EFFECT OF ETHMOZINE* ON RENAL FUNCTION

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UDC 615.22:547.869.2].015.4:612.46

KEY WORDS: ethmozine; renal function.

Ethmozine, synthesized in the Institute of Pharmacology, Academy of Medical Sciences of the USSR, has marked antiarrhythmic properties [3, 4]. Its mechanism of action is due to inhibition of the fast inward sodium current in excitable membranes of the myocardium [5-7]. Since intensive electrolyte exchange takes place in the apical membrane of the tubular epithelium of the kidneys, it was interesting to study the ability of ethmozine to affect renal transport of sodium and potassium, which largely determines the level of urine excretion. The study of the effect of ethmozine on urine excretion is important also because the drug is a phenothiazine derivative, and according to data in the literature [1, 2], many compounds of this series affect renal function.

The aim of this investigation was to study the effect of ethmozine on renal function.

EXPERIMENTAL METHOD

Urine was collected at 15-min intervals from dogs, with ureters exteriorized by the method of Pavlov and Tsitovich, and secured to frames. After stabilization of diuresis ethmozine was injected intravenously in a dose of 0.5 mg/kg. Sodium and potassium concentrations (by flame photometry) and the creatinine concentration (by Folin's method) were determined in the urine and blood plasma. On the basis of these data the glomerular filtration and tubular reabsorption were calculated. The effect of ethmozine on the renal plasma flow was determined on the basis of diodone clearance. In these experiments the dogs were given an intravenous injection of isotonic sodium chloride solution containing 1% diodone at the rate of 0.5 ml/min. Blood for analysis was taken every 30 min. Diodone in the urine and blood was determined iodometrically. Acute experiments were carried out on 8 dogs under morphine–pentobarbital anesthesia. Laparotomy was performed through a short incision and polyethylene catheters were introduced into the ureters. Urine was collected every 10 min. To maintain an adequate level of diuresis, an intravenous infusion of physiological saline containing 0.4% of insulin was given in the course of the experiment at the rate of 3-4 ml/min. The left kidney was exposed through a lateral incision. A needle connected to an infusion pump was inserted into the renal artery, after which physiological saline, replaced during the experiment by a solution of ethmozine, was injected into the renal artery at the rate of 1 ml/min. Ethmozine was infused in doses of 0.25 to 1 mg/min. The diuresis, sodium and potassium excretion, and filtration, determined as insulin, were recorded. Insulin was determined by the resorcin method. In experiments on rats, the animals were kept throughout the experiment in individual cages and given water and food ad lib. The quantity of liquid consumed, diuresis, excretion of sodium, potassium, and also of creatinine, which was the indicator of glomerular filtration, were measured daily. Ethmozine was injected subcutaneously in a dose of 50 mg/kg once or twice a week (other days served as the control).

EXPERIMENTAL RESULTS

Injection of ethmozine into rats in a dose of 50 mg/kg caused considerable changes in urine excretion. Diuresis and sodium and potassium excretion were increased. These changes were evidently due to an increase in glomerular filtration, for creatinine excretion was increased on average by 34% (Table 1).

*2-Carbethoxyamino-10-(3-morpholylpropionyl)-phenothiazine HCl — Translator.

Department of Pharmacology, Lenin Komsomol Altai Medical Institute, Barnaul. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 98, No. 7, pp. 51-53, July, 1984. Original article submitted July 12, 1983.

 0007-4888/84/9807-0912$08.50

TABLE 1. Effect of a Single Injection of Ethmozine (50 mg/kg, subcutaneously) on Urine Excretion in Rats (M ± m)

Parameter	Control (40)	Experiment (30)	P
Diuresis, ml/day	9,8±0,64	13,6±1,11	<0,01
Sodium excretion, μeq/day	15,8±0,98	25,1±3,04	<0,01
Potassium excretion, μeq/day	806±31,9	956±63,2	<0,05
Creatinine excretion, mg/day	3,5±0,18	4,7±0,34	<0,01

Legend. Number of experiments in parentheses.

TABLE 2. Effect of Ethmozine on Urine Excretion in Dogs (8 experiments)

Time after injection of ethmozine, min	Diuresis, ml/min/m²	Filtration, ml/min/m²	Sodium excretion, μeq/min/m²	Potassium excretion, μeq/min/m²	Reabsorption of water		Reabsorption of sodium	
					ml/min/m²	%	μeq/min/m²	%
0—15	0,42±0,041	39,3±1,84	81±7,9	33±4,5	38,89±1,84	98,92±0,102	5816±410	98,56±0,177
30	0,43±0,041	39,9±2,08	86±9,6	35±4,6	39,44±2,09	98,91±0,121	5889±316	98,42±0,226
Injection of ethmozine 0.5 mg/kg (intravenously)								
45	0,40±0,055	34,2±2,15	93±13,8	29±3,4	33,76±2,16	98,78±0,193	5032±323	98,14±0,280
60	0,43±0,069	37,6±4,72	96±17,2	36±7,9	37,16±4,68	98,77±0,201	5542±697	98,25±0,245
75	0,52±0,092	40,3±3,01	118±23,5	44±17,7	39,74±2,99	98,67±0,235	5846±452	98,02±0,349
90	0,79±0,162*	53,2±3,29*	180±27,9*	64±9,3*	52,40±3,21*	98,56±0,260	7798±476*	97,91±0,330
105	1,09±0,164*	52,7±4,52*	239±39,8*	79±9,7*	51,65±4,46*	97,90±0,296*	7671±660*	96,97±0,414*
120	1,07±0,183*	54,6±2,91*	188±23,4*	72±11,3*	53,52±2,91*	98,00±0,355*	8001±431*	97,69±0,255*
135	0,91±0,114*	52,0±4,41*	162±14,0*	79±13,1*	51,13±4,39*	98,19±0,269*	7643±655*	97,87±0,166*
150	0,90±0,109*	55,5±3,53*	187±14,3*	88±11,9*	54,63±3,51*	98,35±0,203	8142±526*	97,70±0,276*
165	0,72±0,072*	50,0±4,71	153±17,3*	67±7,1*	49,26±4,67	98,53±0,150*	7343±703	97,87±0,275
180	0,61±0,063	48,9±5,38	128±18,5	57±6,7	48,25±5,35	98,70±0,136	7202±1068	98,12±0,314
195	0,51±0,054	44,3±5,04	104±17,7	51±6,9	43,76±4,99	98,84±0,064	6535±748	98,37±0,246
210	0,50±0,047	41,7±3,41	95±17,4	46±8,4	41,25±3,39	98,80±0,101	6166±509	98,44±0,297
225	0,46±0,079	39,1±6,52	97±18,4	59±15,6	38,64±6,46	98,81±0,114	5769±965	98,33±0,252

