deep-fried products, and two in baked products. One subject received the unheated oil only. All six subjects had a very satisfactory hypocholesterolemic response to their diets. Heating corn oil to temperatures of 200-400° F. for short periods of time did not impair the hypocholesterolemic response usually noted.

The principles arising from this study permit the preparation of satisfactory vegetable oil diets for long-term use in hypercholesterolemic states.

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EFFECT OF INTRAVENOUS DIGOXIN ON BLOOD PRESSURE, SERUM ELECTROLYTES, RENAL HEMODYNAMICS AND EXCRETORY FUNCTION IN NORMAL AND HYPERTENSIVE SUBJECTS, AND SUBJECTS IN CONGESTIVE HEART FAILURE*

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INTRODUCTION

THE INJECTION of digoxin intravenously into patients with congestive heart failure has been found to produce a number of hemodynamic changes, the most noticeable of which are a rise in cardiac output[1-5] and a fall in pulmonary arterial, right ventricular end diastolic, right auricular and peripheral venous pressures.[2, 3, 5, 6] The diuretic action of digitalis has generally been assumed to be due to the increased renal blood flow which is a part of the hemodynamic action of the drug, but few data are available on the effect of digitalis on renal hemodynamics or tubular function. In 1951, Farber *et al.*[7] reported that digoxin, when injected intravenously into patients with congestive heart failure, caused an increased excretion of both water and sodium, with an associated fall in femoral venous pressure, but without any consistent increase in either renal plasma flow (RPF) or glomerular filtration rate (GFR). Digoxin had the same effect, although less marked, in patients with non-cardiac edema and in patients with compensated heart disease. Farber therefore postulated a primary renal tubular action of digoxin. In 1956, Hyman, Jaques and Hyman[8] reported that digoxin, when injected directly into the left renal artery of nine normal dogs and one dog in congestive heart failure, caused increased renal excretion of sodium, potassium and water by the left kidney but not by the right. Werkö is reported by Staub[9] to have shown that intravenous administration of lanatoside C (Cedilanid) to patients with rheumatic heart disease caused an increase in sodium excretion, RPF and GFR before any measurable increase in cardiac output.

This study was undertaken to yield further information about the action of digitalis on renal hemodynamics and tubular function in both normal and hypertensive patients, and in patients with congestive heart failure.

MATERIAL AND METHODS

Studies have been completed on 17 subjects, five of whom were normal, five hypertensive and seven in congestive heart failure. All subjects were inpatients in either the Kingston General or Ontario Hospitals in Kingston, Ontario. Studies were carried out in the morning in the fasting state, over a period of 3½ hours, and comprised the following procedures. Each patient was hydrated by being given 200 ml. of water by mouth every 15 minutes for the first hour and 100 ml. of water every 15 minutes thereafter, to ensure a good flow of urine. A brachial artery was cannulized with a Cournand needle for measurement of blood pressure and for periodic blood sampling. The urinary bladder was catheterized to ensure accurate collection of urine. Then a priming dose of 30 ml. (3 g.) of inulin and 3 ml. (0.6 mg.) of para-amino-hippuric acid (PAH) was injected intravenously, and this was followed by a sustaining infusion containing 50 ml. of inulin (5 g.) and 7 ml. of PAH (1.4 g.) in 500 ml. of normal saline solution delivered at a rate of about 35 to 40 drops a minute. After a 45-minute period of equilibration, two control urine samples were collected at intervals of 20 minutes and two blood samples at the mid-point of each urine collection. Then 1.5 mg. of digoxin was injected intravenously, and four more urine samples were collected at 20-minute intervals, with matching blood samples

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at the mid-point of each collection period. Blood and urine samples were measured for sodium, potassium, chloride, phosphorus, pH, CO_2, inulin and PAH. Urine samples were also measured for ammonia and total osmolality. Standard biochemical techniques were used throughout. Blood pressure was recorded through the indwelling arterial needle by means of a Sanborn electromanometer.

