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Effect of toxic dose of levamisole on electrocardiogram and serum enzymes concentration in lambs

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Abstract
The present study was conducted to assess probable organ and system defect related with levamisole poisoning experimentally in lambs. For this reason, fifteen healthy lambs (five lambs of each group different breeds genders, were aged from 1-3 months. in Baghdad city / Iraq (between October 2016 to December 2017). The lambs poisoning by levamisole in the present study was showed a significant increase of serum aspartate aminotransferase (AST) 98.34±2.52 mmol/l after 96 hr and alanine aminotransferase (ALT) 32.11±0.13 mmol/l after 144 hr. alkaline phosphatase (ALP) 30.17±5.31 mmol/l) after 96hr. but no significant increase in the cardiac troponin I. was observed. Electrocardiographic changes many arrhythmias such as sinus tachycardia, ventricular premature contraction, increase in P amplitude, PR interval, and T-wave inversion were recorded in the experimental sheep. Levamisole poisoning seems to cause numerous arrhythmias in sheep which might be due to the effect of Levamisole poisoning on the myocardium pathological. We the present concluded that the lambs were drenched in a dosage of 25 mg/kg body weight causes signs of poisoning and changes in the biochemical, and electrocardiographic pattern.

Keywords: Iraqi lambs, levamisole poisoning, serum aspartate aminotransferase (AST) alanine aminotransferase (ALT), alkaline phosphatase (ALP) concentration, cardiac troponin and electrocardiographic pattern

1. Introduction
Levamisole is an imidazothiazole derivative which wide variety application for animal and human [1]. It was discovered in 1966 by Janssen Pharmaceutica [2]. Levamisole is used as an anthelmintic drug to control parasite infection and infestation [3]. It Is given as oral tablet, pastes, gels, boluses or soluble powder [4]. It is well absorbed when given orally and become distributed through all body tissue When the liver gets infected, the enzymes inside the liver cells enter the bloodstream When the liver is wounded the liver cell enzymes enter the circulatory system [5]. Alkaline phosphatase (ALP) is widely distributed in the body synthesized in the liver, kidney epithelium, intestinal, placental, osteoblasts, in the case of higher osteoblastic activity the increased production of AP and its activity can be noted [6]. when the dysfunctional of liver the enzymes values of the listed above go up. The biochemical tests are used in the diagnosis of kidney and liver diseases, furthermore usually used the response to exposure to exogenous toxic substances. AST In ruminants is habitually tested along with ALP and LDH to estimate when the liver is injured or unhealthy [6]. When the liver is dysfunctional, the levels of the enzymes listed above go up. ALT is liver specific in dog and cat but and approved the final manuscript. There is tiny activity of liver ALT, in sheep the ALT concentration as an indicator of liver cell necrosis, particularly in cats and dogs [7]. Electrocardiograph (ECG) is the most commonly important tool that use in the Veterinary Medical practice which use to detect rate, rhythm and nature of depolarization and re polarization [8]. It can use to detect the myocardial mass, conductivity between skin and heart and the presence of metabolic abnormality that affect the heart [9]. The study was to determine serum biochemical values that used to evaluate the heart and liver function such as (Troponin, AST, ALT and ALP, levels and electrocardiographic changes in levamisole poisoning in Iraqi lambs.

2. Materials and Methods

A total number of 15 lambs of the Iraqi breed, were divided to three groups (five lambs of each group) ages three months age. The feeding of animals basically constitutes between straw and grass, sometime grain the clinical signs were tested every day. Each lamb was restrained by human before blood sample was taken, the skin was disinfected with alcohol 10% concentrate, and blood sample was collected from the jugular vein by using avacutainer tube. The collected blood samples were placed at room temperature for 30 minutes. The samples were centrifuged (4000 round/min),the serum only was transferred with apipette to another test tube to analyzed to determine (serum troponin, AST, ALT and ALP, levels and electrocardiography) according the procedures mentioned by [10]. The samples of serum were analyzed by refelatron apparatus and use specific kit to determine these serum enzymes values and ECG was taken in animal at resting and calm without anesthesia in the department of Internal and Preventive Medicine/University of Baghdad**.**

