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Alterations Induced by Large Doses of Furosemide in Chronic Renal Insufficiency

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Eleven patients with different degrees of renal failure with creatinine clearances between 7 and 32 ml/min have been studied. After a standard water overload and control periods of clearances, furosemide 1 g was given/i.v. There followed significant increase of renal plasma flow and glomerular filtration rate. In one case the increase was maintained during a follow up period of 3 hours. A significant increase was evident in phosphate, uric acid, sodium, potassium, and calcium clearances, as well as an increase in the sodium delivery to the distal nephron and a decrease in tubular reabsorption of phosphate. All this may be interpreted as the result of renal vasodilation induced by furosemide and its effect upon the proximal tubule and on Henle's loop.

In advanced renal insufficiency, the residual nephrons find their functional limits progressively narrowed. Concentration and dilution capacity diminishes to the point in which practically all concentrating and diluting activity disappears. The same occurs in sodium and chloride excretion, in which case, although maximum elimination values are lowered, the minimum excretion is also altered to the point that patients may suffer losses and at times it may be necessary to replace them (5, 6, 18).

Under these conditions of renal insufficiency, diuretics lose efectiveness when employed to decrease extracellular volume in cases of edemas, cardiac insufficiency or volume dependant arterial hypertension

The purpose of our work was to study the capacity of response which the kidney, with different degrees of insufficiency, has with elevated doses of furosemide. The data are consistent with an increase in the renal plasma flow and glomerular filtration rate in the hours inmediately following administration. The increase in the urine flow, sodium, phosphate and uric acid excretion are compatible with decrease in reabsorption in the proximal tubule.

Materials and Methods

The study included 11 patients with glomerular filtrates between 7.2 and 37 ml/min. In 4, the basic disorder was unilateral hydronephrosis examined at least four weeks after derivation, 6 were chronic pyelonephritis and one was nephroangiosclerosis. All of the patients were given water in excess orally, 20 ml/kg. During the first 30 minutes, urine losses were replaced by water given orally and later by 0.45 % saline solution until a stable urinary volume was obtained. Once done, two 60 minutes clearance periods were initiated. When these were concluded, 1 g of furosemide i.v. was given (4, 250 mg ampules) and another two 60 minutes clearances were collected. Patient's weight was controlled during the study by constant inspection using and electric bedscale. In patients lacking drainage catheters because of hydronephrosis, uretral catheterization was done.

In blood, the microhematocrit was determined, as well as total protein content, calcium, phosphorous, uric acid and creatinine, using an autoanalyzer. Sodium and potassium were determined with a flame photometer, osmolarity by cryoscopy and PAH using the BRUN method (8). In urine we measured diuresis, the autoanalizer parameters described above, sodium, potassium, osmolarity an PAH. The standard clearance formula was used to calculate creatinine (C_{cr}) and PAH (C_{PAH}) (equivalent to renal plasma flow) clerarances, the filtration fraction (FF), osmolar clearance (C_{osm}), free water (C_{H_2O}), sodium (C_{Na}), potassium (C_k), uric acid (C_{ua}), phosphorous (C_{PO_4}) and calcium (C_{Ca}) clearances. The sodium delivery to the distal nephron per 100 ml of glomerular filtrate was obtained using the formula: $[(C_{Na} + C_{H_2O})/C_{Cr} \times 100]$.

The filtration fraction was calculated using the formula: C_{Cr}/C_{PAH}.

Tubular resorption of phosphorous: $1 - (C_{PO_4} \times 100/C_{Cr})$.

Statistical methods employed were the no parameter Wilcoxon test, the Student's test and the coefficient of correlation.

Results

Effect of furosemide on renal plasma flow and the glomerular filtrate. In 9 of the 11 cases, with respect to the values obtained after loading with water, an increase in the glomerular filtrate was produced. The same occurred in 9 of the 10 cases in which C_{PAH} was measured (table I) both variations being statistically significant. The percentage filtration fraction increased as glomerular filtrate values decreased before and after furosemide (fig. 1). In the patient in which three collection periods of one hour were collected the increases in C_{cr} and C_{PAH} were sustained (fig. 2).

