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Biochemical Effect of Damperidone on Cardiac Functions after Induction of Peptic Ulcer in Albino Rats

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Abstract

The objective of the present study was to evaluate the biochemical effect of Domperidone on the cardiac functions after induction of peptic ulcer on albino rats. Sixty white male albino rats, average body weight 200-250 gm and 12-16 weeks old were used in the experimental investigation of the study. Rats were randomly divided into two large groups Group A consist of thirty rats divided into three subgroups (subgroup G1,G2,G3) and this group is completely healthy without ulcer induction receiving Domperidone three times per day half an hour before meal each sub group receives a different dose using subgroup G1 as control. Group B consist of thirty rats undergo stomach ulcer induction and it is divided in to three subgroup (subgroup G4,G5,G6) receiving Domperidone three times per day half an hour before meal with different doses according to the subgroup. Blood samples were collected for biochemical examination three times during the study after one week, two weeks and four weeks. Tissue specimens where taken from heart for histopathological examination. We found elevated levels of Troponin (cTnT), CK-MB, LDH, and AST in groups treated with high doses of Domperidone and results was time dependent. Histopathological examination of heart showing coagulative necrosis, swollen, vacuolated myocytes with disruption and hyperesinophilia.

Keywords: Domperidone, CK-MB, (cTnT), Stomach ulcer.

1.Introduction

Domperidone is adopamine (D) antagonist with particular affinity for the D2 subtype receptors in the brain and the peripheral nervous system including the gastrointestinal tract [**1**]. Domperidone also related to the benzimidazole derivatives with molecular weight 426 it acts peripherally by dopamine blockade. Its higher molecular weight and lower lipid solubility are explained it's in ability to cross the blood brain barrier [**2**]. Domperidone is used for the treatment of symptoms associated with upper gastrointestinal motility disorders such as diabetic gastroparesis, gastroesophageal reflux, nausea and vomiting associated with therapy for parkinsons disease and cancer [3]. Domperidone was firstly synthesized in 1974 and it has been approved for patient use throughout the world with specific clinical applications such as gastroparesis, gastroesophageal reflux and general antiemetics [4]. The cardiovascular safety of Domperidone came into question in the mid 1980. when intectable formulation withdraw from the market after serious cardiac events, ventricular arrhythmia, cardiac arrest and sudden cardiac death were reported in cancer patients receiving high doses of Domperidone for chemotherapy related nausea and vomiting[5]. Science then, information about possible association between oral Domperidone and increased risk of ventricular arrhythmia and sudden cardiac death accumulated for spontaneous reports in several countries [6]. In march ,2012 health Canada issued an alert regarding Domperidone use, warning practioners about risk of ventricular tachyarrhythmias and sudden cardiac death with its use, particularly in dose exceeding 30mg/day and in patients older than 60[7]. Our study demonstrates that appropriate use and monitoring of Domperidone are required as we found from measuring cardiac parameters that its using have a negative effect on heart. So the increased awareness of indications, dosage and adverse effects of Domperidone will result in improved patient safety, quality of care and healthcare expenditure.

2.Materials and methods

2.1 Rats and experimental design

Sixty white male albino rate, average body weight 200-250 gm and 12-16 weeks old were used in the experimental investigation of the study. Rats were housed in a separate metal cages and they were kept at constant environmental and nutritional conditions during the period of the experiament.rats were left two weeks for acclimatization before the beginning of the experimental animals were divided in to two large groups the first one is Group1 which is a normal group without inducing stomach ulcer consist of three subgroups. The second group Group2 where rats undergo stomach ulcer induction. Subgroup A1is a normal control group. Subgroups B1and B2 receiving recommended dose of Domperidone 10 mg three times per day [8]. Subgroup C1 and C2 receiving double dose of Domperidone and the subgroup A2 was ulcer induced group without any treatment. Animals received Domperidone for four weeks according to[9].