RESULTS

Blood Pressure (Fig. 1)

The intravenous injection of 1.5 mg. of digoxin caused a prompt rise in blood pressure in all three groups of patients, affecting the systolic more than the diastolic pressure, and producing a widening of pulse pressure. The rise in the control group was slight, averaging 7% for systolic pressure and 5.3% for diastolic pressure. In three of the five patients, the blood pressure had returned to control levels by the completion of the study. The increase in pressure was more marked in the hypertensive group, averaging 11.2% for systolic and 4.2% for diastolic pressure, and the duration of the rise was more sustained, persisting throughout the study. The rise in pressure was most marked in the group

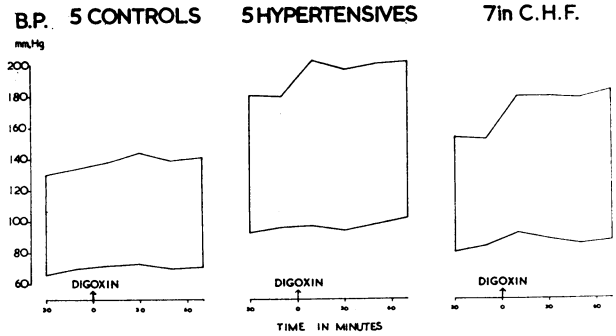

Fig. 1.—The effect of 1.5 mg. of intravenous digoxin on the blood pressure of five normal and five hypertensive subjects, and seven subjects in congestive heart failure. Digoxin caused a rise in systolic pressure and a widening of pulse pressure in all three groups, most marked in the group with congestive heart failure.

with congestive heart failure, averaging 20% systolic and 10% diastolic. Blood pressure was still rising at the completion of the study in four of the seven patients. The statistical significance of these changes is shown in Table I.

Serum Electrolytes (Table I)

Digoxin caused a prompt and consistent rise in serum potassium (Fig. 2), although the change was of statistical significance only in the group with congestive heart failure. Digoxin caused no significant change in serum sodium, chloride, pH or CO_2.

Renal Hemodynamics and Excretory Function

Digoxin caused no significant change in renal hemodynamics in the three groups of patients. Despite the rise in arterial blood pressure, RPF and GFR did not increase; rather, they declined slightly, although not significantly (Table II). The

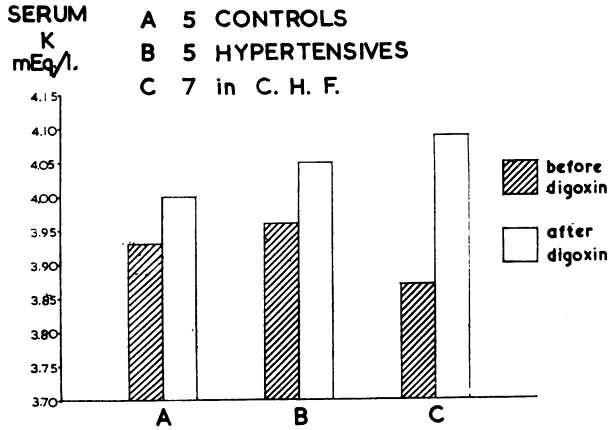

Fig. 2.—The effect of 1.5 mg. of intravenous digoxin on the serum potassium of five normal and five hypertensive subjects and seven subjects in congestive heart failure. The rise in serum potassium was most marked in the patients with heart failure.

action of digoxin on renal tubules varied slightly from one group to another, but the effects were minor and inconsistent. Excretion of sodium and chloride increased in five of the seven patients with congestive heart failure, despite the slight reduction in RPF and GFR, but the average increase was not statistically significant. There was a tendency for urinary ammonia to fall in almost all patients, but the change was statistically significant only in the normal group. Urinary CO_2 was noted to decline in the hypertensive group. A typical pattern of response to the intravenous injection of digoxin in a case of congestive heart failure is shown and contrasted with the subsequent effect of an intravenous injection of chlorothiazide in Fig. 3.

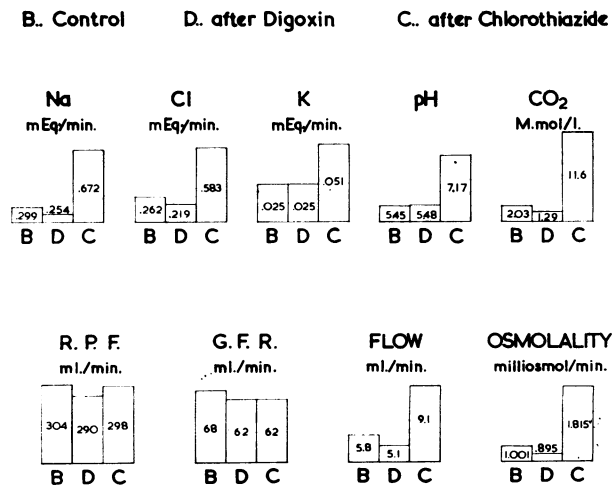

Fig. 3.—The effect of 1.5 mg. of digoxin, followed by 500 mg. of chlorothiazide (both injected intravenously), on renal hemodynamics and excretory function in a patient in congestive heart failure. Neither drug altered renal hemodynamics. Only chlorothiazide had a diuretic effect.

