DIURETIC ACTION OF POLYETHYLENE GLYCOLS

Yu. V. Natochin and E. I. Shakhmatova

UDC 615.254.1:547.422.22

Polyethylene glycols, if injected intraveneously, have a well-marked diuretic effect, and if given in large doses, they also stimulate sodium excretion, by depressing sodium reabsorption in the proximal tubule.

Intravenous injection of hypertonic solutions of osmotic diuretics (mannitol, sucrose, etc. for example) leads to a marked increase in diuresis. Since these substances must be given with a large volume of water, it is interesting to discover whether anhydrous liquid polymers, which can be injected intravenously, can also be used as diuretics.

The object of the present investigation was to study the effect of polyethylene glycols (PEG) with a molecular weight of 200, 300, and 400 on the kidney.

EXPERIMENTAL

Experiments were carried out on 42 female albino rats weighing about 200 g, anesthetized with a nembutal-chloralose mixture (2.3 and 1.3 mg/100 g body weight, respectively). To collect urine, a fistula was made into the urinary bladder, and connected by means of a rubber tube to a micropipet. The test compounds* were injected into the femoral vein. Injection of PEG-400 in doses of up to 0.2 ml/100 g body weight was given over a period of 3 min, and injections of larger doses were given continuously by means of an automatic doser at the rate of 0.028 ml/min so as not to produce rapid changes in the composition of the blood.

The Na concentration in the blood serum and urine was determined by means of a Zeiss-III flame photometer; creatinine was determined by the method of Bonsnes and Taussky [2] with an SF-4a spectrophotometer. A statistical analysis of the results was carried out by comparing sets with paired variables: changes in renal function due to injection of the compound were compared with the initial values of the same animal [1].

EXPERIMENTAL RESULTS AND DISCUSSION

After intravenous injection of PEG-400, an increase in diuresis developed toward the end of the first minute. The increase in diuresis in a rat weighing 200 g could be detected after an injection of as little as 0.01 ml of the compound: it increased from 0.004 to 0.007 ml/min. After injection of PEG-400 in doses of between 0.01 and 0.8 ml into 21 rats, the increase in diuresis observed in 16 animals was dependent on the dose of the compound injected (Fig. 1). After injection of PEG-400 in a dose of 0.2 ml/100 g, the diuresis increased sharply and the Na concentration in the urine fell to very low levels, while the excreted fraction of filtered Na showed no significant change (Table 1). The increase in the degree of creatinine clearance during the first minutes after injection of the compound was probably due both to a true increase in glomerular

*The writers are grateful to the firm of Sandoz, A. G. for providing the PEG.

Laboratory of Development of Excretory Function, I. M. Sechenov Institute of Evolutionary Physiology and Biochemistry, Academy of Sciences of the USSR, Leningrad. (Presented by Academician V. N. Chernigovskii.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 69, No. 4, pp. 79-81, April, 1970. Original article submitted June 26, 1969.

TABLE 1. Effect of Intravenous Injection of 1 mmole Polyethylene Glycol and Mannitol into Rats on Kidney Function

Compound	V, ml/min		C_{cr}, ml/min		U_{Na}, meq/liter		E_{Na}, %		V, ml/h		$U_{Na} \cdot V$, μeq/h	
	1	2	1	2	1	2	1	2	1	3	1	3
PEG-200	0,003	0,038	0,56	1,57	69	35	0,32	0,65	0,2	1,26	13,8	50,3
Δ	0,035±0,0046		1,01±0,16		34±2,6				1,06±0,24		36,5±8,36	
(8)	$P<0,001$		$P<0,001$		$P<0,001$				$P<0,01$		$P<0,01$	
PEG-300	0,002	0,045	0,31	1,95	87	29	0,46	0,57	0,13	1,37	11,0	37,0
Δ	0,043±0,0044		1,64±0,34		58±4,6				1,24±0,028		26,9±8,49	
(5)	$P<0,001$		$P<0,01$		$P<0,001$				$P<0,001$		$P<0,05$	
PEG-400	0,005	0,054	0,78	1,35	57	8	0,17	0,23	0,22	1,78	8,9	21,8
Δ	0,049±0,0067		0,57±0,16		49±14,8				1,56±0,29		12,9±6,04	
(4)	$P<0,01$		$P<0,05$		$P<0,05$				$P<0,05$			
PEG-400	0,002	0,246	0,27	1,34	102	95	0,5	18,8	0,1	4,26	23,0	346,0
Δ	0,244±0,032		1,07±0,37				18,3±6,5		4,16±0,58		323±71	
(5)	$P<0,01$		$P<0,05$				$P<0,05$		$P<0,01$		$P<0,05$	
Mannitol	0,003	0,049	0,41	1,36	76	23	0,58	1,1	0,2	1,65	10,8	31,0
Δ	0,046±0,0062		0,95±0,33		53±11,5				1,45±0,02		20,2±7,48	
(7)	$P<0,001$		$P<0,05$		$P<0,01$				$P<0,001$		$P<0,05$	

Legend: V, diuresis; C_{cr}, creatinine clearance; U_{Na}, Na concentration in urine; $U_{Na} \cdot V$, Na excretion; E, excretable fraction of Na filtered in glomeruli; 1) initial period; 2) kidney function at maximum of diuretic response; 3) diuresis and excretion of Na during 1 h after injection of compound. Value of Δ not shown in cases when changes in paired variables were not in the same direction. Number of experiments given in parentheses.