Effects at the level of the proximal tubule. The effects which furosemide might have on the proximal tubule were inferred from the variations occasioned by its administration on the urine flow, distal sodium delivery, C_{PO_4} TRP and C_{ua}. All of these parameters increased significantly, excluding TRP, which de-

Table I. *Effect of furosemide (1 g, i.v.) on renal plasma flow and the glomerular filtrate, clearances of sodium and potassium.*

	Treatment		
	Pre	Post	P
Urine flow (ml/min)	3.7± 2.4	10.1± 5.4	<0.0025
C_{cr} (ml/min)	19.1±10.7	23.4±12.8	<0.05
C_{PAH} (ml/min)	78.7±52,4	103.2±69.8	<0.05
F. F. (%)	30.2± 7.8	29.3± 9.5	N.S.
C_{Na} (ml/min)	1.1± 0.5	7.7± 4.3	<0.0005
C_K (ml/min)	11.1± 4.5	23.7± 8.5	<0.0005

C_{cr} = clearance of creatinine; C_{PAH} = clearance of para-aminohipurate; F. F. = percentual filtration fraction; C_{Na} = clearance of sodium; C_K = clearance of potassium. N.S. = not significant.

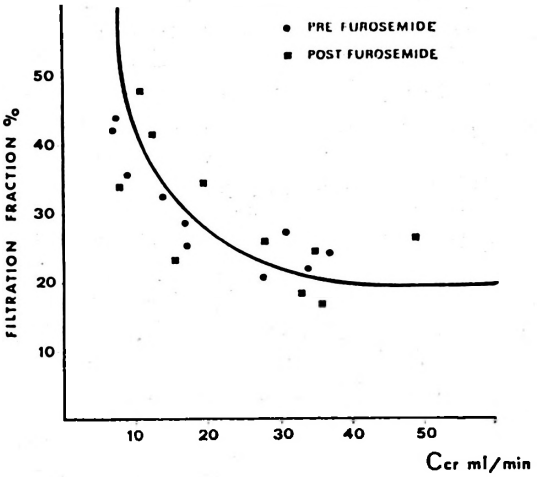

Fig. 1. *Relationship between F. F. and Ccr.* There is a inverse relationship with increment in F. F. when C_{cr} decrease.

creased (tables I and II). This means that even in situations such as in chronic renal insufficiency where resorption by the proximal tubule is diminished (18), this resorption can be reduced even more by administration of furosemide. The urine flow increased from 3.7 to 10 ml/min as a consequence of an increment in the percentage of water filtered and excreted which changes from 19.4 to 41.5 %. The percentage of sodium distal delivery changed from 16.6 to 45.9 %.

The clearances of phosphate and uric acid increased from 9.7 and 5.1 to 14.5 and 12.1 ml/min respectively.

In the range of GFR that our patients are moving around, C_{PO_4} is directly related to C_{cr} (fig. 3). In larger clearances, C_{PO_4} should trace a line parallel to the abscisa as has been repotred (2). Nevertheless, corrected to 100 ml of C_{cr}, C_{PO_4} is greater for the smallest glomerular filtration rates (fig. 4). We can say the same for the TRP (fig. 5).

Effects at the level of the distal nephron. The action on the loop of Henle is more difficult to evaluate in patients whose maximum capacity of concentration and dilution are seriously affected. Although in normal subjects the inhibitory effect on C_{H_2O} generation is notarious (13), with chronic renal insufficency this effect is not so clear and even increases in C_{H_2O} have been reported (1). This last phenomenon occurs in half of the patients.

Table II. *Effect of furosemide (1 g. i.v.) on the different parameters of the proximal tubule, osmolar clearance and clearance of free water.*

	Treatment		
	Pre	Post	P
C_{osm}	2.04± 0.8	1.4± 1.7	<0.0025
C_{H_2O} (ml/min)	1.4± 1.7	0.9± 0.7	N.S.
C_{ua} (ml/min)	5.2± 3.4	12.2± 6.6	<0.01
C_{PO_4} (ml/min)	9.7± 4.9	14.5± 6.7	N.S.
T.R.P.	44.5±13.3	36.7±12.5	<0.01
C_{Ca} (ml/min)	0.9± 0.8	7.6± 7.2	<0.01
Distal Na/C_{cr} ×100	16.6± 6.5	46.9±10.1	<0.01

C_{osm} = osmolar clearance; C_{ua} = clearance of uric acid; C_{PO_4} = clearance of inorganic phosphate. T.R.P. = tubular reabsorption of phosphate; C_{Ca} = clearance of calcium; Distal Na/C_{cr} × 100 = C_{Na} + C_{H_2O}/C_{cr} × 100. N.S. = not significant.

