دراسة الاثار الباثولوجية لبعض مبيدات القوارض

الجـزء الأول

عن مبيد القوارض المـانع لتجلط الدم « راكومين ٥٧ »

ع . هـ . عمر ، ط . ى . هلال ، م .ص.عرفه ، ع . م . سليـط ، ع . م . على

الملخص

عرضت الفئران والجرذان المنزلية والمشاركة للجرعات القاتلة وتحت القاتلة للراكومين«٥٧»لمعرفة التغيرات الباثولوجية فى أنسجتها . وقـد أظهـرت النتائج أن سبب الموت فى حالة التركيزات القاتلة يرجع أسـاسا الى حالة عـدم توارد الدم المحمـل بالاكسجين الى المخ وكذلك الكليتين مما يؤدى لحالة تسمم بولينا فى الدم ويرجع ذلك لحدوث نزيف خارجى وداخلى وخاصة بالرئتين مما يوحى بحساسية الرئتين على وجه الخصوص لهذا السـم – ويدعم هـذا الاستنتاج ما حدث من نزيف وثوى نتيجة لاعطاء تلك الحيوانات جرعات تحت قاتلة بينمـا كان النزيف ضئلا فى الاحشاء الاخرى وقد القت هذه الدراسة الضـوء على أثر هذا المركب بما يفيـد فى مجالات الطب الوقائى والشرعى والعلاجى .

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ON THE PATHOLOGIC EFFECTS OF SOME RODENTICIDES

PART I

THE ANTICOAGULANT RACUMIN$_{57}$

(With 5 Figures)

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(Received 12/3/1975)

SUMMARY

Animals which died from lethal dose of Racumin$_{57}$ showed wide spread external, internal and interstitial haemorrhages, which were extensive in the lungs. Secondary to the servere haemorrhages, the majority of organs suffered from the effect of ischaemia. The severity of pulmonary haemorrhages points out to a selective susceptibility of pulmonary blood vessels to the injurious effect of excess Racumin$_{57}$. This finding may be supplemented by the occur rence of pulmonary haemorrhages in case of the sublethal dose of Racumin$_{57}$, although haemorrhage at other sites of the same animals was relatively scanty.

INTRODUCTION

The main aim of this study was to explore the anatomical changes that may occur in animal tissues as an effect of some slow and quick acting rodenticides, and to correlate them with the cause or causes of death. The importance of such observations regarding human being is derived from three points. First, man may be accidentally exposed to the effect of rodenticides. The second point is that the observations may help workers of toxicology, preventive medicine and hygeine, especially in the field of rodent control. Thirdly, similar adverse effects may take place in patients receiving overdosage or long course of anticoagulants of same group.

MATERIAL AND METHODS

The study was done on 150 rats and mice of different species of domestic, commensal and field rodents (*Rattua norvegicus,* (B.) *R.r. alexandrinus* (G).

R.r. Frugivorus (H.), *Arvicanthis niloticus* (D.), and *Acomys cahirinus* (G.H.). The ratio between males and females was 1 : 1 and 10 % of the females were pregnant. Five animals of each species were used as a control.

Three different types of rodenticides were utilized. These were Racumin$_{57}$ (Coumateralyl), Crimidine (castrix), and Zinc phosphide. Racumin$_{57}$, is 3-(a-tetralyl) - 4 - hydroxycoumarin. It is an accumulative anticoagulant. Crimidine is an organic quick acting rodenticide. It is 2-chloro-4-dimethylamino-6-methyl pyrimidine. Zinc phosphide is an inorganic quick acting poison ($Zn_3 P_3$).

The dosage of each rodenticide was estimated as mg/kg body weight of the active ingredient. Lethal and sublethal doses of Rucumin$_{57}$ and Crimidine, and lethal doses of Zinc phosphide were prepared. The dose of Racumin^{57} was divided into 5 equal portions and given to the animals over 5 successive days with the minimal daily requirement of the diet. The latter consisted of crushed sorghum, 2 % sucrose and a sufficient amount of vegetable oil. While crimidine and Zinc phosphide were offered to animals as a single dose with the same diet.

The animals were divided into 3 batches, 60 animals for Racumin$_{57}$ (35 for lethal and 25 for sublethal doses), 50 for Crimidine (25 for lethal and 25 for sublethal doses) and 15 animals for lethal dose of Zinc phosphide.

The animals were put under observation for any abnormal signs. The control animals and those treated with the sublethal doses were killed at variable intervals by ether. One or two animals of the latter were sacrificed every 24 hours to detect any pathologic changes in various organs.

Postmortem study included external and internal examination of the brain, heart, lungs, liver, spleen, kidneys, and intestine of all test animals. Autopsy specimens were then obtained, from each organ. These were used to prepare haematoxylin & eosin sections which were fully examined by light microscopy.