2.1 Statistical methods

The results obtained were statistically analyzed by using SAS program. Data were analyzed (ANOVA) and the mean was significantly compared with the T- test at $P<0.05$

3. Results

The aspartate aminotransferase (AST) alanine aminotransferase (ALT), alkaline phosphates (ALP) concentration, cardiac troponin concentrations and electrocardiographic pattern. for Iraqi lambs are illustrated in the Table 1,2,3,4 and 5.There was no significant increase in the cardiac troponin I concentrations in all animals. The statistical analysis indicated no significantly differences ($P>0.05$), the mean value were recorded in Serum (AST) 98.34±2.52 mmol/l after 96hr and in serum (ALT) 32.11±0.13 mmol/l after 144 hr., (ALP) 30.17±5.31 mmol/l) after 96hr. and the cardiac troponin I (0.29±0.01 mmol/l. The electrocardiographic changes many arrhythmias such as sinus tachycardia, ventricular premature contraction, increase in P amplitude, PR interval and T-wave inversion were recorded in the experimental sheep. Levamisole poisoning seems to cause numerous arrhythmias in sheep which might be due to the effect of Levamisole poisoning on the myocardium. pathological.

Table 1: Mean ± SE values of AST (mmol/l) in therapeutic and toxic lamb groups

	Zero time	2hr	24hr	48hr	96hr	144hr
Therapeutic group	D 56.12±1.27 a	CD 60.11±2.03 b	BC 62.11±2.75 b	A 78.52±1.22 b	A 82.21±3.38 b	B 64.22±1.45 a
Toxic group	D 58.31±1.25 a	C 64.75±1.09 a	B 89.42±2.18 a	A 94.38±3.04 a	A 98.34±2.52 a	C 67.51±1..27 a
LSD	4.35					

Table 2: Mean ± SE values of ALT (mmol/l) in therapeutic and toxic lamb groups

	Zero time	2hr	24hr	48hr	96hr	144hr
Therapeutic group	D 15.80±1.68 a	CD 16.5 ± 1.08 a	C 19.11±0.33 B	B 23.04±0.36 a	AB 25.20±1.72 b	A 28.21±0.06 b
Toxic group	D 15.67±2.11 a	D 18.12± 1.15 a	C 22.53±0.12 a	B 26.10±1.62 a	A 29.52±0.24 a	A 32.11±0.13 a
LSD	3.21					

Table 3: Mean ± SE values of ALP (mmol/l) in therapeutic and toxic lamb groups

	Zero time	2hr	24hr	48hr	96hr	144hr
Therapeutic group	CD 16.13±4.84 a	C 17.50±2.63 a	BC 20.08±2.21 b	A 24.01±2.57 b	A 26.50±1.24 B	AB 22.37±2.23 a
Toxic group	C 16.39±2.02 a	C 19.27±1.18 a	B 25.25±1.37 a	A 29.25±3.05 a	A 30.17±5.31 A	B 25.13±2.18 a
LSD	3.52					

Table 4: Mean± SE values of cardiac troponin enzyme (mmol/l) in therapeutic and toxic lamb groups

	Zero time	2 hr	24 hr	48 hr	96 hr	144 hr
G1	0.26±0.03	0.26±0.01	0.25±0.02	0.28±0.03	0.25±0.04a	0.25±0.01
G2	0.24±0.01	0.27±0.02	0.26±0.02	0.29±0.01	0.27±0.005b	0.26±0.02
LSD	0.0679					

Table 5: Abnormal morphology of P wave amplitude, PR intervals elevation and elevation, QT-prolongation and toxic lamb groups after 24,48,90.144 hrs.