2.2 Drugs and chemicals

A. Domperidone molecular formula: C22H24CIN5O2 molecular weight: 425.917 g/mol Domperidone obtained in a suspension form. A bottle

of 100 ml oral suspension of Domperidone 1 mg per ml. with a commercial name motilium manufactured by Minapharm under license of Janssen- cilag.

B. Ethyl Alcohol (Ethanol) molecular formula: C2H5OH molecular weight: 46.07 Ethyl alcohol was manufactured by El Nasr for pharmaceutical chemicals Co. Abuzaabal, Egypt.

Gasteric ulcer induction

Rats were fasted for 18 hours and allowed free access of water prior to the administration of ethanol for gastric ulcer induction. Certain groups of rats once orally administrated with absolute ethanol at a dose of 1ml/rate [10]**.** After one hour, rats were sacrificed to make sure that ulcer present.

2.3 Blood samples

Blood samples were collected by ocular vein puncture for serum separation in dry, clean and screw capped tubes and serum were separated by centrifugation at 2500 r.p.m. for 15 minutes. Serum was separated by automatic pipette, received in dry sterile sample tube, and freezed at -20 c until used for biochemical examination.

2.4 Tissue sampling

Tissue specimens were taken from heart. the specimens were preserved in 10% buffered formalin and subjected for microscopical examination.

2.5 Blood parameters

Cardiac parametrs: CKMB test according to **[11**], (cTnT) test according to [**12**]. LDH according to [13], AST according to **[14]**.

2.6 Histopathological examination

According to technique described by [15].

3.Statistical analysis

All the obtained data were analyzed and graphically represented using the statistical package for social science (**IBM SPSS, 20.0 software, Duncan**) for obtaining mean and standard deviation and error. The data were analyzed using one-way ANOVA to determine the statistical significance of differences among groups. Duncan's test was used for making a multiple comparisons among the groups for testing the inter-grouping homogeneity.

4.Results

The obtained data in table (1) revealed that there is a significant increase in serum cardiac marker Troponin following treatment by Domperidone (G2, G3, G5, G6) for the three different time periods (1w, 2w, and 4w) as compared to control groups (G1 and G4). Within the same time point, the gastric ulcer groups given Domperidone (G5, G6) showed higher (cTnT) level than the healthy groups administrated Domperidone (G2, G3). Comparing the three time points, troponin level was gradually increased with increasing the time period, i.e. the highest level was observed at 4w and lowest at 1w. In all groups, higher significant levels of troponin noticed in animals receiving higher doses of Domperidone.

The obtained data in table (2) revealed that there is a significant increase in serum cardiac marker CK-MB following treatment by Domperidone (G2, G3, G5, G6) for the three different time periods (1w, 2w, and 4w) as compared to control groups (G1 and G4). Within the same time point, the gastric ulcer groups given Domperidone (G5, G6) showed higher CK-MB level than the healthy groups administrated Domperidone (G2, G3). Comparing the three time points, CK-MB level was gradually increased with increasing the time period, i.e. the highest level was observed at 4w and lowest at 1w. In all groups, higher significant levels of CK-MB noticed in animals receiving higher doses of Domperidone

The obtained data in table (3) revealed that there is a significant increase in serum cardiac marker LDH. Following treatment by Domperidone (G2, G3, G5, G6) for the three different time periods (1w, 2w, and 4w) as compared to control groups (G1 and G4). Within the same time point, the gastric ulcer groups given Domperidone (G5, G6) showed higher LDH level than the healthy groups administrated Domperidone (G2, G3). Comparing the three time points, LDH level was gradually increased with increasing the time period, i.e. the highest level was observed at 4w and lowest at 1w. In all groups, higher significant levels of LDH noticed in animals receiving higher doses of Domperidone.

Our results table (4) revealed a significant ($P \leq 0.05$) increase in the serum level of the AST following treatment by Domperidone (G2, G3, G5, G6) for the three different time periods (1w, 2w, and 4w) as compared to control groups (G1 and G4) within the same time point, the gastric ulcer groups given Domperidone (G5, G6) showed higher AST level than the healthy groups administrated Domperidone (G2, G3). Comparing the three time points, AST level was gradually increased with increasing the time period, i.e. the highest level was observed at 4w and lowest at 1w. In all groups, higher significant levels of AST noticed in animals receiving higher doses of Domperidone. On the other hand, no significant difference in AST level was detected between control group (G1) and ulcer group (G4) in each time point.

