Short communications

Effect of digoxin on human red blood cell electrolytes

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Red blood cell electrolytes were measured during 48 h after administration of digoxin to twelve patients. The concentrations of some red cell electrolytes changed: sodium increased while potassium decreased significantly. These findings agree with *in vitro* experiments on red cells and other tissues including myocardium. Change in membrane ATPase activity is probably responsible for the electrolyte changes both *in vitro* and *in vivo*.

For many years there has been interest in the cellular action of cardiac glycosides. Calhoun & Harrison (1931) observed that toxic and lethal doses of digitalis reduced the myocardial potassium in animal preparations. More recently digitalis glycosides were found to inhibit the sodium pump of human and animal blood cells *in vitro* (Schatzmann, 1953; Glynn, 1957) and further work showed this action to be mediated by the inhibition of the sodium-potassium activated adenosine triphosphatase at the cell membrane (Post, Merritt, Kinsolving & Albright, 1960; Dunham & Glynn, 1961). This enzyme has since been identified in many tissues (Bonting, Caravaggio & Hawkins, 1962), including heart muscle, and shown to be similarly affected by cardiac glycosides (Gibson & Harris, 1968). The concentration of the membrane ATPase is, however, highest in neuromuscular and secretory tissue and lowest in red blood cells (Bonting *et* al., 1962).

The expected effect of inhibition of the cell membrane ATPase would be a reduction of the intracellular potassium and an increase in sodium concentrations. These changes have not been observed in man *in vivo* and we have therefore studied the changes in red blood cell electrolytes in patients undergoing digoxin therapy.

Methods.—Twelve unselected patients, five male and seven female, were given digoxin in a dose appropriate to their physical state at varying times after admission to hospital. Twenty millilitres of venous blood were withdrawn at approximately 10.30 a.m. from each subject before digoxin administration and again 24 and 48 h afterwards. No other drug therapy was started during this study.

Plasma electrolytes were assayed in duplicate by flame photometry. Red cell electrolytes were measured in triplicate by the method of Beilin, Knight, Munro-Faure & Anderson (1966). Plasma digoxin concentrations were estimated in five patients to ensure adequate therapeutic digitalization using a radioimmunoassay (Smith, Butler & Haber, 1969).

Results.—A progressive fall in red cell potassium was found throughout the 48 hours. The fall was from a mean of 141·6 meq/l. cell water (92·0 meq/kg red cells) to 133·3 meq/l. cell water (87·3 meq/kg cells) representing a 6% drop overall ($P<0·001$). The mean red cell sodium increased from 10·2 meq/l. cell water (6·6 meq/kg red cells) to 12·0 meq/l. cell water (7·8 meq/kg cells), a 16% rise ($P<0·05$). The mean red cell water content rose slightly from 649 ml/kg cells to 654 ml/kg cells ($P<0·05$). There were no significant changes in plasma electrolyte concentrations. The mean plasma digoxin concentration in the five subjects studied after digitalization was 1·36 ng/ml.

Discussion.—*In vitro* experiments have shown that cardiac glycosides inhibit the sodium pump of the red cell (Schatzmann, 1953; Glynn, 1957). The reduction of active sodium efflux leads to a rise in intracellular sodium content. Since sodium efflux is coupled to potassium influx at the cell membrane (Harris & Maizels, 1951; Glynn, 1956) a rise in intracellular sodium is associated with a fall in cellular potassium concentration.

The present study shows for the first time that similar changes occur *in vivo* during routine therapeutic digitalization. The increase in the cell sodium concentration in this series is less than a one for one exchange with potassium. This may be due to the influx of other cations or increase in the mean cell water content; a small increase in the mean cell water content was found. Increases in red cell water have also been obtained following incubation of red cells with cardiac glycosides (Tosteson & Hoffman, 1960), and this

Effect of digoxin on red cell potassium, sodium and water

			Potassium			Sodium			Water		
Name	Age	Digoxin dose	(1) Pretreatment Meq/l.	(2) 48 h Meq/l.	1-2 change Meq/l.	(1) Pretreatment Meq/l.	(2) 48 h Meq/l.	2-1 change Meq/l.	(1) Pretrial ml/kg	(2) 48 h ml/kg	2-1 change ml/kg
D.W.	58	0·5 mg×1 0·25 mg b.d.	141·5	137·9	− 3·6	7·85	9·45	+1·6	647·5	651	+ 2·5
S.B.	71	0·25 mg×1 0·125 mg d.d.	145	141·1	− 3·9	9·24	11·82	+2·58	663	674·5	+13·5
G.C.	64	0·5 mg every 8 h ×3 0·25 mg b.d.	144·4	133·0	−11·4	9·04	13·7	+4·66	651·5	667	+13·5
C.M.	55	0·5 mg×1 0·25 mg b.d.	139·2	131·2	− 8·0	10·5	8·4	−2·1	650	665	+15
L.P.	73	0·5 mg×1 0·25 mg d.d.	149·1	140	− 9·1	9·72	12·27	+2·55	658	653	− 5
E.B.	45	0·25 mg every 6 h ×3 0·25 mg b.d.	154	141	−14·0	11·56	10·92	−0·64	650	650	0
L.A.	19	0·5 mg every 6 h ×3 0·25 mg b.d.	139	121	−18·0	14·9	14·2	−0·7	630	646	+16
K.T.	71	0·25 mg every 6 h ×3 0·25 mg d.d.	142	130	−12·0	9·6	8·44	−0·72	644	651	+ 7
E.D.	75	0·5 mg×1 0·25 mg b.d.	145	137·4	− 7·6	9·42	12·1	+2·68	640	651	+11
P.F.	66	0·5 mg every 6 h ×4	132·6	128·6	− 4·0	10·61	15·57	+4·96	658	648	−10
A.H.	61	0·5 mg every 8 h	132·5	132	− 0·5	9·17	12·5	+3·33	665	665	0
M.H.	55	0·5 mg every 6 h ×4 0·25 mg b.d.	135·4	126·9	− 8·5	10·9	14·3	+3·4	633	629	− 4
Mean			141·6	133·3	− 8·38	10·2	12·0	+1·8	649	654	+ 5·0
S.E.M.			±1·9	±1·8	± 1·43	±0·52	±0·67	±0·67	±0·2	±3·5	± 2·41
Significance					$P<0·001$			$P<0·05$			$P<0·05$
% change					+6%			+16%			+0·8%

d.d.=daily. b.d.=twice daily.

will tend to reduce the intracellular concentration of both sodium and potassium.

The plasma digoxin concentrations in the five patients in whom it was measured were within the therapeutic range (Smith *et al.*, 1969; Chamberlain, White, Howard & Smith, 1970).

The patients studied acted as their own controls since blood samples were taken at the same time each day. The administration of digoxin was the only change in the therapeutic regime instituted during the study. We therefore suggest that the electrolyte changes observed in these patients may be attributed to the digoxin and are representative of patients being treated with the drug. It is possible that similar changes occur, *in vivo*, in other tissues in which the membrane sodium-potassium activated ATPase has been found. Muller (1965) has suggested that a reduction of intracellular potassium is an integral factor in the therapeutic action of digitalis.

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