

# EFFECT OF DEGRANOL AND THIOPHOSPHAMIDE ON THE REDISTRIBUTION OF WATER IN RATS

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A single dose of thiophosphamide (9 mg/kg) and of degranol (80 mg/kg) causes no significant changes in the distribution of water in rats on subsequent days, although the diuresis and salt excretion are increased. Administration of degranol as a series of small doses (2 mg/kg on alternate days for 5 doses) was followed by water retention due mainly to an increase in the intracellular space. Under these conditions the diuresis and electrolyte excretion were undisturbed.

Data in the literature indicate that the development of malignant neoplasms is accompanied by significant changes in water and electrolyte metabolism (see the survey in [2]). It was therefore decided to investigate the effect of cytostatic compounds on renal functions and the water and electrolyte balance, in order to obtain more complete information of the possible side effects of these compounds.

The object of the investigation described below was to study the effect of representatives of the chloroethylamines (degranol) and ethylenimines (thiophosphamide) on the distribution of water in rats and to compare these effects with the renal excretion of water and of the principal electrolytes.

## EXPERIMENTAL METHOD

Experiments were carried out on 106 albino rats weighing 170-230 g, in 56 of which the water spaces were determined, and in 50 the 24-hourly water consumption, diuresis, and excretion of sodium and potassium. Determination of the total water (by the antipyrin method) and subsequent calculation of the volume of the intracellular fluid were carried out by the method of Ivanov and Pakhmurnyi [1] on the after administration of the single dose or the last of a series of small doses of the compound. The results were

TABLE 1. Effect of Degranol (80 mg/kg) and Thiophosphamide (10 mg/kg) on 24-Hourly Water Balance and Excretion of Electrolytes in Rats ( $M \pm m$ )

Compound and mode of administration	Nature of experiment	Water intake (in ml)	Diuresis (in ml)	Na excretion (in $\mu$ eq)	K excretion (in $\mu$ eq)
Degranol single dose	Control	18,0 $\pm$ 0,60	2,8 $\pm$ 0,26	6,6 $\pm$ 0,50	581 $\pm$ 44,2
	Experiment	10,0 $\pm$ 1,70	5,2 $\pm$ 0,89	25,5 $\pm$ 7,59	925 $\pm$ 100,0
	P	<0,01	<0,05	<0,05	<0,01
	Control	17,0 $\pm$ 0,60	3,0 $\pm$ 0,40	5,4 $\pm$ 0,60	469 $\pm$ 15,0
over a period	Experiment	15,5 $\pm$ 0,86	3,1 $\pm$ 0,64	4,7 $\pm$ 0,49	413 $\pm$ 38,4
	P	>0,1	>0,5	>0,2	>0,2
	Control	16,6 $\pm$ 0,67	2,0 $\pm$ 0,29	4,0 $\pm$ 0,47	297 $\pm$ 31,6
	Experiment	12,0 $\pm$ 0,56	2,3 $\pm$ 0,20	11,0 $\pm$ 0,15	443 $\pm$ 45,2
Thiophosphamide single dose	P	<0,001	>0,2	<0,001	<0,02
	Control	15,8 $\pm$ 0,74	2,2 $\pm$ 0,24	5,5 $\pm$ 0,57	313 $\pm$ 37,8
	Experiment	13,5 $\pm$ 0,53	1,6 $\pm$ 0,18	23,8 $\pm$ 3,77	324 $\pm$ 46,7
	P	<0,05	>0,05	<0,001	>0,5

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TABLE 2. Effect of Degranol (80 mg/kg) and Thiophosphamide (10 mg/kg) on Distribution of Water (in ml) in Rats ( $M \pm m$ )

Compound and mode of administration	No. of rats	Water		
		total	extracellular	intracellular
Control	11	61,2 $\pm$ 1,61	20,0 $\pm$ 0,26	41,1 $\pm$ 1,50
Degranol				
single dose	12	60,3 $\pm$ 1,27	20,9 $\pm$ 0,57	39,0 $\pm$ 0,99
<i>P</i>		< 0,05	> 0,05	> 0,05
over a period	12	72,5 $\pm$ 1,03	23,0 $\pm$ 1,41	48,5 $\pm$ 1,97
<i>P</i>		< 0,001	< 0,05	< 0,01
Thiophosphamide				
single dose	10	63,9 $\pm$ 1,41	20,5 $\pm$ 0,92	43,4 $\pm$ 1,60
<i>P</i>		> 0,5	> 0,5	> 0,5
over a period	11	58,0 $\pm$ 1,62	20,9 $\pm$ 0,57	36,4 $\pm$ 1,62
<i>P</i>		> 0,05	> 0,05	> 0,05

compared with those obtained by determination of the water spaces in a group of intact rats kept under identical conditions. The Na and K concentrations in the urine were determined by flame photometry. The rats were kept on a constant ration of food and water in metabolism cages.

Degranol was injected intraperitoneally as a single dose of 80 mg/kg or as a series of doses of 20 mg/kg on alternate days. Thiophosphamide was also given intraperitoneally as a single dose of 9 mg/kg or as 5 daily doses of 2 mg/kg each.

#### EXPERIMENTAL RESULTS

The results given in Table 1 show that administration of a single dose of the compound caused a marked increase in the excretion of electrolytes on the following day, and degranol also increased the diuresis. The water intake was reduced. Meanwhile, the water content in the body and the distribution between the individual sectors were unchanged after administration of both compounds as a single dose (Table 2). Comparison of these results suggests that the extrarenal losses of water were slightly reduced in the rats.

A different picture was seen after administration of the compound as a series of small doses. Whereas thiophosphamide caused no significant changes in the total and extracellular water and slightly reduced the content of intracellular fluid (Table 2), degranol caused a definite increase in the water content in the body on account of an increase in the extracellular and, in particular, of the intracellular water. Since this retention of water was not accompanied by changes in the water intake or elimination in the urine, it can be postulated that it took place, first, on account of extrarenal losses of fluid and second, that it was associated with a decrease in the quantity of adipose tissue in the animals, leading to an increase in the relative content of water in the body.

To sum up, administration of the compounds as a series of small doses had a more marked effect on the content and distribution of water in the body than their administration as a single dose, and degranol gave rise to more marked changes than thiophosphamide.

#### LITERATURE CITED

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