Comparison between groups as Adult *T. spiralis* count in intestine and larva count in muscles

Studied groups	Adult *T. spiralis* count in intestine		Larva *T. spiralis* count in muscles	
	Mean ±SD	P value[b]	Mean ± SD	P value[b]
Gl (-ve control)	0.00±0.00	<0.001	0.00±0.00	0.042
Gll (+ve control)	20.50±3.42	-	2807.00± 2562.65	-
GllI (albendazole treated)	3.50±2.38	<0.001	117.50±57.61	0.050
GlV (antacids treated)	26.75±7.37	0.059	3719.50±2358.33	0.473

*P<0.05 significant, **P<0.01 extremely significant Test b Data from positive control compared to others.

Table 2: Comparison between groups regarding IL-4 (ng/L)

Groups	Acute infection		Chronic infection	
	Mean ±SD	P value[b]	Mean±SD	P value[b]
Gl (-ve control)	41.61 ±9.40	0.027	40.05 ±6.74	0.005
Gll (+ve control)	53.60 ±11.66	-	54.25 ±13.69	-
GllI (albendazole treated)	42.32 ±12.73	0.037	38.15 ±13.74	0.002
GlV (antacids treated)	53.05 ±12.54	0.916	56.56 ±4.83	0.627

Table 3: Comparison between groups regarding IL-10 (pg/mL)

Groups	Acute infection		Chronic infection	
	Mean ±SD	P value[b]	Mean ±SD	P value[b]
Gl (-ve control)	61.56±10.74	<0.001	57.57±15.13	0.005
Gll (+ve control)	89.81 ±15.21	-	80.56±13.66	-
GllI (albendazole treated)	60.40 ±14.98	<0.001	58.28±18.62	0.002
GlV (antacids treated)	91.43 ±14.63	0.797	86.31±13.77	0.627

Table 4: Comparison between groups regarding GSH (mmol/gm tissue)

Groups	Acute infection		Chronic infection	
	Mean ±SD	P value[b]	Mean ±SD	P value[b]
Gl (-ve control)	4.58±0.90	0.001	4.32±0.65	0.013
Gll (+ve control)	2.98±0.61	-	3.06±1.04	-
GllI (albendazole treated)	4.30±1.36	0.006	4.66±1.41	0.002
GlV (antacids treated)	2.92±1.06	0.899	2.97±1.04	0.839

Table 5: Comparison between groups regarding MDA (nmol/gm tissue)

Groups	Acute infection		Chronic infection	
	Mean ±SD	P value[b]	Mean ±SD	P value[b]
Gl (-ve control)	32.75±10.58	<0.001	34.12±11.34	0.001
Gll (+ve control)	89.39±17.71	-	77.66±27.14	-
GllI (albendazole treated)	35.99±10.50	<0.001	32.14±12.89	<0.001
GlV (antacids treated)	89.14±18.00	0.969	82.08±17.87	0.545

Discussion

Trichinosis spiralis infected muscles for long time interacts strongly with host immune system causing inflammation of muscles (Bruschi and Chiumiento, 2011).

Drugs reduce gastric acid; acid suppressing was highly effective in treating upper digestive tract conditions caused by acid (Scarpignato *et al*, 2016). Pepsin, lipase, mucus, and acidity protect body from bacteria and parasites (Waldum *et al*, 2014).

In the present study, adult *T. spiralis* in intestine and larva muscle in antacids treated mice increased (30.5%, 32.5%) respectively compared to positive control. This agreed with Di Genova *et al.* (2016), who found that parasite burden in hypochlorhydria increased. Also, giardiasis was linked to prolonged PPIs use and ranitidine after stomach surgery (Francois *et al*, 2008). In 54% of patients with giardiasis, hypochlorhydria was linked to sever symptoms in chronic atrophic gastritis (Sheen and Triadafilopoulos, 2011). Also, proton pump inhibitors (PPIs) for two years led to stomach strongyloidiasis (Shafaghi *et al*, 2012). Strongyloidiasis was linked to hypochlorhydria and immune-compromised patients (Puthiyakunnon *et al*, 2014). However, *in vitro* omeprazole inhibited giardiasis triosephosphate isomerase (Reyes-Vivas *et al*, 2014). Also, ASDs as adjuvants improved schistosome vaccination by cimetidine activity and omeprazole promoted praziquantel effectiveness (Almeida *et al*, 2015). In vivo, artificial gastric and intestinal fluids prevented *Entamoeba histolytica* excystation (Makioka *et al*, 2006). Also, antacids treated amoebiasis as three days of antacid use declined amoeba, mucus and occult blood (Jaisen et *al*, 2007).

Although it is not cell type specific, yet down-regulatory cytokine IL-10 is extensively expressed by a wide range of immune cells (Hedrich and Bream, 2010). Thus, to minimize tissue damage from more immuno-inflammatory responses, especially during the resolution phase of infection and inflammation, and to preserve gut microbiota balance, it targets components of innate and adaptive immunity and carries out immunosuppressive actions (Ouyang and O'Garra, 2019).

