

EFFECT OF 6-MERCAPTOPURINE ON SECRETORY  
FUNCTION OF THE KIDNEYS

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Prolonged administration of 6-mercaptopurine to dogs (2, 3.5, and 5-6 mg/kg) and rabbits (5 mg/kg) caused marked inhibition of tubular secretion estimated by excretion of diodone.

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Secretory processes taking place in the cells of the tubular epithelium and associated with definite expenditure of energy are an important aspect of kidney activity [2, 3]. It may therefore be expected that substances modifying cell metabolism may have some influences on tubular secretion. It has been shown, in particular, that 6-mercaptopurine actively influences purine metabolism and disturbs the synthesis of nucleic acids performing the many different functions of the living cell.

The effect of 6-mercaptopurine on tubular secretion was studied in this investigation.

## EXPERIMENTAL METHOD

Experiments were carried out on 6 dogs weighing 7-15 kg with ureters exteriorized by the Pavlov-Tsitovich method and on 7 rabbits weighing 2.6-3.6 kg. During the experiment the dogs were kept on Pavlov stands. The experiments on rabbits were carried out on special "hammock" stands; urine was collected by chronic catheterization of the urinary bladder. To maintain the diuresis at an adequate level, warm water was administered rectally to the rabbits every 30 min in a dose of 2 mg/kg body weight.

6-Mercaptopurine was given by mouth daily for 10 days in doses of 2, 3.5, and 5-6 mg/kg for dogs and 5 mg/kg for rabbits. The investigations were carried out before the beginning of administration of the compound (3-4 times), in the middle of the course, and on the 1st, 3rd, 7th, and 14th day after its end. Altogether 92 experiments were carried out.

The secretory function of the kidneys was estimated by determining the excretion of diodone after a single intravenous injection of this substance in a dose of 0.3-0.4 g/kg for dogs and 0.9-1 g/kg for rabbits. As preliminary experiments showed, these doses ensure maximal saturation of the secretory power of the tubules in the first 20-30 min after its injection. Diodone was estimated by the method of White and Rolfe as modified by Bak and co-workers [1] during the first 30 min and over a total period of 2 h, during which on the average 75-85% of the injected dose of diodone was excreted.

The glomerular filtration relative to endogenous creatinine was also determined at the same times. To obtain some idea of the general response of the animal to administration of 6-mercaptopurine, in some of the experiments the total plasma protein concentration (refractometrically), the erythrocyte and leukocyte counts in the circulating blood, and the body weight of the animals were determined.

## EXPERIMENTAL RESULTS

Table 1 shows that 6-mercaptopurine in a dose of 2 mg/kg caused no regular changes in the secretory function of the kidneys, but in a dose of 3.5 and, in particular, of 5-6 mg/kg, it has a marked inhibitory effect. This inhibition was most marked on the 7th day after the end of administration of the compound, both during the first 30 min and during a period of 2 h after injection of diodone. No direct relationship was found between the observed effects of 6-mercaptopurine on tubular secretion and the changes in diuresis and glomerular filtration. Even when the compound was given in a dose of 5-6 mg/kg,

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TABLE 1. Effect of Prolonged Administration of 6-Mercaptopurine on Excretion (in %) of Diodone in Dogs (M±m)

Dose of compound (in mg/kg)	Time after administration of compound	Control values	First week after end of course	P
2	30 min 2 h	38,4±1,02 82,6±1,66	37,4±1,99 83,2±2,95	>0,5 >0,5
3,5	30 min 2 h	39,2±1,49 79,5±1,98	30,8±3,05 73,0±3,69	<0,05 >0,05
5-6	30 min 2 h	37,1±0,88 82,7±1,60	17,4±6,62 51,1±12,19	<0,02 <0,05

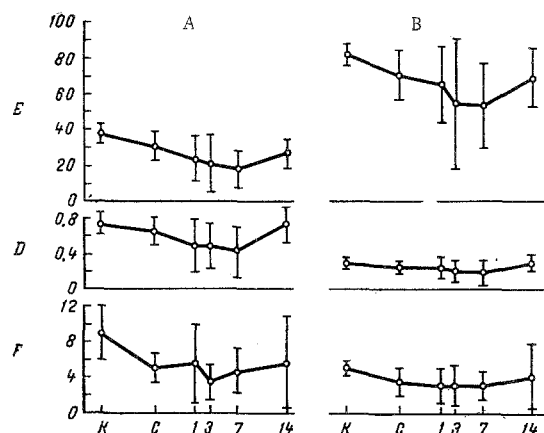


Fig. 1. Effect of prolonged administration of 6-mercaptopurine (5 mg/kg) on some indices of kidney function in rabbits during the first 30 min (A) and 2 h (B) after injection of diodone. E) Excretion of diodone, in percent; D) diuresis (ml/min); F) glomerular filtration (in ml/min); K) mean of control values; C) investigation in middle of course of administration; 1, 3, 7, and 14) days after end of administration of 6-mercaptopurine. Vertical lines indicate confidence limits.

by the results of determination of the erythrocyte and leukocyte counts in the circulating blood and the body weight of the rabbits. The possibility likewise is not ruled out that a decrease in the renal blood flow may also be of some significance in the rabbits, evidence of this being given by the reduction in glomerular filtration.

#### LITERATURE CITED

1. B. Bak, C. Brun, and F. Roaschon, *Am. J. Physiol.*, **151**, 621 (1947).
2. K. H. Beyer, R. H. Painter, and V. D. Wiebelhaus, *Am. J. Physiol.*, **161**, 259 (1950).
3. H. W. Smith, *The Kidney—Structure and Function in Health and Disease*, New York (1951).

producing the most marked inhibition of secretion, no significant changes in diuresis and filtration were observed.

Administration of 6-mercaptopurine to dogs in doses of 2 and 3.5 mg/kg, especially the latter, considerably lowered the leukocyte count (by more than 50%) but caused no significant change in the erythrocyte count. Under these circumstances the plasma protein concentration and body weight showed no significant change. In a dose of 5-6 mg/kg, 6-mercaptopurine caused death of the dogs (Kashtanka died on the 10th day and Aza on the 16th after the end of administration of the compound).

The results of the experiments on rabbits showed that 6-mercaptopurine causes a marked decrease in the secretory function of the kidneys greatest on the 7th day after discontinuing administration, both during the first 30 min and a period of 2 h after injection of diodone (Fig. 1). At the same time a decrease in diuresis and in the glomerular filtration was observed, most marked in the period of maximal saturation of the secretory power of the tubules (the change in diuresis during 2 h of observation was not significant).

Blood analyses revealed depression of erythropoiesis, likewise more marked on the 7th day after the end of administration (by 38%), while the leukocyte count was also reduced (by 55.2%) at this time, although the total plasma protein concentration was unchanged. At the time of maximal decrease in secretory function of the kidneys, the body weight of the rabbits was reduced (by 14.5%).

Considering the inhibitory effect of 6-mercaptopurine on protein biosynthesis, it can be assumed that the inhibition of tubular secretion produced by this compound is connected with changes in cell metabolism. This is confirmed