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List of Abbreviations

ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration time curve
AVM	Avermectins
BCG	Bromocresol green
C _{max}	The maximum plasma concentration
GABA	Gamma amino butyric acid
GGT	γ-glutamate – transferase
GOT	Glutamic – Oxaloacetic Transaminase
GPT	Glutamic – Pyruvic Transaminase
Hb	Haemoglobin
IVM	Ivermectin
LD ₅₀	Lethal dose 50
MRT	Mean residence time
No.	Number
PCV	Packed cell volume
RBCs	Red Blood Corpuscles
s.e.m	Standard error of mean
SD	Standard deviation
t _{max}	Time to reach maximum concentration
t _{1/2α}	Half life (distribution)
t _{1/2β}	Half life (terminal, elimination)
t _{1/2a}	Half life (absorption)

UV

Ultra violet

WBC

White blood cells

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Abstract

Two studies were conducted to evaluate the toxicity of ivermectin in donkeys. In the first experiment two groups of donkeys each of six animals were subjected to fasting for 48 hours as stress and then were either treated with ivermectin injection at the recommended dose i.e. 200 µg/kg (T1) or five times the recommended dose i.e. 1 mg/kg (T2) body weight for seven successive days. Animals were monitored for 15 days to evaluate any change that may occur following each treatment. Selected haematological and blood biochemical parameters were evaluated to determine any changes that may occur.

In the second experiment a group of six male donkeys was subjected to a 48 hours fasting period and then animals were treated with a single subcutaneous dose of ivermectin equal to 10 times the recommended dose once and then animals were evaluated for haematological and biochemical changes, if any.

In the first experiment, immediately following injection of the drug signs of intoxication appeared in animals in treatment group (T2), such as: animal fell down, roll in the ground with prominent tremors at the peripheral muscles approximately for 3 minutes, then the animal stood up and continued to feed and drink normally, before death animals refused to eat or drink for a whole day or more. Four animals out of six in T2 group died following treatment with five times the recommended dose at days 6, 8, 10 and day 11 following the first treatment.

At necropsy, congestion in the main visceral organs was the prominent feature in animals. Necrosis in the liver and trabeculations in the spleen, viscous yellow fluids were also observed in kidneys and pericardium. The liver was pale yellow and the kidneys were also pale with

sticky yellowish fluid inside. The pericardium contained large amount of yellowish fluid. Haematomas were observed at the injection site in all animals.

Histopathological changes were observed in all selected organs of ivermectin-treated animals viz: lungs, liver, kidneys, spleen and heart. Ivermectin was found to pose risks of renal and hepato-toxicity in donkeys, since the biochemical parameters of liver function (i.e. aspartate aminotransferase activity, alanine aminotransferase activity) and kidney function (urea concentration) were severely affected. Changes in biochemical parameters were more intense in donkeys from group T2 than those reported in group T1. Four animals out of six died following treatment in group T2. The level of ALT, AST, and urea were significantly elevated in donkeys from group T2 when compared to the pretreatment values. Post-mortem and Histopathological examination ensured biochemical alterations of liver and kidneys. Likewise, some haematological indices (i.e. erythrocyte count, leukocyte count and haemoglobin concentration and PCV) were also influenced. It is to be concluded that repeated administration of ivermectin injection formulation at five times the recommended dose is fatal.

In the second experiment, immediately following treatment animals tend to be ataxic and start to circle and within 48 hours of treatment signs of intoxication started to appear viz: inability to move, salivation, and food rejection. Two animals died in the 3rd and 13th day following treatment during such period the animal tends to be ataxic, with tremors in all muscles.

Non-significant increase in Hb concentration and PCV started immediately following fasting and treatment and continued up to the end of the experiment.

No significant ($P>0.05$) change in total proteins, albumin, triglycerides and cholesterol concentration was observed following fasting and treatment. The Increase in ALT and AST concentration started following treatment to reach significance level at the 4th day of treatment, and continued to be higher up to the end of the experiment. While only significant ($P<0.05$) increase in urea concentration was observed during the fasting period, no significant ($P>0.05$) increase in urea concentration was observed in treated animals during the whole period of the experiment.

No significant fluctuation in phosphorus concentration was observed during the course of the experiment. No significant change was observed in sodium and potassium concentration following treatment, while slight non-significant decrease was the only change during the course of the experiment.

The results of this study demonstrate that sub-acute administration of ivermectin at five times the recommended dose for seven successive days induces toxic effects on biochemical functions which correlate well with the histopathological changes in the lung, liver, kidneys, spleen and heart of donkeys. Although the data on donkeys cannot be directly applied to horses, it may be concluded that use of ivermectin may cause hazardous effects at various levels to equine species.

بسم الله الرحمن الرحيم

المستخلص

تم إجراء دراستين لتقويم سمية الأيفرمكتين في الحمير. في التجربة الأولى تم استخدام مجموعتين من الحمير كل منها مكون من ستة حيوانات. تم إخضاع الحيوانات للصيام لمدة 48 ساعة و ذلك لاحداث إجهاد ومن ثم تم حقن الإيفرمكتين اما بالجرعة الموصى بها 200 ميكروجرام/ كجم (T1) أو خمسة أضعاف الجرعة الموصى بها أي 1 مغ / كغ (T2) من وزن الجسم لمدة سبعة أيام متتالية. تم مراقبة الحيوانات لمدة 15 يوما لتقييم أي تغييرات قد تحدث عقب كل معاملة. و اجرى تقييم بعض مكونات الدم الماخوذ و القياسات الكيموحيوية في الدم وذلك لتقييم وتحديد أي تغييرات قد تحدث.