An important mechanism of helminthes-

induced immunoregulation was increased synthesis of IL-10, which recurred feature of host's immunological response in helminthiasis (Ilic *et al*, 2021). Ironically, it was reported that IL-10 plays a crucial role in the *Trichinella* immune response and trichinellosis immunoregulation by the small intestine's immune system in skeletal muscles (Fabre *et al*, 2009; Bruschi and Dupouy-Camet, 2014). Beiting *et al* (2007) reported that Tregs, IL-10, and TGF- have an interaction with effector T cells allowed *T. spiralis* muscle larvae to survive while protected host from excessive inflammatory reactions. Also, chronic *T. spiralis* infection in rats with duodenum atresia led to a significantly higher CD4+ CD25+ Foxp3+ cells and high levels of IL-10 production (Gruden-Movsesijan *et al*, 2010). Jin *et al* (2020) found that *T. spiralis* muscle larvae increase the production of cytokines IL-4 and IL-10 but decreased the synthesis of cytokines interferon (IFN), IL-12, and tumor necrosis factor (TNF).

In the present study, mice treated with antacids showed higher level of IL4, IL10, MDA but, lower one of GSH at acute and chronic compared to infected control. Yu *et al.* (2013) showed that the Th1 response dominance early in *T. spiralis* intestinal stage of infected mice and subsequent Th2 response dominance later on during muscular stage activating the immune system. They added that in early infection, IFN and IL-12 mRNA expressions were elevated, and during muscle stage, IL-4 & IL-10 expressions rose. Also, during early intestinal phase of *T. spiralis* infection, host launches a Th1-type immune response in an effort to get rid of infection (Munoz-Carrillo *et al*, 2017). The Th2 cytokine IL 4 showed enhanced expression via the whole intestinal phase. Th2 cytokine IL-10 was markedly upregulated in intestinal phase, and showed a mixed systemic Th1/Th2 response to *T. spiralis* in mice, with predominating Th2 response in this phase (Jing Ding *et al*, 2017).

In the present study, antacids treated mice showed significant infiltrations with inflammatory cells mostly in submucosa and villi core, more elongated Lieberkuhn crypts, more goblet cells, declined in crypt depth ratio to villous height, and significant muscles ulceration. This agreed with Elgendy *et al*. (2020), they that positive control showed inflammation in mucosa, submucosa, and center of villi, with neutrophils and eosinophils as main components of inflammatory infiltrates. Younis *et al.* (2022) reported that control-positive mice on 7th day PI showed a distorted villous pattern (short broad villi), scattered adults in mucosa, moderate inflammation, and inflammatory infiltrate of lymphocytes and plasma cells.

Conclusion

Antacids treated *T. spiralis* showed higher number of adults in intestine and larvae in muscle, higher IL4, & IL10, MDA levels but lowest GSH level compared to control. Such patients must avoid antacids.

The authors declared they equally shared in the study and neither have conflict of interest nor received any funds.

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Explanation of figures

Fig. 1: Small intestine sections of positive control showed wide inflammatory infiltrations mostly in villi's centre up to submucosa (Red arrow), Lieberkuhn crypts showed marked elongation, increased number of goblet cells (black arrows), a reduction in ratio of villous height to crypt depth, flattening of villi with some ulceration (yellow arrow) (H&E, X100).

Fig. 4&5: Small intestine sections of albendazole-treated showed improvements intestinal alterations with a clear reduction in inflammatory cell infiltrates (red arrows) reduced goblet cell count (black arrows) (H&E, X100).