DISCUSSION

Blood Pressure

The evaluation of systolic blood pressure and the widening of pulse pressure noted in this study suggests that digoxin increased myocardial contractile force and improved stroke volume, not only

TABLE I.—EFFECT OF INTRAVENOUS INJECTION OF 1.5 MG. OF DIGOXIN ON BLOOD PRESSURE AND SERUM ELECTROLYTES OF FIVE NORMAL SUBJECTS

Subjects	*Age*	*pH*		*CO_2 m. mol./l.*		*Na mEq./l.*		*Cl mEq./l.*		*K mEq./l.*		*P mEq./l.*		*Blood pressure*	
		before	*after Digoxin*	*before*	*after*	*before*	*after*	*before*	*after*	*before*	*after*	*before*	*after*	*before*	*after*
W.B.	53	7.43	7.43	21.8	21.6	145.8	145.0	103.1	104.2	4.25	4.16	2.11	2.13	132/68	149/71
R.N.	48	7.41	7.41	22.6	22.4	145.0	151.7	102.4	101.9	3.75	4.03	1.95	1.99	98/48	102/49
S.M.	24	7.41	7.41	26.2	26.8	141.5	141.5	103.5	104.6	3.60	3.80	1.76	1.81	140/76	145/79
W.B.	38	7.40	7.37	27.5	27.8	142.0	141.0	98.8	100.8	4.20	4.10	1.79	2.00	136/73	142/75
K.C.	16	7.42	7.40	25.1	24.7	141.1	142.7	102.2	104.3	3.85	3.89	1.81	1.91	155/80	171/83
Average % change		−0.1		0		+0.9		+1.2		+1.9		+4.6		+7.0/+5.2	
Standard deviation		0.18		1.55		2.15		1.15		4.45		4.29		4.25/5.01	
Standard error of the mean		0.08		0.691		0.959		0.513		1.986		1.915		1.9/2.2	
P. values		0.3 - 0.20		.....		0.50 - 0.40		0.10 - 0.05		0.40 - 0.30		0.10 - 0.05		$\frac{0.05 - 0.02}{0.10 - 0.05}$	

FIVE HYPERTENSIVE SUBJECTS

		before	*after Digoxin*	*before*	*after*	*before*	*after*	*before*	*after*	*before*	*after*	*before*	*after*	*before*	*after*
H.L.	56	7.42	7.42	25.3	25.4	145.9	141.6	98.7	100.9	4.23	4.11	1.48	1.45	213/105	230/104
M.D.	50	7.37	7.38	23.6	23.7	140.0	141.0	107.5	107.9	4.04	3.99	1.57	1.63	180/93	196/95
L.L.	44	7.40	7.40	26.2	25.6	139.0	141.5	103.3	103.8	4.16	4.14	1.48	1.52	151/92	165/94
A.R.	50	7.62	7.62	24.0	24.6	147.4	145.1	103.4	105.7	3.57	3.95	1.50	1.55	176/86	200/84
D.N.	53	7.31	7.33	25.0	24.7	141.4	141.6	109.8	110.8	3.82	4.15	1.21	1.26	178/98	207/117
Average % change		+0.08		−0.04		−0.5		+1.2		+3.58		+2.3		+11.2/+4.2	
Standard deviation		0.11		1.53		1.76		0.963		6.30		2.48		3.57/8.81	
Standard error of the mean		0.05		0.68		0.79		0.43		2.817		1.11		1.59/3.93	
P. values		0.20 - 0.10		.....		0.60 - 0.50		0.05 - 0.02		0.3 - 0.2		0.20 - 0.10		$\frac{<0.01}{0.40 - 0.30}$	

