EFFECT OF INTERVALS BETWEEN DOSES OF POTASSIUM BICHROMATE ON THE STATE OF THE RENAL PARENCHYMA AND MORTALITY IN ALBINO MICE

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The state of the tubular apparatus of the kidney was studied in 360 albino mice receiving frequent subcutaneous injections of potassium bicromate at intervals of 1 day, 1 week, or 1 month. More frequent administration of the toxic agent was shown to give rise to a lower mortality among the animals and to have a milder toxic action on the tubular apparatus.

KEY WORDS: rhythm of action; mortality; renal parenchyma; potassium bichromate.

Carbon tetrachloride and furfural have been shown to have a weaker toxic action on the liver in animals and to cause their death less frequently if administered at shorter intervals [4, 5]. Every chemical substance can evidently influence the adaptive systems of the body which to some degree or other become tuned to its rhythm of action. Chromium and its compounds can enter the human and animal body by various ways. They are removed mainly through the kidney, which may thereby suffer a varied degree of damage [1-3, 6].

The object of this investigation was to study the relationship between the rhythm of the reparative response of kidney tissue and the mortality of the animals and the frequency of administration of potassium bichromate.

EXPERIMENTAL METHOD

Experiments were carried out on 360 noninbred albino mice (males and females) weighing 20-25 g. The animals were divided into three series: series I) 70 mice which received 10 injections of potassium bichromate at intervals of 1 day between injections; series II) 70 mice which received 10 injections at intervals of 1 week; and series III) 50 mice which received 10 injections at intervals of 1 month. The potassium bichromate was injected subcutaneously in a dose of 30 mg/kg. The course of the destructive and reparative processes in the renal parenchyma in the course of the experiment was monitored by studying the kidneys in series I on the second day and in series II on the second, fourth, and seventh days after a routine injection. Two mice were used at each time of the investigation. The kidneys of the animals were examined 1 and 3 days, 1 and 2 weeks, and 1 and 2 months after the last dose of bichromate had been given. Changes in the renal epithelium after a single injection of bichromate were studied in 25 mice; five mice kept under the same conditions as the experimental animals acted as the control. During the experiment and for 2 months after the last injection of potassium bicromate, the number of animals dying was recorded in all series and the kidneys of the dying animals were investigated histologically. Material was fixed in 10% neutral formalin and embedded in paraffin wax. Sections 4-6 μ in thickness were stained with hematoxylin–eosin, by Van Gieson's method, and, when necessary, by Kossa's reaction for lime. The experiments of series I and II were repeated twice.

EXPERIMENTAL RESULTS

A single injection of potassium bichromate led to death of 7.1% of the animals on the fourth, fifth, and seventh days. Extensive areas of necrotic tubules, mainly in the outer two-thirds of the cortex, were observed

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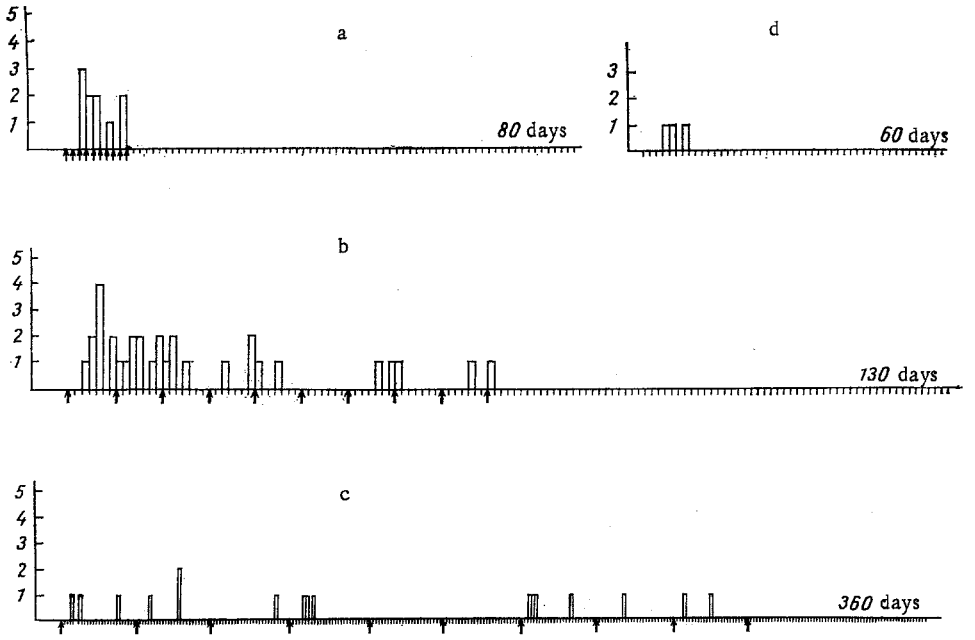