Histopathological examination

Approximately 20% - 30% of the myocardium was multifocally to focally extensively effaced by large intersecting bands of coagulative necrosis characterized by loss of cellular details and retention of tissue architecture, occasionally accompanied by myofiber loss and stromal collapse. Cardiac myocytes were necrotic with fragmented,

hypereosinophilic sarcoplasm, loss of cross striations and pyknotic or karyorrhectic nuclei. Less commonly, cardiac myocytes were swollen and vacuolated with loss of sarcoplasmic detail (degeneration). There was rare regeneration characterized by invasion of lightly basophilic myofibers by satellite cells, rowing up and centralization of nuclei. Multifocally, few blood vessels were congested and lined by hypertrophied endothelial cells.

5. Discussion

The obtained data in table (1) revealed a significant increase in serum concentration of the cardiac marker troponin following treatment by Domperidone (G2,G3,G5,G6) for the three different time periods(1w,2w,4w) as compared to control groups (G1,G4).Within the same time point , the gastric ulcer groups given Domperidone (G5,G6) showed higher (cTnT) level than healthy groups (G2,G3). Troponin level was gradually increased with increasing the time period, i.e. the highest level was observed at 4w and lowest at 1w.this obtained data indicates increased risk of cardiac events.

These results come in accordance with [16], who reported that elevated concentrations of (cTnT) increased risk of cardiac events and the higher the (cTnT) the more frequent cardiac complications.

On the other hand[17] indicates that elevation of cTnT levels have been reported in cases of drug induced cardiac toxicity and that is come in accordance with[18] who indicates that the cardiac toxicity of Domperidone found to be described with both intravenous and orall administration.

Both (cTnT) and cTn1 has been used as biomarkers for detection of drug induced cardiac injury in humans and animals [19]. The obtained data in table(2) revealed that there is an increase in the serum level of the cardiac marker CKMB following treatment by Domperidone (G2,G3,G5,G6) for the three different time periods(1w,2w,4w) as compared with the control group(G1,G4).within the same time point , the gastric ulcer groups given Domperidone(G5,G6) showed higher CKMB level than the healthy groups administrated Domperidone (G2,G3) .comparing the three time points, CKMB level increased with increasing time period, their highest level at w4 and lowest level at w1.

These results come in accordance with [20], who reported that CK-MB concentration rises following myocardial injury. and in accordance with **[21],** illustrated that serum CKMB is considerably more specific for myocardial damage. Since, Domperidone has aproarrhythmic properties as demonstrated by [22] and it is recently one of the main causes of cardiac arrhythmia as reported by [23] so we can use CK-MB as a biocardiac marker to detect cardiac problems resulted from using of Domperidone as mentioned on our study.

Despite, [24] illustrated that CK-MB should not be used for the diagnosis of myocardial injury unless used in combination with other specific cardiac marker, [25] demonstrated that the diagnostic specificity of serum CK-MB For the detection of AMI has been reported to be very close to 100%.

The obtained data in table(3) revealed that there is an increase in the serum level of the cardiac marker LDH following treatment by Domperidone (G2,G3,G5,G6) for the three different time periods(1w,2w,4w) as compared with the control group (G1,G4) at the same time point , the gastric ulcer groups given Domperidone (G5,G6) showed higher LDH level than the healthy groups administrated Domperidone (G2,G3) .comparing the three time points, LDH level increased with increasing time period, their highest level at w4 and lowest level at w1.

These results come in accordance with [26], who indicates that there is active correlation between LDH activity, cardiac index and LDH activity increase in patients with cardiac diseases. [27] reported that LDH activity may be an early marker for myocardial problems like MI. On the other hand [28] indicates that increased myocardial LDH activity can be considered as an early indicator for acute myocardial infarction. That indicates that the side effect of Domperidone on cardiac functions that may leads to SCD as reported by **[29]** can be measured by the cardiac bio markef LDH. and that is come in accordance with our study results.