Shapes		C group toxi after 24 hrs	C group toxi *48*afters	C group toxi after 90 hrs	C group toxi afrer 144 hrs
Arrhythmia	10	1	5	2	2
Tachy cardia	10	2	3	3	2
Brady cardia	10	2	4	3	1
P amplitude	10	1	5	2	2
PRinterval	10	2	6	1	1
QTinterval	10	2	2	3	3

4. Discussion

The Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) concentration, cardiac troponin concentrations and electrocardiographic pattern were ued in this study. Drug-induced liver injury is reported to be the most common reason for drug withdrawal from the [market] [11]. Clinical chemistry variables considered useful in identifying liver toxicity include ALT, ASTand ALP, [12]. Elevation in the level of ALT, AST, concentration in current research were in accordance with previous values the interpretation result from leakage from damaged tissues as a result of hepatocellular necrosis [13]. While increase in ALP level is because of overproduction and release in blood due to hepatobiliary injury and cholestasis [14]. According with previous studies except troponin I in interpretation due to toxic effects of levamisole on liver cells due to the metabolic mechanisms of the liver cells; this was supported by increased liver enzym es such as ALT, AST, and ALP. Levamisole induced a significant increase in the activities of AST, ALT, ALP concentration. The presence of macroscopic lesions and the increase in these concentrations on the kidney and liver were reliable with several studies indicating that levamizole causes damage in both kidney and liver and affects its function in dogs and humans [15]. But no significant differences in the cardiac troponin Iwas observed. The results of presented study are disagreeing with results of many researchers there is no damage in the heart muscle of lambs [15]. Due to Cardiac troponins are a marker of all heart muscle damage, other conditions that directly or indirectly lead to heart muscle damage and death can also increase troponin levels, such as renal failure [16]. The presence of macroscopic lesions and the increase in these concentrations on the kidney and liver were reliable with several studies indicating that levamizole causes damage in both kidney and liver and affects its function in dogs and humans

ECG changes

In the ECG through different mechanisms, such as metabolic imbalances, electrolyte and hypoxia these changes caused by most of the drugs [17].

Cardiac disrhythmia are heart rate disturbances, conduction or rhythm and can be classify based on rate of aerial and ventricle, anatomic origin of the impulse, the way by which impulse is formed and conduction sequence [18]. Our result is in agreement with the study of [19]. and [20]. in which sinus tachycardia and supra ventricular tachycardia due to levamisol poisoning was found. These results showed myocardial degeneration is not limited to a specific location, failure of calcium ion retrieval from the cytosol and, ultimately, myofibril hypercontraction, degeneration and necrosis occur. Therefore, highly energetic tissues of the body such as myocardium and skeletal muscle are primarily affected. It should be mentioned that changes in transmembrane ion gradients and electrical potential often produce profound effects on cellular functions and metabolism [21]. In the recent study, various types of arrhythmias occurred in experimental levamisole poisoning in sheep. Some types of these dis arrhythmia may be related to the impulse trouble formation (tachycardia, sinus tachycardia and ventricular premature contraction). These results might be due to the myocardial degeneration caused by levamisole poisoning. Increase in P wave in this study due to right atrial enlargement, cor pulmonale, (*P pulmonale* rhythm), [22]. The increase of QT duration in ECG is regarded as a main sign in shaping cardiotoxic effects of drugs [23]. This increase also pose a risk for Torsades de pointes or polymorphic ventricular tachycardia [24]. The increase of the PR duration in ECG may be mainly due to the delay of the atrioventricular node conduction as well as being associated with the delay of the atrium conduction, his, bundle branches and Purkinje fibers [25]. The Prolonged P-R duration in case of (first degree atrioventricular block) occasionally seen in normal animals Age-related degeneration of atrioventricular conduction system hypokalaemia, dilated cardiomyopathy, hyperkalaemia, heart disease, increased vagal tone and Drugs/toxins Beta-blockers Calcium channel blockers [26].