SEVEN SUBJECTS IN HEART FAILURE

		before	*after Digoxin*	*before*	*after*	*before*	*after*	*before*	*after*	*before*	*after*	*before*	*after*	*before*	*after*
W.W.	79	7.26	7.27	24.2	23.9	140.0	139.5	110.0	111.5	3.89	3.95	1.39	1.48	127/65	146/66
C.W.	54	7.38	7.37	23.1	21.8	134.3	134.3	110.0	101.9	4.11	4.19	1.59	1.56	134/83	165/87
S.K.	59	7.36	7.36	18.8	19.4	138.9	137.8	104.4	106.6	4.25	4.49	1.78	1.78	150/80	180/89
A.B.	79	7.36	7.39	25.2	24.4	136.8	136.4	101.9	101.0	3.49	3.81	1.57	1.56	132/66	172/80
V.V.	65	7.47	7.47	23.9	23.7	144.3	143.9	102.6	104.3	3.68	3.95	1.79	1.83	178/98	207/117
I.H.	69	7.31	7.34	23.9	24.4	140.0	140.0	105.6	107.2	4.00	4.31	2.31	2.39	139/83	160/88
C.W.	74	7.34	7.35	24.6	24.7	141.1	141.1	109.0	110.3	3.65	3.93	1.59	1.60	181/80	209/84
Average % change		+0.13		−0.74		−0.23		+1.11		+5.80		+1.59		+19.3/+9.9	
Standard deviation		0.70		3.02		0.29		1.02		2.92		2.89		5.76/7.71	
Standard error of the mean		0.27		1.14		0.11		0.39		1.10		1.09		2.176/2.913	
P. values		0.7 - 0.6		0.6 - 0.5		0.10 - 0.05		0.05 - 0.02		0.01		0.30 - 0.20		$\frac{<0.001}{0.02 - 0.01}$	

TABLE II.—EFFECT OF INTRAVENOUS INJECTION OF 1.5 MG. OF DIGOXIN ON RENAL HEMODYNAMICS AND EXCRETORY FUNCTION OF FIVE NORMAL SUBJECTS