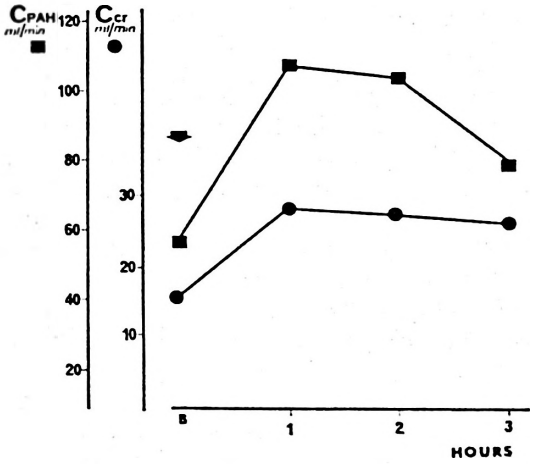

Fig. 2. *Increase in C_{cr} and C_{PAH} induce by furosemide and mantained during the three hours of experimental period.*

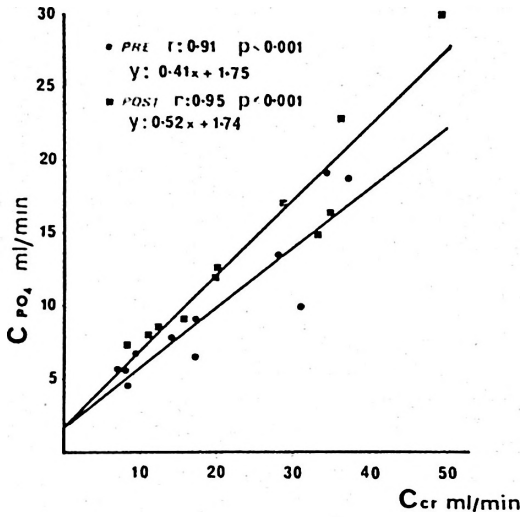

Fig. 3. *Both pre and post furosemide there were a cleare cut relationship between C_{cr} and C_{PO_4}.*

The increase in C_k is very clear after furosemide administration as consequence of both. The increase in the delivery of sodium to the distal tubule where it is interchanged with potassium and the direct excretion of potassium not reabsorbed in the proximal tubule.

C_{Na} is significantly increased probably because of proximal and distal effects.

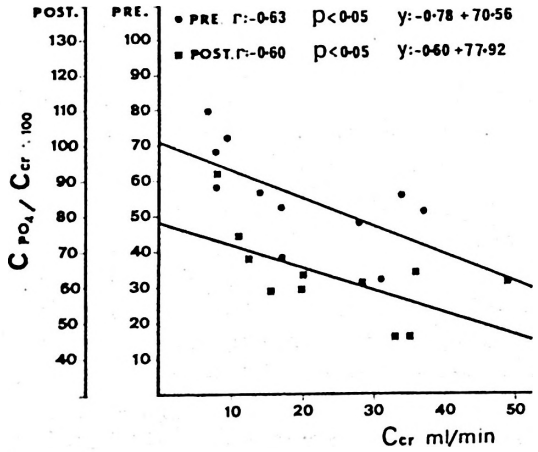

Fig. 4. *$C_{PO_4}/C_{cr} \times 100$ increase when the C_{cr} decrease in a inverse relationship.*

C_{osm} in the control phase and before furosemide is directly related to C_{cr}. Likewise C_{PO_4} when corrected to 100 ml of GFR, we can see that C_{osm} is greater for the smallest GFR (fig. 6).