Legend. Asterisk denotes significant changes compared with initial value.

To study the time course of changes in urine excretion over the next few hours, experiments were carried out on five dogs. Injection of ethmozine in doses of 1-3 mg/kg, such as are used for the treatment of experimental arrhythmias in dogs [5], caused an increase in diuresis which, in most cases, did not return to its initial level after 4-5 h of observation. Accordingly, in the subsequent experiments a dose of 0.5 mg/kg (intravenously) was used. As Table 2 shows, the diuresis began to increase 45-60 min after injection of ethmozine, and by the 75th-90th minute it was more than twice as high as initially, and 2-2.5 h after injection it had returned to its initial value. The increase in diuresis was accompanied by increased excretion of sodium and potassium. The possible cause of these changes was an increase in the glomerular filtration rate on average from 39.3 ± 1.84 to 55.5 ± 3.53 ml/min/m². Naturally in this case the absolute reabsorption of water and sodium was increased, although relative reabsorption was reduced. Because of the change in filtration charge of sodium, the effect of ethmozine on its renal transport under the conditions of this particular experiment cannot be judged. Injection of ethmozine also caused a significant increase in the renal plasma flow. The drug began to act after about 45 min, and continued to do so on average for 75 min (Fig. 1).

To determine whether the changes in diuresis, filtration, and sodium excretion were due to the direct action of ethmozine on the kidneys acute experiments were carried out on dogs with direct injection of the drug into the renal artery. It will be clear from Table 3, which shows relationship between parameters of function of the experimental and control kidneys, that the drug did not give a unilateral effect. With an increase in dose, there was a delayed bilateral increase in diuresis, filtration, renal blood flow, and sodium excretion, i.e., the same result was obtained as after intravenous injection of ethmozine. Consequently, no direct action of ethmozine on the kidney was found.

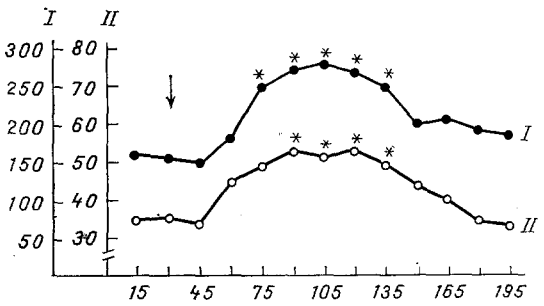

Fig. 1. Effect of ethmozine on renal plasma flow. Abscissa, time after injection of ethmozine (in min); ordinate: I) renal plasma flow (in ml/min/m^2), II) glomerular filtration rate (in ml/min/m^2). Arrow indicates time of injection of drug; asterisks indicate significant changes compared with initially.

TABLE 3. Relationship between Parameters of Function of Experimental and Control Kidneys after Injection of Ethmozine into Renal Artery

Time after injection of ethmozine, min	Diuresis	Filtration	Sodium excretion	Potassium excretion
0—10	0,95±0,037	0,98±0,066	0,89±0,042	1,05±0,082
20	0,96±0,039	0,98±0,061	0,90±0,054	1,09±0,064
Beginning of ethmozine infusion (0.25-1 mg/min)				
30	0,96±0,047	0,96±0,059	0,91±0,062	1,06±0,070
40	0,98±0,069	1,03±0,074	0,93±0,089	0,98±0,093
End of infusion				
50	0,97±0,066	1,05±0,077	0,92±0,126	1,14±0,123
60	1,03±0,077	1,04±0,074	0,87±0,081	1,20±0,167
70	1,03±0,090	1,01±0,062	0,83±0,057	1,16±0,179
80	1,00±0,079	1,02±0,067	0,81±0,062	1,14±0,098
90	1,05±0,062	0,98±0,052	0,82±0,063	1,13±0,091
100	1,05±0,071	0,97±0,063	0,95±0,058	1,05±0,053

In therapeutic doses ethmozine thus gives rise to a diuretic and sodium-excreting effect of extrarenal origin, linked with an increase in the glomerular filtration rate and renal blood flow. The absence of any direct action of ethmozine when injected into the renal artery is evidence that the drug does not alter the permeability of the renal tubular epithelium for sodium and potassium ions.

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