The obtained data in table(4) revealed a significant increase in serum level of AST following treatment with Domperidone (G2,G3,G5,G6) for the three different time period (1w,2w,4w) as compared with control groups (G1,G4). Within the same time point, the gastic ulcer groups given Domperidone (G5,G6) showed higher ALT and AST level than the healthy groups (G2,G3). AST level increased with increasing time period, their highest level at w4 and lowest level at w1.

These results come in accordance with [30]. Who illustrated that the elevated level of AST indicates that there is a myocardial in fraction, because AST considered the first diagnostic tool in biochemistry for MI. On the other hand[31] reported that elevated levels of serum transaminases indicate that heart suffers from MI. [32] demonstrated that elevation in transaminases usually result from ischemic injury due to decreased cardiac output which affect hepatocytes.

Table (1) Effect of Domperidone on the serum concentration of Troponin

Group	1w		2w		4w	
	Mean	SE	Mean	SE	Mean	SE
G1 (control)	0.01 [e]	0.003	0.02 [e]	0.003	0.02 [e]	0.004
G2 (Domperidone 1ml/kg Bwt)	0.03 [d]	0.005	0.04 [d]	0.003	0.06 [d]	0.007
G3 (Domperidone 2ml/kg Bwt)	0.05 [c]	0.004	0.07 [c]	0.006	0.09 [c]	0.003
G4 (Ulcer)	0.02 [d,e]	0.003	0.03 [d,e]	0.005	0.04 [d,e]	0.005
G5 (Ulcer + Domperidone 1ml/kg Bwt)	0.07 [b]	0.005	0.09 [b]	0.007	0.13 [b]	0.006
G6 (Ulcer + Domperidone 2ml/kg Bwt)	0.09 [a]	0.004	0.11 [a]	0.005	0.20 [a]	0.004

Data was represented as means± SE. Means within the same column of each time point carrying different superscript letters are significantly different ($P \leq 0.05$).

Table (2) Effect of Domperidone on the serum level of CKMB

Group	**1w**		**2w**		**4w**	
	Mean	**SE**	**Mean**	**SE**	**Mean**	**SE**
G1 (control)	23.20	0.753	26.40	0.658	28.40	0.658
G2 (Domperidone 1ml/kg Bwt)	28.80	1.252	40.00	0.913	57.80	1.111
G3 (Domperidone 2ml/kg Bwt)	33.00	1.225	49.00	1.225	69.80	1.378
G4 (Ulcer)	25.20	0.749	31.40	0.876	45.33	0.882
G5 (Ulcer + Domperidone 1ml/kg Bwt)	51.20	1.317	63.00	1.683	93.67	2.333
G6 (Ulcer + Domperidone 2ml/kg Bwt)	70.80	1.549	88.80	1.889	127.50	2.041

Data was represented as means±SE. Means within the same column of each time point carrying different superscript letters are significantly different ($P \leq 0.05$).

Table (3) Effect of Domperidone on the serum level of LDH

Group	**1w**		**2w**		**4w**	
	Mean	**SE**	**Mean**	**SE**	**Mean**	**SE**
G1 (control)	43.40	1.390	50.72	2.113	53.74	1.652
G2 (Domperidone 1ml/kg Bwt)	51.60	1.197	64.60	3.550	82.40	3.479
G3 (Domperidone 2ml/kg Bwt)	55.00	1.291	83.40	4.408	109.00	6.124
G4 (Ulcer)	44.20	1.798	57.80	1.494	61.00	1.528
G5 (Ulcer + Domperidone 1ml/kg Bwt)	102.20	6.343	132.20	4.367	222.00	8.737
G6 (Ulcer + Domperidone 2ml/kg Bwt)	153.60	6.319	190.00	5.050	276.00	11.43

Data was represented as means±SE. Means within the same column of each time point carrying different superscript letters are significantly different ($P \leq 0.05$).