Fig. 1. Mortality among mice after injections of potassium bichromate: a) series I; b) series II; c) series III; d) single injection of bichromate. Abscissa, times of experiment (in days); ordinate, number of mice dying. Arrows indicate injection of poison. Scale in series I and II, 1 day = 5 mm; in series III, 1 day = 2 mm.

in the mice which died. In animals killed 24 h after injection of potassium bichromate, vacuolar degeneration of the proximal tubules lying beneath the kidney capsule was observed, and in animals killed after 3 days the lumen of many tubules in the cortex was dilated, the epithelium was vacuolated, and the lumen of the tubules contained hyaline casts. The changes described were located chiefly in the outer two-thirds of the renal cortex. The structure of the renal tubules was back to normal 7 days after a single injection of bichromate and it still remained normal 2 weeks and 1 and 2 months later.

In the animals of series I death occurred after not less than three or four injections of bichromate (Fig. 1). The overall mortality in this series was 15.2%. Although none of the mice died after two injections, maximal destruction of the epithelium of the proximal tubules was observed after the second injection of bichromate, and later (third, fourth, fifth, and sixth injections) the external appearance of the renal epithelium differed only slightly from the control. After seven, eight, and nine injections the structure of the renal tubules of some animals showed changes. Some of the tubules became irregularly dilated and the epithelium lining them was flat. In other mice no such hydronephrosis was observed at these times and the predominant change was vacuolar degeneration of the epithelium, chiefly of the proximal tubules. The epithelium of the tubules lying beneath the capsule of the kidney 1-3 days after the tenth injection of bichromate consisted of vacuolated cells, the proximal and distal portions of the convoluted tubules were difficult to distinguish, and the lumen of many tubules was dilated. One week after the tenth injection of bichromate proliferation of the epithelium of the proximal tubules was observed and the number of mitoses was increased. No destruction in the renal epithelium of the experimental animals could be found 2 weeks and 1 and 2 months after the tenth injection. Features of edema of the stroma predominated in mice dying after seven, eight, and nine injections of bichromate, accompanied by proliferation of the epithelium in nearly all parts of the nephron.

In the mice of series II the highest mortality was observed after one and two injections of potassium bichromate (Fig. 1). Later the mortality fell appreciably although individual animals still contined to die in the course of the experiment. The over-all mortality in this series was 27.5%. Well-marked manifestations of vacuolar degeneration, amounting in some cases to necrosis, together with perivascular edema were seen 2 days after the second injection of bichromate in the epithelium of the proximal and of some distal tubules. By the seventh day of observation the number of binuclear cells in the epithelium of the convoluted tubules was increased and papillary outgrowths of epithelium appeared in the lumen of the tubules. Similar changes were observed in animals receiving three injections of potassium bichromate. Infrequent deposits of potassium salts at the site of dying cells of the proximal tubules and focal hydronephrosis of the kidney cortex also were

observed in these animals. Changes of this sort also were present after four, five, six, seven, and eight injections. From 1 to 3 days after the tenth injection of bichromate, against the background of moderately severe hydronephrosis, in the renal epithelium of the animals of series II, islands consisting of several proximal tubules lined with cubical epithelium were seen. Foci of infiltration with histiocytes lay among the tubules in the outer part of the cortex. Proliferation of epithelium in some tubules led to the appearance of papillary outgrowths and in others to the formation of syncytial structures, crossing the lumen of the tubule, and in a third group, to complete occlusion of the lumen. Seven days after the tenth injection the manifestations of hydronephrosis were less severe, numerous "cell ghosts" could be seen in the lumen of the tubules, and deposits of calcium were present. The hydronephrosis was still present after 2 weeks and 1 and 2 months, the foci of histiocytic infiltration had the appearance of bands in the cortex, and deposits of calcium were present. In the animals of this series which died after one, two, three, four, and five injections extensive areas of necrosis were found in the epithelium of the proximal and distal tubules, together with edema and congestion of the kidney and the presence of numerous cellular and hyaline casts. In the animals which died after nine and ten injections of bichromate the predominant changes were edema and a syncytial appearance of the tubular epithelium.

The animals of series III, which received potassium bichromate at intervals of 1 month, died 5, 8, 17, 24, and 25 days after its injection. The overall mortality in this series was 30%. Histological changes in the kidneys were similar to those observed in the mice of series II.

The fact observed in the experiments with furfural [5, etc.], namely that the more frequent action of a pathogenic factor gives rise to a lower mortality among animals and produces relatively less severe destruction of the renal parenchyma, was confirmed by the present experiments. The organism tuned itself to the rhythm of action of the potassium bichromate and the course of the destructive and reparative processes in the renal epithelium corresponded to that rhythm; the animals died at different times in the different series. The appearance of massive zones of infiltration with lymphocytes and histiocytes in the renal tissue of the mice in series II and III suggests that in the case of the more infrequent action of a pathogenic factor immune mechanisms participate in the response of the organ.

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