5. Conclusion

Concluded that the lambs were drenched in a dosage of 25 mg/kg body weight causes signs of poisoning and changes in the biochemical, and electrocardiographic pattern.

6. Acknowledgement

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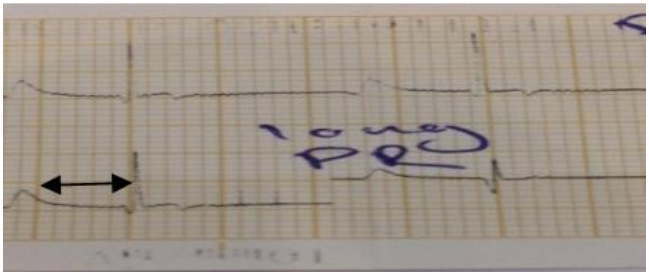

Fig 1: long duration in PR wave

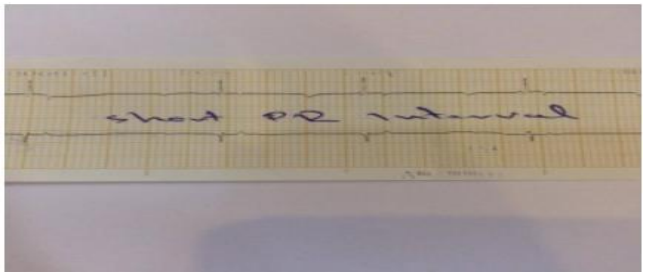

Fig 2: Illustrate short duration of PR wave

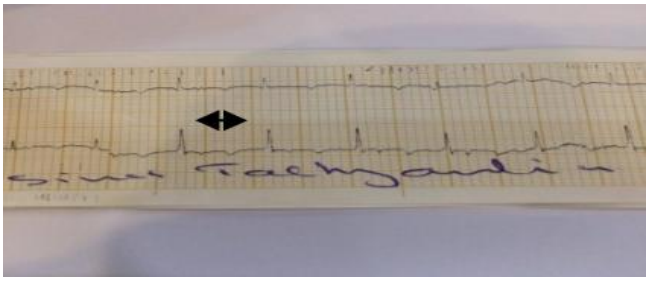

Fig 3: Illustrate sinus tachycardia

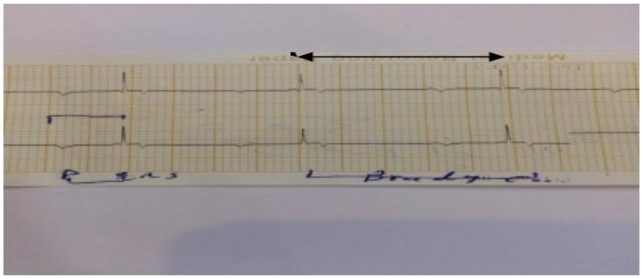

Fig 4: Illustrate bradycardia

7. References

1. Chandy ML, Cristalle S, Sreeja P, Kumar SK, Renju J. Understanding molecular mechanisms in multivariant actions oflevamisole as an anti-helminthic, anti-inflammatory, antioxidant, anti-neoplastic and immunomodulatory drug. G Model JOMSMP; 2016; 494:4.
2. Prevenier MH, Walter. From reliable sources: An introduction to historical methods Ithaca: Cornell university press. 2001; 1:77.
3. Pahor-Filho E, Castillo ASC, Pereira NL, Pilarski F, Urbinati EC. Levamisole enhances the innate immune response and prevents increased cortisol levels in stressed pacu (Piaractus mesopotamicus). Fish & Shellfish Immunology. 2017; 65:96-102.
4. Lintemoot J. Levamisole: An Unusual Finding in a Cocaine Related Forensic Toxicologists, 2005.
5. Woreta TA, Alqahtani SA. Evalua tion of Abnormal Liver Tests. Med Clin North Am 2014; 98:1-16.
6. Thrall MA, Baker DC, Campbell TW. Hematologiae Bioquímica Clínica Veterinária. São Paulo: Roca, 2007, 582.
7. Spano JS, August JR, Henderson RA, Dumas MB, Groth AH. Serum gamma-glutamyl trans- peptidase activity in healthy cats and cats with induced hepatic disease. American Journal of Veterinary Research. 1983; (11):442049-2053.
8. Dennis S. How to record and interpret ECGs and What is an ECG ? RVC Cardiology Elective Course, Royal Veterinary College, 2011.
9. Walraven G. Basic arrhythmias (7th ed.). 2011; 1-1141:9.
10. Hoffman R, Benz JEJ, Shattil SJ. Hematology: basic principles and practice, 4th edn. Churchill Livingston, Philadelphia, 2005, 768.
11. Pandit A, Sachdeva T, Bafna P. Drug-induced hepatotoxicity: A review. J Appl Pharm Sci. 2012; 02(05):233-243.