RESULTS

I. *Effect of Lethal Dose of Recumin$_{57}$*

Signs before death :

On the first day, the animals were careless, and consumed more food than usual. On the 2nd day, bleeding occured from the nose and haematomas developed in the legs and tail of animals. On the 3rd day, they showed

decreased activity and inability to walk especially by the hind legs. At the same day, the pregnant females showed vaginal and rectal bleeding with often abortion. On the 3rd and 4th days, swellings were observed on the dorsum of the head, the front of the chest and on the fore feet of animals. Conjunctival ecchymosis was noticed in majority of animals on the 4th day. On the 5th and 6th days, the smell of animals, became offensive and they finally got collapsed and died.

Post-mortem examination :

External examination revealed a curved contracted appearance of dead animals with the tail ventrally reflexed reaching close to the nose, Subcutaneous haematomas were observed at the dorsum and lateral surfaces of the head and front of the chest. Large haematomas were found inbetween the muscles of legs (Fig. 1).

Internal examination showed large amount of unclotted blood in the abdominal cavity. Grossly, the lungs were the seat of patchy haemorrhages. Areas of haemorrhage were round, oval or irregular in shape, 1-15 mm in diameter reddish brown in colour and soft friable in consistency (Fig. 2). Microscopically, they were found to involve the alveoli ,bronchi and interstitial tissue of lungs. The alveoli and bronchi were almost stuffed by the red cells. In some sections, the alveoli and bronchial tissues were partially destroyed and replaced by the blood elements. The areas of haemorrhage appeared consolidated and greatly mimicing the picture of the lung with the red hepatization stage of lobar pneumonia (Fig. 3).

The heart showed no gross abnormality and histologically, there was only cloudy swelling. The liver was slightly enlarged and pale with a mild yellowish tinge and patchy areas of dark colouration. Histologically, it had the picture of cloudy swelling, focal fatty change and venous congestion. The spleen presented a mild degree of pallor with multiple patchy areas of venous congestion.

The kidneyes were slightly enlarged, greyish white in colour and soft in consistency with the capsule easily stripped off. The cut surface showed little bulging, marked pallor and soft consistency. Microscopically, the glomeruli appeared bloodless, the convoluted tubules had cloudy swelling. The number of demonstrable blood vessels was scanty in the field, as compared with that of normal control kidney. The intestine was grossly and histologically normal.

No intracranial haemorrhage was found and the brain showed marked pallor and diminished vascularity. Histologically, both the meningeal and deep blood vessels were less encountered than in the normal control brain.

II. *Effect of the Sublethal Dose of Racumin$_{57}$*

Signs before sacrifice :

Mild bleeding from the nose, mouth and ears and diminished activity of the animals were noticed on the first three days, then the animals recovered on the subsequent days. Recovery was more rapid among female animals, particularly those of middle age.

Post-Mortem Examination :

After 24 hours, the lungs showed few minute areas of haemorrhage (Fig. 4). These gradually became larger and after 72 hours the picture approarhed that of the lethal dose of Racumin$_{57}$ (Fig. 5). The kidneys after 72 hours were pale and swollen. Histopathologically there was the picttre of cloudy swelling with decreased vascularity. The brain revealed the picture of pallor and decreased vascularity. The other organs showed no significant pathologic changes.

DISCUSSION

The lethal dose of Racumin$_{57}$ resulted in abundant external, internal and interstitial haemorrhages. The latter were most severe in the lungs, a matter which reflects high and selective sensitivity of pulmonary blood vessels probaly to Racumin$_{57}$. Moreover, the severity of hacmorrhage was marked in the Norway and grey-bellied rats and spiny mouse and less in the white bellied and grass rats. This observation points out the variable sensitivity of various rodent species to over-effects of anticoagulants. Toxicologic studies on the susceptibility of Egyptian rodents to the same rodenticide done by SALIT et al (Under publication) agree with our histopathologic findings.

The other organs revealed the pathologic picture of ischaemia that was greatly illustrated in the kidney and brain in the form of oustanding pallor and decreased, vascularity. The ischaemic status of most organs could be secondary to the widespreod haemorrhages and to the haemolytic tenedency of blood. The latter has been proved by a haematologic study carried out by HELAL et al. (Under publication).

It may be concluded that the lethal effect of Racumin$_{57}$ occurs through a rapid decrease in blood volume secondary to massive haemorrhage, with the final development of renal and cerebral ischaemia. The degree of participation of renal and cerebral ischaemia, however, in killing the animals is open for discussion and needs further investigations. HERMANN and HOMBRECHER (1962) reported that Racumin$_{57}$ caused uraemia by blocking the renal tubules with blood. The role of cerebral ischaemia was not, however, mentioned in their report.

The absence of intracranial of haemorrhage in animals killed by Racumin^{57} stands in contradistinction with what reported in the human medical literature about the occurrence of intracranial haemorrhage in man as a complication of anticoagulant therapy (MOORMANN, 1969). This contrast appears to be the result of species variation. Several case reports on haemorrhage occuring in man in association with anticoagulant therapy have been described in the literature (LEYMERIOS, 1967; HAMAKER et al., 1969; MOORMANN, 1969 and MARKLE, 1970). However, complete exploration of the histopathologic effect of anticoagulants in man was not noticed in the available literature.

