LOW SERUM POTASSIUM IN HYPERTENSIVE SUBJECTS IN A HYPERTENSION CLINIC IN JOHANNESBURG, SOUTH AFRICA.

Effie Schultz June 1986; edited May 2012

INTRODUCTION

The hypertension clinic at Hillbrow Hospital in Johannesburg was opened in August 1977. It served an exclusively Black African population. By the end of 1985 more than 4000 patients had been enrolled. About 350 patients attended every week. About 15% of the patients were also diabetic.

Specially trained nurses attended to all the patients. Doctors acted as consultants. A strict management protocol was followed. During encounters at 4-weekly intervals extensive data were entered on structured clinic-retained manual medical records[1] making it easy to track secular trends in individual patients and patterns of group responses to interventions, and to extract data for analysis. Customised and detailed recommendations referred to as non-drug (ND) measures[2] on what to eat, how and why to stop using tobacco and abusing alcohol, prescription, OTC (over the counter) and other recreational drugs, how to be physically active as part of daily living, and how to manage stress and pain without medication were discussed, monitored, and reinforced at each encounter. Potassium chloride (KCl) and magnesium chloride salts were supplied. Compliance with punctual attendance and correct drug use was good as was adherence with ND measures.

In October 1985 several very low serum potassium (K) readings were recorded in clinic subjects suffering from severe hypertension who, when their blood pressures were refractory to step 6 of the then current clinic hypertension treatment protocol (table 1), were prescribed sotalol a non-selective β-blocker instead of atenolol as per an earlier protocol in addition to ND measures and a diuretic. If the blood pressure reading was still high prazosin a vasodilating α1-blocker was added replacing hydralazine in the earlier protocol. Two formulations of the diuretic drug moduretic were used in the clinic: before 1985 full-strength moduretic (MF) which consisted of 50mg hydrochlorothiazide and 5 mg amiloride and from 1985 half-strength moduretic (MH) consisting of 25mg hydrochlorothiazide and 2.5mg amiloride.

The recent very low serum K findings were of concern. Hypokalaemia is a risk factor for cardio-vascular complications. It prolongs the QT interval, is associated with arrhythmias and cardiac arrest, and is predictive of a bad outcome after myocardial

infarction. Moreover drugs like sotalol which also prolong the QT interval should not be used in the presence of hypokalaemia

Table 1: step-care treatment protocol 1985

steps	prescription
step 1	ND only
step 2	ND + MH
step 3	ND + MH + reserpine 0.1 mg
step 4	ND + MH + reserpine 0.2 mg
step 5	ND + MH + guanethidine 10 mg
step 6	ND + MH + guanethidine 25 mg
step 7	ND + MH + β blocker (atenolol or sotalol)
step 8	ND + MH + β blocker + vasodilator (hydralazine or prazosin)

It was postulated that sotalol and prazosin either alone or in combination may have reduced serum K levels in a subset of subjects by an effect on the renin-angiotensin-aldosterone system (RAS). This effect may have been exaggerated by the concomitant use of a thiazide diuretic and a low sodium (Na) diet especially in subjects with a low serum K base-line possibly induced by previous medication. Support for this hypothesis was sought by analysing data extracted from clinic-retained medical records.

The RAS system regulates blood pressure and fluid and electrolyte balance. Renin release by initiating the angiotensin-aldosterone cascade increases Na retention, renal K excretion, and blood pressure. Renin is released from the juxtaglomerular cells in the kidney in response to a reduction in afferent arteriolar pressure and extra-cellular fluid expansion as caused by vasodilators and a reduction in serum Na due to diuretics and a low Na intake. β blockers on the other hand inhibit the secretion of renin and some also block renin release caused by Na deprivation. A rise in the flow rate of tubular fluid as occurs with diuretics and vasodilators also stimulates K secretion and excretion. High aldosterone levels increase these responses.

Instead of lowering blood pressure the drugs used in the clinic may have elevated blood pressure by stimulating renin-release while simultaneously reducing serum K levels. The likely relationships between blood pressure, plasma renin activity (PRA) and serum K levels are represented in table 2.

Table 2: relationship between BP, RAS, and serum K

	BP	RAS	serum K
low Na intake	↓	↑	↑
high K intake	↓	↓	↑
low serum Na	↓	↑	↑
low serum K	↑	↑	↓
amiloride	↓	?	↑
β-blockers	↓	↓	↑
thiazide diuretics	↓	↑	↓
vasodilators	↓	↑	↓
hypertension	↑	↑	↓
renin activation	↑	↑	↓

METHODS AND MATERIALS

1 STUDY POPULATION

The study population consisted of all hypertensive patients at the clinic who were not diabetic and whose serum K and serum creatinine levels had been measured between 1 September and 31 December 1985 (study period or SP). It was clinic policy to measure biochemical variables routinely every year and more frequently if previous readings were abnormal or if abnormal readings were anticipated as became the case in subjects on sotalol and prazosin.

The study population was therefore biased.

2 STUDY SAMPLE

The study sample consisted of 160 members of the study population selected because:

- their serum creatinine was less than 200 umol/l
- they had been on the clinic ND programme and on current medication with fair compliance (=/> 80% pill count) for at least 4 weeks prior to blood sampling
- serum K had been measured between 8 and 16 months before the study started on 1 September 1985 (pre-study period or PS).
- they were not using alcohol or other recreational drugs.

Several subjects were included in the sample more than once because they complied with the inclusion criteria on more than one occasion. The features of the subjects in the study sample are shown in table 3.