12. EMAE (European Medicines Agency); Committee for Medicinal Products for Human Use (CHMP), editor Doc. Ref. EMEA/CHMP/SWP/150115/2006. London: Jan 26, Non-clinical guideline on drug-induced hepatotoxicity, 2008.
13. Amacher DE. A toxicologist's guide to biomarkers of hepatic response. Human & experimental toxicology. 2002; 21(5):253-262.
14. Ramaiah SK. A toxicologist guide to the diagnostic interpretation of hepatic biochemical parameters. *Food* and chemical toxicology. 2007; 45(9):1551-1557.
15. Bulugahapitya DTD. Liver toxicity in a nephrotic patient treated with levamisole. Arch. Dis. Child. 1997; 76:289-291.
16. Ammann P, Pfisterer M, Fehr T, Rickli H. Raised cardiac troponins. BMJ. 2004; 328(7447):1028-1029.
17. Lionte C, Bologa C, Sorodoc L. Toxic and Drug-Induced Changesof the Electrocardiogram. In: Millis RM, editor. Advances in Electrocardiograms-Clinical Applications. Shanghai: Intech. 2012, 271-296.
18. Reef VB, McGuirk SM. Diseases of the cardiovascular system. In: Smith, BP (Ed.), Large animal internal medicine. 3rd Edn., St Louis, Mosby. 2002, 443-445.
19. Dzhurov A, Chushkov P, Juorov A. Biochemical, electrocardiographic and patho- logical studies of monensin. Vet. Med. Nauki. 1981; 18:12-21.
20. Agaoglu Z, AkgulY, Keles I, Ugras S, Aksoy A, Cinar A. Accidental salinomycin intoxication of Angora goats in Turkey. Small Rumin. Res. 2002; 45:159-161.
21. Fahim M, Del Valle G, Pressman BC. Comparison of the effects of the ionophore salinomycin and adrenaline on the haemodynamics and work efficiency of the dog heart. Cardiovasc. Res. 1986; 20:145-152.
22. Longmore, Murray. Oxford Handbook of Clinical Medicine 8th edition page 90. Oxford University Press. ISBN 2004 0-19-852558-3.
23. Braam SR, Tertoolen L, van de Stolpe A, Meyer T, Passier R, Mummery CL. Prediction of drug-induced cardiotoxicity using human embryonic stem cell-derived cardiomyocytes. Stem Cell Res. 2010; 4:107-116.
24. Namboodiri N. Bradycardia-induced torsade de pointes-an arrhythmia less understood. Indian Pacing Electrophysiol Journal. 2010; 10:435-438.
25. Aro AL, Anttonen O, Kerola T, Junttila MJ, Tikkanen JT, Rissanen HA et al. Prognostic significance of prolonged PR interval in the general population. European Heart Journal. 2014; 35:123-129.
26. Wright KN. Supraventricular tachycardia in four young dogs Journal of the American Veterinary Medicine. 1996; 208:75-80.