The effect of sublethal dose of Racumin$_{57}$ approached qualitatively that of the lethal dose, but quantitatively it was far less severe. Haemorrhage was only siginficant in the lungs indicating a selective senistivity and involvement.

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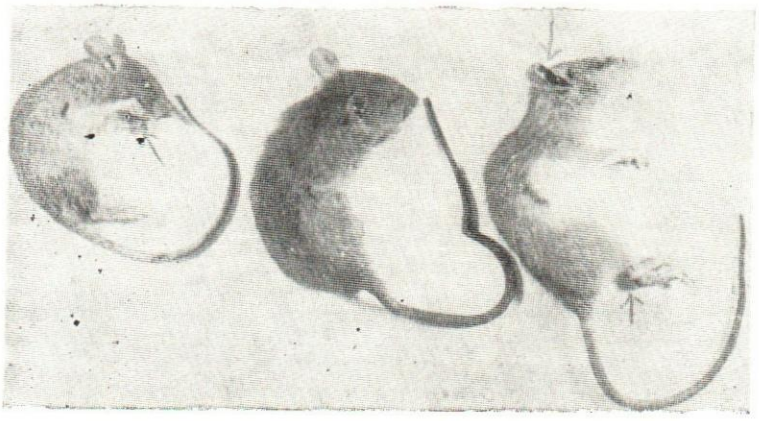

Fig. 1.—Three rats kiled by Racumin$_{57}$ showing bleeding from the nose, ears, eyes, and legs.

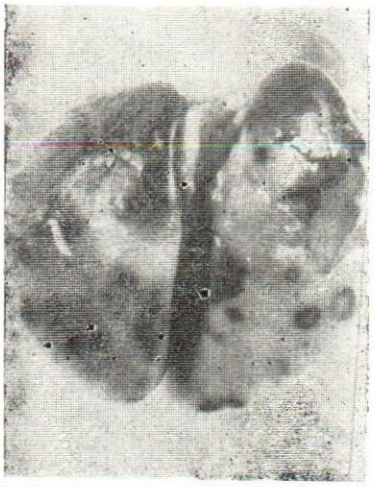

Fig. 2.—Lungs of a rat killed by Racumin$_{57}$ showing multiple large areas of haemorrhage.

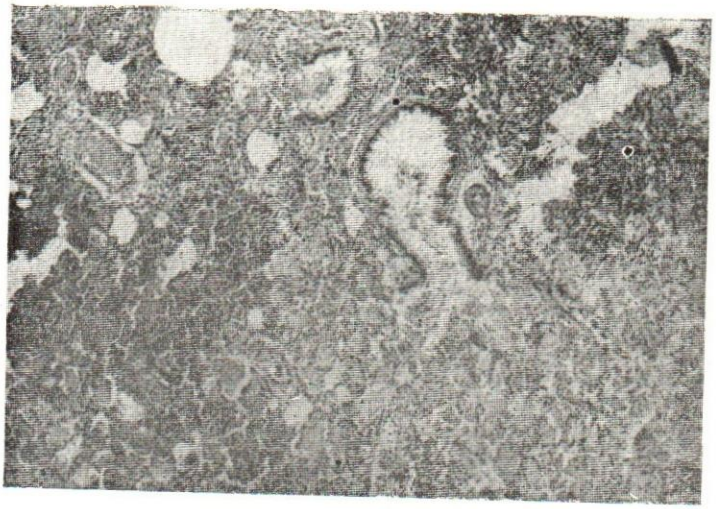

Fig. 3.—Histologic picture of the lungs shown in Fig. 2. Consolidation of pulmonary tissue is noted (H. and E. × 80).

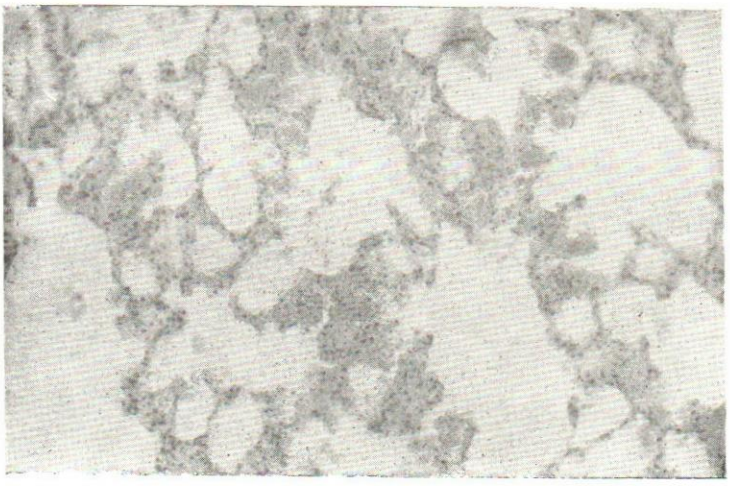

Fig. 4.—Interstitial pulmonary haemorrhage in a rat, 24 hours after giving sublethal dose of Racumin$_{57}$. (H. and E. × 80).

Fig. 5.—The haemorrhage increased in severity after 72 hours (H. and E. × 80).