Table (4) Effect of Domperidone on the serum level of AST

Group	**1w**		**2w**		**4w**	
	Mean	**SE**	**Mean**	**SE**	**Mean**	**SE**
G1 (control)	41.60	1.13	43.60	1.51	45.50	2.33
G2 (Domperidone 1ml/kg Bwt)	47.00	1.47	79.60	2.85	105.80	3.69
G3 (Domperidone 2ml/kg Bwt)	51.40	1.20	96.00	3.85	131.00	5.48
G4 (Ulcer)	42.74	1.25	48.24	2.66	67.67	2.60
G5 (Ulcer + Domperidone 1ml/kg Bwt)	61.74	2.65	139.50	6.60	186.67	6.64
G6 (Ulcer + Domperidone 2ml/kg Bwt)	78.50	3.04	155.24	7.25	219.00	8.98

Data was represented as means±SE. Means within the same column of each time point carrying different superscript letters are significantly different ($P \leq 0.05$).

6.Histopathological findings

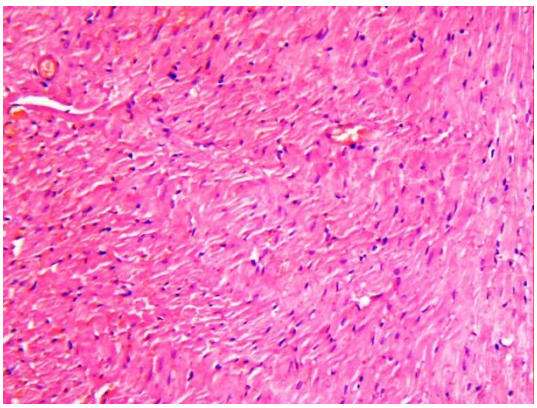

Fig (1) Heart of control rat showing normal histological appearance of myocardial muscle fibers (MF) and intermuscular blood vessels (V). H&E stain x 200

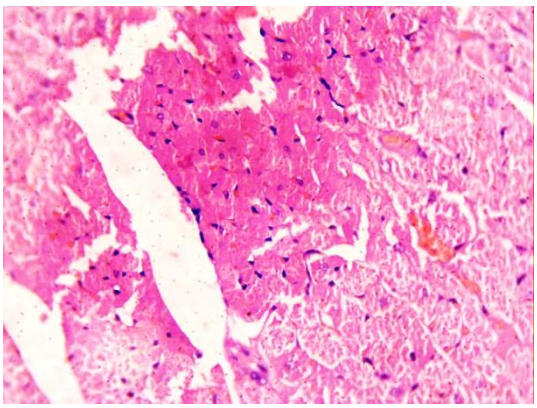

Fig (2) Heart of rat administered therapeutic dose of Domperidone for 4 weeks showing large intersecting bands of coagulative necrosis characterized by loss of cellular details and retention of tissue architecture. H&E stain x 200.

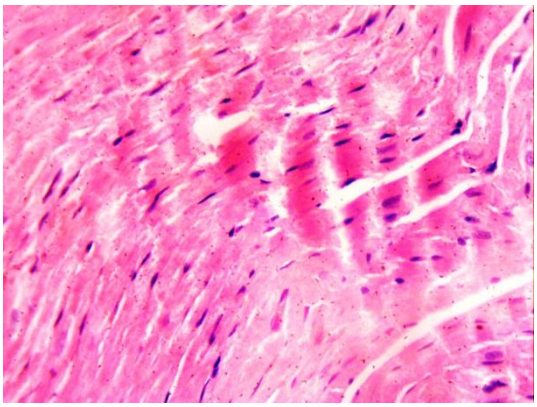

Fig (3) Heart of rat administered therapeutic dose of Domperidone for 4 weeks showing coagulative necrosis of cardiac myocytes with fragmented, hypereosinophilic sarcoplasm and loss of cross striations. H&E stain x 400