Discussion

In this series of cases and before the administration of furosemide, it can be seen that as GFR decreases, F.F. increases (fig. 1). In other words, the relation C_{PAH}/GFR increase when the GFR is going down. This fact has been reported (22) and could be explained by the decrease in the Tm_{PAH} observed in uremic environment (4). Another, fact to take into account in our data is relative to, the clearance of creatinine that increases over the clearance of inuline, when the GFR is down 30 ml/min (21). At the level of the proximal tubule, resorption of fluid seems to lessen, as manifested by an increase of the delivery of sodium to the distal nephron while GFR declines (fig. 7). Likewise, we find a decline in TRP coupled with an increase in the clearances of phosphate and uric acid for 100 ml of GFR (fig. 5) all of which is compatible with the progressive decrease in the quantity of fluid resorbed in the proximal tubule when the GFR

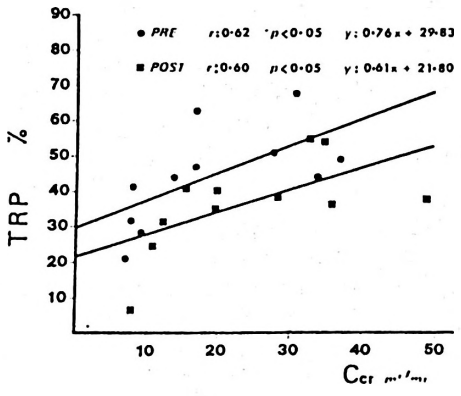

Fig. 5. *Relationship netween T. R. P. and C_{cr} both pre and post furosemide.*

descends. A cause of this lowered resorption might be the osmotic diuresis to which the residual nephrons are submitted. The data shows that the C_{osm}/100 ml GFR increases while the GFR declines (fig. 6). It is known that in osmotic diuresis the rate of proximal resorption decreases (12) because when the passive water retrodiffusion which habitually follows sodium resorption is impeded, a moment comes when the later is reduced due to the rise in the gradient against which sodium is resorbed. At the same time, there seem to be unidentified natriuretic factors in renal insufficiency (7) which act at the proximal level.

With respect to the increase in elimination of phosphorous, aside from the reasons already put-forth, the role of PTH can be mentioned. There is evidence (10) that the decrease in PTH values subsequent to intravenous infusion of calcium increases TRP. On the other hand, in experimental animals, the expansion of extracellular volume with saline solution (19) can reduce TRP. Probably, both factors, osmotic diuresis and PTH, take part in the final reduction of the phosphate resorption.

Administration of large doses of furosemide produced significant increases in C_{cr} and C_{PAH}. Although it has been said that in chronic renal insufficiency C_{PAH} is not and index of RPF (22) due to factors which inhibit the tubular secretion of PAH, the fact that the patients were controls of themselves and that increments in C_{PAH} coincide with those of C_{cr} induce one to think that the results are trustworthy. In the only patient in which we did three clearances, periods of 60 minutes, the changes induced by furosemide were maintained all this time (fig. 2) which exclude the washout phenomenon (24) as the explanation for these changes caused by furosemide. Several authors have communicated similar results (15, 17, 25) although others have been unable to objectify them (1, 14, 16) the causes of this discrepancy migth be, on the one hand, in the failure to replace urinary losses occasioning rapid hydrosaline depletion, on the other hand in the doses of furosemide used. Furosemide has a vasodilator effect on the kidney (9) which

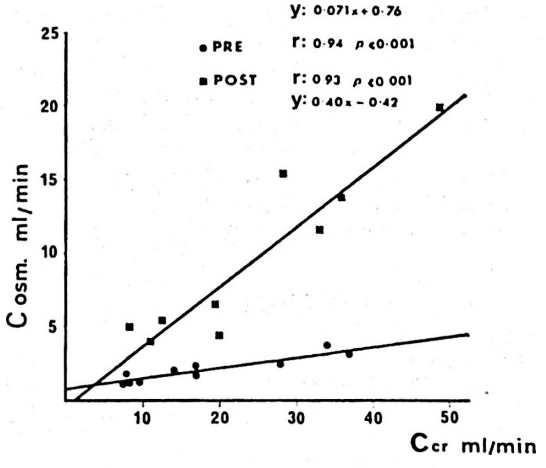

Fig. 6. *Direct relationship between C_{osm} and C_{cr} both pre and post furosemide.*