Subjects	Age	R.P.F. ml./min.		G.F.R. ml./min.		Urine flow ml./min.		Osmolality m. osmoles/min.		Na mEq./min.		Cl mEq./min.		K mEq./min.		P mEq./min.		pH		CO_2 m. mol./l.		NH_3 mEq./min.	
		before Digoxin	after Digoxin	before	after	before	after	before	after	before	after	before	after	before	after	before	after	before	after	before	after	before	after
W.B.	53	757	736	119	105	9.6	5.9	0.993	0.911	0.329	0.302	0.224	0.224	0.034	0.036	0.047	0.050	6.45	6.20	2.2	2.0	0.101	0.089
R.N.	48	487	514	100	103	13.5	3.8	1.001	0.928	0.212	0.243	0.205	0.208	0.017	0.021	0.202	0.018	5.84	5.03	1.6	1.5	0.134	0.091
S.M.	24	661	529	70	71	7.7	7.1	0.499	0.499	0.121	0.107	0.055	0.059	0.012	0.012	0.013	0.010	6.18	6.23	2.7	3.3	0.102	0.078
W.B.	38	553	455	105	94	9.7	8.9	0.846	0.792	0.094	0.098	0.069	0.068	0.074	0.029	0.016	0.031	6.68	6.32	2.7	1.4	0.219	0.188
K.C.	16	586	446	105	90	13.2	13.0	1.246	0.949	0.261	0.215	0.270	0.191	0.035	0.024	0.016	0.018	6.61	6.56	1.9	3.0	0.173	0.119
Average % change		−11.8		−6.4		−24.0		−9.2		−3.8		−4.4		−14.6		+15.9		−4.6		+3.3		−22.8	
S.D.		12.55		7.85		29.62		8.85		13.01		14.71		33.58		45.69		5.73		39.38		9.35	
S.E.M.		5.60		3.50		13.22		3.95		5.81		6.57		14.99		20.40		2.56		17.58		4.17	
P. values		0.20 - 0.10		0.20 - 0.10		0.20 - 0.10		0.10 - 0.05		0.60 - 0.50		0.60 - 0.50		0.40 - 0.30		0.50 - 0.40		0.20 - 0.10		0.9 - 0.80		<0.01	
FIVE HYPERTENSIVE SUBJECTS																							
H.L.	56	375	382	77	80	6.2	6.4	1.267	1.112	0.522	0.435	0.407	0.317	0.067	0.059	0.020	0.021	7.04	7.02	12.15	9.5	0.083	0.092
M.D.	50	669	533	97	95	8.3	5.4	0.663	0.549	0.150	0.211	0.105	0.117	0.026	0.025	0.012	0.020	7.03	6.93	6.0	4.6	0.135	0.115
L.L.	44	340	253	65	53	10.0	6.4	0.784	0.639	0.160	0.126	0.150	0.115	0.042	0.030	0.022	0.023	6.55	6.61	3.12	2.94	0.094	0.081
A.R.	50	369	326	70	74	12.0	7.3	0.780	0.672	0.211	0.218	0.168	0.148	0.041	0.033	0.023	0.024	7.10	6.88	7.2	5.0	0.106	0.096
D.N.	53	294	217	63	57	14.3	11.3	1.367	0.994	0.595	0.460	0.373	0.238	0.051	0.062	0.023	0.024	5.10	4.94	6.45	5.85	0.090	0.079
Average % change		−16.3		−4.1		−25.5		−17.8		−16.5		−16.4		− 8.45		+14.4		−1.4		−19.2		−7.9	
S.D.		11.69		9.94		17.56		5.87		30.51		17.96		19.06		22.03		1.75		8.92		10.62	
S.E.M.		5.22		4.44		7.84		2.62		13.62		8.02		8.51		9.83		0.78		3.98		4.74	
P. values		0.05 - 0.02		0.5 - 0.4		0.05 - 0.02		<0.01		0.4 - 0.30		0.20 - 0.10		0.40 - 0.30		0.30 - 0.20		0.20 - 0.10		<0.01		0.20 - 0.10	
SEVEN SUBJECTS IN HEART FAILURE																							
W.W.	79	304	290	68	62	5.8	5.1	1.001	0.895	0.299	0.254	0.262	0.219	0.025	0.025	0.022	0.026	5.45	5.48	2.03	1.29	0.91	0.083
C.W.	54	394	421	104	113	1.3	1.3	0.760	0.642	0.085	0.094	0.066	0.097	0.042	0.035	0.047	0.042	5.31	5.43	0.20	0.20	0.133	0.114
S.K.	59	561	423	98	80	12.4	8.8	1.951	1.475	0.480	0.587	0.445	0.560	0.067	0.049	0.044	0.021	5.39	6.23	0.68	0.95	0.172	0.089
A.B.	79	419	329	99	91	1.2	4.9	0.734	0.800	0.131	0.223	0.071	0.119	0.041	0.024	0.035	0.031	6.65	6.83	1.2	4.1	0.083	0.080
V.V.	65	189	173	55	59	5.5	5.4	0.670	0.890	0.181	0.275	0.088	0.195	0.018	0.022	0.024	0.029	6.49	6.46	2.6	3.2	0.067	0.065
I.H.	69	226	189	69	54	7.5	4.7	0.744	0.712	0.148	0.182	0.190	0.189	0.038	0.042	0.016	0.016	6.33	6.04	1.6	1.1	0.093	0.067
C.W.	74	344	345	62	61	12.8	12.3	1.864	1.966	0.811	0.825	0.625	0.712	0.052	0.063	0.030	0.030	7.13	7.22	6.9	6.7	0.070	0.071
Average % change		−9.5		−6.1		+32.0		−0.06		+23.5		+37.0		−4.46		−5.0		+2.4		+47.65		−14.91	
S.D.		11.7		11.65		38.76		18.32		29.22		46.73		24.57		24.37		6.23		96.84		17.61	
S.E.M.		4.22		4.40		14.65		6.92		11.04		17.66		9.28		9.21		2.35		36.60		6.66	
P. values		0.10 - 0.05		0.30 - 0.20		0.10 - 0.05		....		0.10		0.10 - 0.05		0.70 - 0.60		0.70 - 0.60		0.40 - 0.30		0.30 - 0.20		0.10 - 0.05	