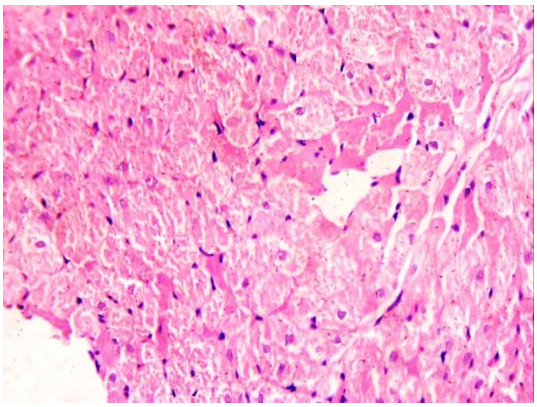

Fig (4) Heart of rat administered therapeutic dose of Domperidone for 4 weeks showing coagulative necrosis of cardiac myocytes with hypereosinophilic sarcoplasm, loss of striations and pyknotic nuclei. H&E stain x 200

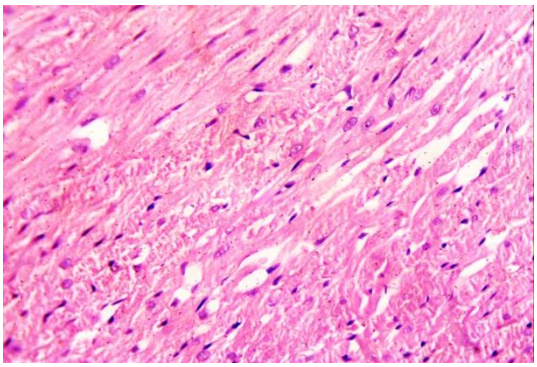

Fig (5) Heart of rat administered therapeutic dose of Domperidone for 4 weeks showing swollen, vacuolated cardiac myocytes with loss of sarcoplasmic detail. H&E stain x 200

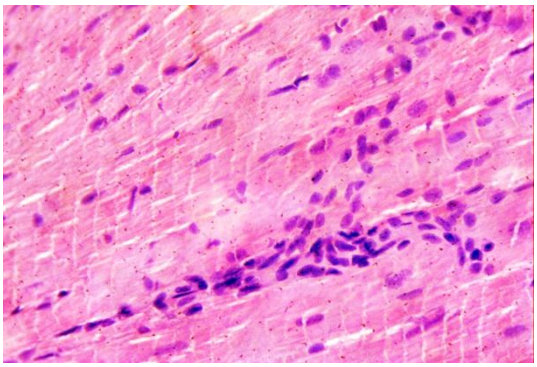

Fig (6) Heart of rat administered therapeutic dose of Domperidone for 4 weeks showing regeneration of muscle fibers characterized by invasion of lightly basophilic myofibers by satellite cells, rowing up and centralization of nuclei. H&E stain x 400

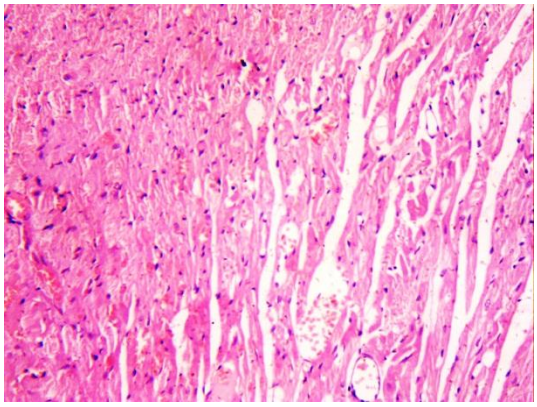

Fig (7) Heart of rat administered therapeutic dose of Domperidone for 4 weeks showing congested blood vessels lined by hypertrophied endothelial cells. H&E stain x 200

7. Conclusion

Based on the obtained data in the current research, treatment with Domperidone the antiemetic drug is unsafe as it may causes myocardial infarction, cardiac cytotoxicity and sudden cardiac death. That is building on its effect on the cardiac biomarkers like; (cTnT), CK-MB, LDH and AST. Causing elvated levels of these biomarkers obviously than normal. This indicates its side effect on cardiac functions.

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