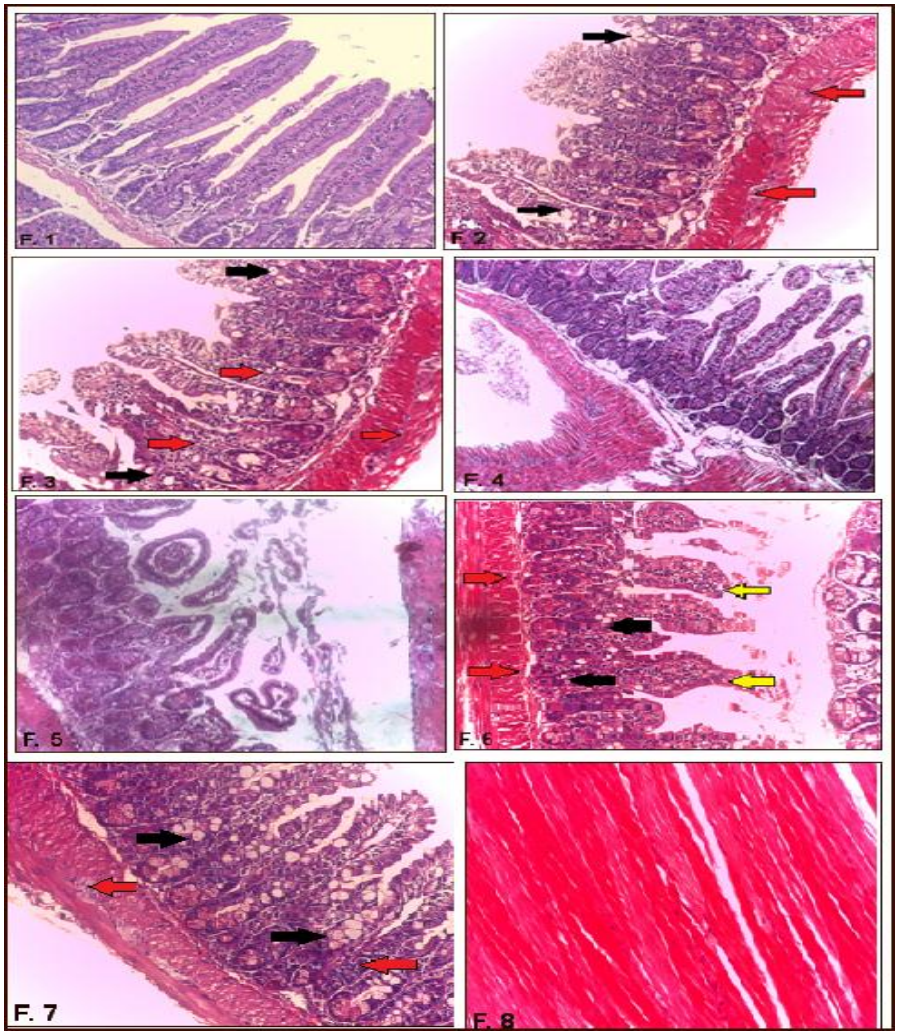
Fig 6&7: Small intestine of antacids treated group showed wide inflammatory infiltrations mostly in villi's centre up to submucosa (red arrow), Lieberkuhn crypts showed more marked elongation, more goblet cells (black arrows), a reduction in ratio of villous height to crypt depth with extensive mucosal ulceration (H&E, X100).

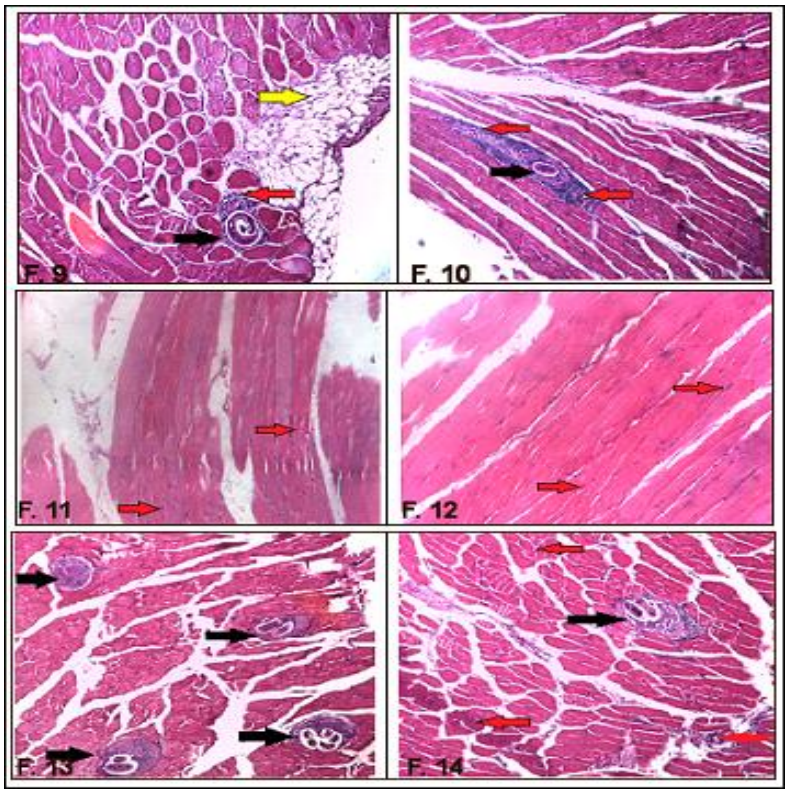
Fig 8: Skeletal muscle of negative control showed normal muscle without edema (H&E, X100).

Fig. 9 &10: Skeletal muscle of positive control showed larvae deposited in muscle fibres (Black arrows), surrounded by a very inflammatory reaction (red arrows) and muscular edema (yellow arrow) (H&E, X100).

Fig. 11&12: Skeletal muscle of albendazole-treated showed decrease in inflammatory cell infiltrates with little or no larvae in muscle (H&E, X100).

Fig. 13&14: Skeletal muscle of antacids treated showed numerous embedded larvae in muscular fibres (Black arrows), surrounded by a severe inflammatory response (H&E, X100).


F. 1
F. 2
F. 3
F. 4
F. 5
F. 6
F. 7
F. 8


F. 9
F. 10
F. 11
F. 12
F. 13
F. 14