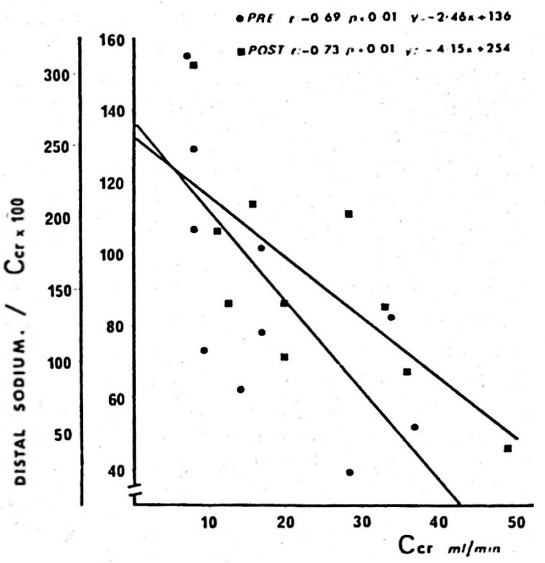

Fig. 7. *Inverse relationship distal sodium supply and C_{cr} probably consequence of a decrease in the proximal reabsorption that is more important at the low levels of GFR.*

might explain the increase in cortical RPF observed in experimental animals (3) coinciding with a decrease in the medullary flow or lack of modification. It has also been observed that furosemide added to the perfusion solution of kidneys before transplant increases the RPF of these kidneys (11).

When resorption in the proximal tubules is reduced, furosemide can further decrease resorption, as has already been communicated (20). This could be the case in chronic renal insufficiency as appears to show the increase in phosphate an uric acid excretion and also the increase in distal sodium delivery which changes from 16.6 to 46.9 %. Even though it has been said, that using clearance techniques to evaluate proximal tubular effect of diuretics the increment must be superior to 50 % (23) however it does not appear reasonable to compare the action of any diuretic on a normal renal mass with our patients with chronic renal insufficiency and previous decrease in proximal tubular resorption. If sodium elimination and consequently C_{Na} were enhanced because of the inhibitory activity of furosemide on chloride and sodium absorption in the ascendent loop of Henle, one would expect that before giving the diuretic this absorption would have been generating $C_{H\,o}$ however it was very low. Arguments for the proximal effect are reinforced by the observation, published by ALLISON (1) that C_{H_2O} in subjects with chronic renal insufficiency and water overloads, increases after giving furosemide, that is, chloride and sodium resorption increased in the ascendent loop. Half of our cases presented the same.

Altough the patients in this study do not include chronic glomerulonephritis, the conclusions could be assumed for the later because it has been reported no diferences in the sodium excretion, urinary acidification or concentration in pielonephritis and glomerulonephritis when the GFR is below 25 ml/min (26, 27).

We conclude that furosemide is an active diuretic in chronic renal insufficiency, even in advanced cases when large doses are employed. Under these circumstances, increase in RPF and GFR are produced and maintained in the case in whom it was followed for 3 hours. Water, sodium, potassium, phosphorous and uric acid also increase in part by the action on the proximal tubular resorption. This action is sufficiently intense that furosemide be used as a first measure in these patients when be necessary to reduce extracellular space for reasons of cardiac insufficiency, hypertension, edemas, etc.

Resumen

Se han estudiado 11 enfermos con diferentes grados de insuficiencia renal cuyos aclaramientos de creatinina estaban entre 7 y 32 ml/min. Después de una sobrecarga estándar de agua, se recogieron varios períodos de aclaramiento como controles. Después se administró a cada enfermo 1 g i.v. de furosemida, con lo cual se produjo un aumento significativo en el flujo plasmático renal y filtrado glomerular. Estos aumentos se mantuvieron durante 3 horas en el único caso en el que se hicieron mediciones durante este tiempo.

También se observó aumento significativo en los aclaramientos de fósforo, ácido úrico, sodio, potasio y calcio, un descenso en la reabsorción tubular de fósforo y un aumento en el aporte distal de sodio al asa de Henle. Todos estos datos pueden interpretarse como el resultado de vasodilatación renal inducida por la furosemida y por el efecto de esta droga sobre el túbulo proximal y asa ascendente de Henle.

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