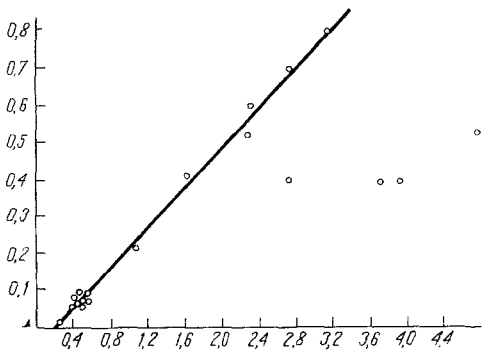

Fig. 1. Relationship between injected dose of PEG-400 and increase in diuresis in rats. Abscissa: diuresis (in ml/h) after intravenous injection of PEG-400; Ordinate: dose of PEG-400 (in ml).

filtration and to the presence of a dead space: the increase in diuresis led to arrival of old portions of urine with a high creatinine concentration from the renal pelvis, ureter, and so on. Later, despite the marked increase in diuresis, the degree of filtration in most cases was indistinguishable from the initial values (Table 1).

Comparison of the action of equimolar doses of mannitol (0.45 ml/100 g of a 20% solution) on the kidney demonstrated the basic similarity between the actions of PEG-400 and mannitol. It was noted that in both cases the Na concentration in the urine was very low, although because of the increase in diuresis its elimination in the urine increased (Table 1). The experimental results indicate that whereas proximal reabsorption was reduced in these experiments, the increase in load on the distal segment of the nephron did not exceed the capacity of its cells to reabsorb Na; the diuresis increased on account of a decrease in the distal reabsorption of water only.

The diuresis which took place cannot be regarded as a true osmotic diuresis, which is characterized by a higher Na concentration in the urine.

The picture described above was observed in 16 experiments on rats receiving PEG-400, and in 5 rats the diuresis and sodium excretion increased by an incomparably greater degree. To explain these differences in the response of the rats to injection of PEG-400, it was suggested that rats differ in their sensitivity to the compound, and in some cases a sharp decrease in proximal reabsorption was observed. The increase in volume of urine and in the quantity of Na excreted in the urine could depend on arrival in the distal segment of the nephron of an excess of fluid which had not been reabsorbed in the proximal tubule. Micropuncture experiments showed that during osmotic diuresis in rats the Na concentration in the proximal tubule falls to 110 meq/liter [4]. Because of these data, the experiments with high sodium excretion were interpreted as follows. Each sample of urine excreted after injection of PEG-400 can be regarded as a mixture of "unprocesses proximal urine" and "ordinary distal urine," from which Na was reabsorbed, because its

concentration had fallen to 6-8 meq/liter. To calculate the excess of fluid arriving from the proximal tubule (A), the following formula was used:

$$A = \frac{U_{Na}}{F^{p}_{Na}} \cdot V,$$

where U_{Na} represents the Na concentration in the urine; F^{p}_{Na} the Na concentration in the fluid in the proximal tubule (110 meq/liter), and V the diuresis (in ml/min). As an example, the results of the experiment on rat No. 32 are given below. During the hour after injection of 0.2 ml/100 g PEG-400 the diuresis rose from 0.14 to 4.7 μeq, and the sodium excretion from 23 to 370 μeq. The volume of the excess of "proximal fluid" reaching the distal portion of the nephron was 3.4 ml, and the increase in diuresis on account of the decrease in reabsorption of fluid in the distal tubule was 1.3 ml, in agreement with the results obtained in experiments on most of the rats, in which the proximal reabsorption of Na was not reduced (Fig. 1).

Because of these data, it was decided to investigate the effect of PEGs of different molecular weight on the kidney. PEG-200 and PEG-300 were injected in doses equimolar with PEG-400, and they were found to have a basically similar action on the kidney (Table 1). After injection of all these compounds the diuresis and also the excretion of Na with the urine increased.

The results obtained indicate that PEG-200, PEG-300, and PEG-400 all possess a well-marked diuretic action. The largest dose of PEG-400 which was injected into a rat was 400 mg/100 g (10 mmoles/kg). This dose is close to the dose of mannitol which is usually given in man when it is necessary to produce osmotic diuresis: 100 g mannitol (for a patient weighing 70 kg this is equivalent to about 8 mmoles/kg). However, unlike mannitol, which must first be dissolved in water and given by intravenous infusion in a volume of up to 500 ml of the 20% solution, PEG can be injected without dilution, thereby preventing overloading of the cardiovascular system with the injected fluid.

There are, therefore, very good prospects for the development of diuretics, based on PEG, which can selectively increase diuresis without producing any marked increase in the sodium excretion, or which can be used in large doses to stimulate sodium excretion. It is very important to ensure that the PEGs are nontoxic when administered over long periods [3].

LITERATURE CITED

1. V. Yu. Urbakh, Biometric Methods [in Russian], Moscow (1964).
2. R. W. Bonsnes and H. H. Taussky, J. Biol. Chem., 158, 581 (1945).
3. C. B. Shaffer, F. H. Critchfield, and C. P. Carpenter, Am. J. Physiol., 152, 93 (1948).
4. K. J. Ullrich, in: Proceedings of the 3rd International Congress of Nephrology, Vol. 1, Basel (1967), p. 48.