في التجربة الثانية تم استخدام مجموعة واحدة من الحمير مكونة من ستة من ذكور من الحمير ، تم تصويم الحيوانات لمدة 48 ساعة بغرض احداث الاجهاد و من ثم عولجت الحيوانات بجرعة واحدة تحت الجلد من الإيفرمكتين تعادل 10 أضعاف الجرعة الموصى بها مرة واحدة ثم اجرى تقويم لتغييرات الدم و المقياسات الكيموحيوية, ان وجدت .

في التجربة الاولى: بعد الحقن مباشرة ظهرت علامات التسمم بالدواء في الحيوانات في مجموعة العلاج (T2)، مثل: سقوط الحيوان, و تدرجه على الأرض مع ارتعاش واضح في العضلات الطرفية لفترة تقارب 3 دقائق، بعدها يقف الحيوان ثم يواصل الاكل والشرب بصورة عادية. قبل الموت رفضت الحيوانات تناول الطعام أو الشرب لمدة يوم كامل أو أكثر. أربعة حيوانات من أصل ستة في مجموعة T2 ماتت بعد المعالجة بخمسة أضعاف الجرعة الموصى بها في الأيام 6, 8, 10 و 11 عقب اعطاء اول جرعه من العلاج.

عند اجراء الصفة التشريحية كان هنالك احتقان في الأجهزة الحشوية الرئيسية السمية واضحه في الحيوانات. نخر في الكبد وترييق في الطحال ، لوحظ وجود سوائل لزجة صفراء اللون في الكلى والتأمور. لون الكبد كان مصفرا شاحبا وكانت الكلى شاحبه مع وجود السوائل اللزجة الصفراء في الداخل . لوحظت الأورام الدموية في موقع الحقن في جميع الحيوانات.

تمت ملاحظة التغيرات التشريحية المرضية في جميع الاعضاء المختارة من الحيوانات المعالجة بالإيفرمكتين وهي: الرئتين والكبد والكلى والطحال والقلب. النتائج اظهرت ان الإيفرمكتين يشكل مخاطر علي وظائف الكلي و الكبد وسمية في الحمير. حيث أن ان القياسات الكيموحيوية لوظائف الكبد (أي نشاط AST و ALT) ووظائف الكلى (تركيز اليوريا) تأثرت بشدة. وكانت التغيرات في القياسات الكيموحيوية أكثر وضوحا في الحمير من مجموعة T2 مقارنة مع تلك التي ذكرت في مجموعة T1. ماتت أربعة حيوانات من أصل ستة بعد العلاج في المجموعة T2. مستويات ALT، AST، واليوريا كانت مرتفعة بشكل ملحوظ في مجموعة من الحمير T2 بالمقارنة مع قيم المعالجة الأولية T1. عند فحص الصفة التشريحية المرضية أكدت التغيرات النسيجية الخلل الحادث في القياسات الكيموحيوية للكبد والكلى. كذلك، تأثرت أيضا بعض مؤشرات الدم (مثل عدد كرات الدم الحمراء، عدد الكريات البيض وتركيز الهيموغلوبين والحجم المتكدس لكريات الدم الحمراء). بذلك نستنتج أن الحقن المتكرر للإيفرمكتين بخمسة أضعاف الجرعة الموصى بها هو قاتل للحمير.

في التجربة الثانية: بعد حقن العلاج مباشرة للحيوانات اظهرت الحيوانات الرنح ثم بدات تدور في دوران حلقي، وخلال 48 ساعة من العلاج بدات تظهر علامات التسمم وهي: عدم القدرة على التحرك، سيلان اللعاب، ورفض الطعام. مات اثنان من الحيوانات في اليوم الثالث و الثالث عشر بعد إعطائها العلاج أثناء تلك الفترة تكون الحيوان مترنحه، مع ارتعاش في جميع العضلات.

كانت هنالك زيادة غير معنوية في تركيز الهيموجلوبين والحجم المتكدس لكريات الدم الحمراء بدأت مباشرة بعد الصيام واعطاء العلاج واستمرت حتى نهاية التجربة. لم يلاحظ أي تغيير معنوي في إجمالي تركيز كلاً من البروتينات والايومين والدهون الثلاثية والكوليسترول بعد الصيام والعلاج، بدأت الزيادة في تركيز ALT AST بعد إعطائها العلاج لتصل إلى مستوى معنوي في اليوم الرابع من العلاج واستمر لتكون أعلى حتى نهاية التجربة، في حين لوحظت زيادة في تركيز اليوريا خلال فترة الصيام، لوحظت زياده لامعنويه كبيره في تركيز اليوريا في الحيوانات المعالجة طوال فترة التجربة.

وقد لوحظت زياده غير واضحه مع حدوث تذبذب كبير في تركيز الفسفور أثناء التجربة . لم يلاحظ أي تغيير كبير في تركيز الصوديوم والبوتاسيوم بعد إعطاء العلاج، في حين كان الانخفاض الطفيف غير الواضح هو التغيير الملاحظ فقط أثناء التجربة.

نتائج هذه الدراسة تثبت أن الاعطاء المتكرر للإيفرمكتين في خمسة أضعاف الجرعة الموصى بها لمدة سبعة أيام متتالية يؤدي الي آثار سامة على الوظائف الكيموحيوية التي تتطابق جيدا مع التغيرات التشريحية المرضية في الرئة، الكبد، الكلى، الطحال والقلب في الحمير .على الرغم من أن المعلومات في الحمير يتعذر تطبيقها مباشرة على الخيول، يستنتج أن استخدام آلايفرمكتين قد يسبب آثارا خطيرة على كافة المستويات لأنواع الخيول.