in the group with congestive heart failure where the rise in pressure was most noticeable, but in the hypertensive and control groups as well. Such an effect is in accord with recent observations. Braunwald *et al.*[10] studied the direct effects of acetylstrophanthidin and lanatoside C on the contractile force of the heart using the Walton-Brodie strain gauge arch in 21 patients with compensated heart disease, at the time of open heart surgery during cardiac bypass. Both drugs caused an increased contractile force. In our study, the rise in diastolic pressure was slight, and was statistically significant only in the group with congestive heart failure. It was probably secondary to the increased cardiac output, although output was not measured and peripheral resistance therefore cannot be calculated. One cannot entirely exclude the possibility that an arterial vasoconstrictor action of the drug might have contributed to the rise in diastolic pressure. Previous workers studying cardiovascular hemodynamics by means of cardiac catheterization have reported that intravenous digoxin had variable effects on peripheral resistance, sometimes causing the latter to rise[11, 12] and sometimes to fall.[3, 13] But Braunwald's[10] group have noted an invariable but often very transient arteriolar vasoconstrictor effect

when peripheral vascular resistance has been studied at the time of open heart surgery where it has been possible to separate the heart from the peripheral vascular bed.

Serum Electrolytes

The only change in serum electrolytes noted after the intravenous administration of digoxin was a rise in serum potassium, slight in the normal and hypertensive groups, and moderate in the group with congestive heart failure. A demonstrable rise in serum potassium in patients treated with digitalis has not been reported, but might be anticipated from the work of Lown and his colleagues[14] on dogs. They found that the injection of large amounts of acetylstrophanthidin (to the point of producing ventricular tachycardia) produced an almost invariable rise in serum potassium, averaging 0.64 mEq./l., and in addition, an almost invariable fall in serum sodium, averaging 3.1 mEq./l. In our study, the rise in serum potassium was not accompanied by an increased excretion of potassium in the urine. Previous studies on animals would indicate that the rise in serum potassium is the result of a shift of potassium from tissue cells involving particularly the liver, heart and skeletal muscle,[15-18] and in addition, a reduced uptake of potassium by skeletal muscle.[19] The much greater rise in serum potassium in the group of patients with congestive heart failure may be related to tissue anoxia; in animals[20] this has been shown to cause a shift of potassium from cells, thereby enhancing the action of digitalis.

Renal Hemodynamics and Excretory Function

It was not possible to demonstrate in this study an increase in RPF and GFR within a 90-minute period following the intravenous injection of digoxin, even in the group of patients with congestive heart failure where digitalis might have been expected to increase substantially cardiac output and thus improve renal blood flow. Nor was it possible to demonstrate a definite direct action of digoxin on the renal tubules. It is true that urinary excretion of sodium and chloride increased in five of the seven patients with congestive heart failure, despite a slight reduction in RPF and GFR, and excretion of water. These changes might indicate a renal tubular action of the drug, but they were not large enough to be statistically significant in this small group of patients. Certainly, digoxin has no effect on renal tubules comparable to that of chlorothiazide (Fig. 3). These data are in contrast to those of Farber *et al.*,[7] who found that digoxin usually produced a slight increase in both RPF and GFR, but who were not able to find any correlation between the increase, when it occurred, and the diuresis of salt and water which took place, not only in their patients with congestive heart failure, but also in patients with non-cardiac edema and in patients without edema. In the study of Hyman, Jaques and Hyman, when digoxin was injected directly into the left renal artery of a dog, producing a diuretic effect in the left kidney, it is significant that they were unable to demonstrate any diuretic effect on the other kidney.

SUMMARY

The effect of intravenous digoxin on blood pressure, serum electrolytes, renal hemodynamics and excretory function has been studied in a group of five normal and five hypertensive patients, and in seven patients with congestive heart failure.

Digoxin caused a rise in systolic pressure and a widening of pulse pressure in all three groups of patients. The changes were slight and transient in the normal subjects, more noticeable and sustained in the hypertensive subjects, and most marked in the subjects in congestive heart failure. A significant rise in diastolic pressure occurred only in the patients with congestive heart failure.

Digoxin caused a rise in serum potassium in all three groups of patients, slight in the control and hypertensive subjects, and moderate in the subjects in congestive heart failure. It caused no change in other serum electrolytes.

Digoxin had no effect on renal plasma flow or glomerular filtration rate, and no consistent effect on renal tubular function. There was a slight increase in urinary excretion of sodium and chloride in five of seven patients with congestive heart failure, but the increase was not statistically significant.

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