Table 3: features of study sample

variable	average	2 SEM	95% CI	
1984				
serum K - mmol/l	3.96	0.08	3.88	4.04
serum creatinine - mmol/l	95.00	3.20	91.80	98.20
n drugs	1.92	0.23	1.69	2.15
n on MF	74			
n on MH	39			
1985				
serum K - mmol/l	3.96	0.08	3.81	3.97
serum creatinine - mmol/l	95.00	3.24	91.70	98.20
n drugs	1.58	0.18	1.40	1.80
n on MF	3			
n on MH	94			
1984 + 1985				
age - years	53.70	1.23	52.40	54.90
BMI	30.5	0.95	29.60	31.40
BP code	1.76	0.15	1.61	1.87
K compliance	0.95	0.12	0.83	1.07
time interval - minutes	231	33	198	263
female:male ratio	3.3 : 1			

3 TREATMENT

All clinic patients were instructed and motivated to eat a low Na and high K diet as part of the ND programme. If their blood pressure levels were not controlled on the ND programme alone drugs were added in steps as shown in table 1. The daily dose of drugs used by the study population is shown in table 4.

Table 4: drug dose/unit and maximum dose/day

drug	dose/unit	maximum dose
MH	half tablet	one tablet
atenolol	50 mg	100 mg
guanethidine	25 mg	50 mg
hydralazine	100 mg	200 mg
prazosin	4 mg	10 mg
reserpine	0.1 mg	0.2 mg
sotalol	80 mg	160 mg

4 BIOCHEMICAL VARIABLES

Biochemical measurements were performed in the hospital laboratories. Blood samples were drawn from all patients in the clinic during the course of a medical encounter and the time was routinely recorded.

5 OTHER VARIABLES

The following were calculated or extracted from routinely collected patient data:

body mass index (BMI)

BMI was calculated with the formula: mass (kg)/height(m)^2.

time interval

The time interval was the difference in minutes between the time food was last eaten and the time blood was drawn. Both times were routinely recorded at each encounter.

compliance with the use of KCl salt (K compliance)

K compliance was recorded on a 5 point scale with perfect compliance at 0.

blood pressure (BP code)

The mean blood pressure (BP) over a period of 6 months before the study period was coded on a 5 point scale as in table 5.

Table 5: BP code

category	blood pressure levels		code
normal		<140/90	0
borderline	140/90	159/94	1
mild	160/95	179/104	2
moderate	180/105	209/119	3
severe	210/120 +		4

number of drugs prescribed (n drugs)

Because compliance with prescribed drugs was good it was assumed that the number of drugs prescribed was a reliable measure of the number of drugs used. Daily doses of individual drugs were arbitrarily assigned a single value at levels shown in the second column (dose/unit) in table 4. Whole or partial multiples of the unit doses were counted as two or more drugs ad seriatim.

6 ANALYSIS

The null hypothesis was rejected when the mean was outside the 95% confidence intervals (CI) both ways.

RESULTS

Seventeen of the 32 subjects not on drugs in 1984 were on drugs in 1985 and 15 subjects who had been on drugs in 1984 were not on drugs in 1985. MF was replaced with MH in 1985 in all but 3 subjects. Only MH was used in subjects on sotalol and prazosin.

The subjects were separated into two groups according to their pre-study serum K values – <3.5mmol/l and >4mmol/l – and labelled low and high K respectively. As there was no statistically significant difference between the number of subjects with low and high serum K readings in the pre-study periods in 1984 and 1985 as shown in table 6 the data for the 2 years were combined in the later tables.

Table 6: comparison between patients in 1984 and 1985

	1985		1984	
	low K	high K	low K	high K
ND only	2	16	0	16
ND + drugs	32	46	20	45

Odds ratio 1985 = 0.18 and for 1984 = 0.14

As shown in tables 7 and 8 there were more females than males in the low K group but age, body mass index, time interval between the last meal or snack and blood sampling, compliance with KCl salt use, serum Na, and serum creatinine (neither shown) did not differ between the two groups. There was an increase in the serum K value from pre-study levels to study levels in the low K group and a decrease in the high K group but study period serum K levels in the low K group remained lower than in the high K group. The BP in the low K group was higher than the BP in the high K group and subjects in the low K group were on more drugs.

In these tables statistically significant differences between PS and SP values within each K group are marked in the columns labelled “intra” and differences between values in the low and high K groups in the columns labelled “inter”.

Because the dose of reserpine did not affect serum K levels (table 9) the data on reserpine were not separated by dose in subsequent tables. Tables 10 - 12 show the number (n) and percentage (%) of subjects on different forms of treatment in the low and high serum K groups.

Table 9: mean serum K and reserpine ± diuretic

	reserpine 0.1 mg			reserpine 0.2 mg		
variable	K mmol/l	95% CI		average	95% CI	
low K group	3.9	3.75	4.06	3.88	3.7	4.07
other K group	3.81	3.65	3.97	3.88	3.7	4.07

Table 7: features of low K group (pre-study serum K level <3.5mmol/l)

variable	average	2 SEM	95% CI		significant* intra	inter
1984 (n = 20)						
PS K - mmol/l	3.17	0.11	3.06	3.28		x
SP K - mmol/l	3.54	0.20	3.34	3.73	x	x
n drugs	2.25	0.58	1.67	2.83		x
1985 (n = 33)						
PS K - mmol/l	3.22	0.08	3.13	3.30		x
SP K - mmol/l	3.65	0.14	3.52	3.79	x	x
n drugs	2.48	0.24	0.69	1.18		x
K compliance	0.94	0.48	2.00	2.96		
BP code	2.03	0.33	1.70	2.36		x
age - years	53	2.5	50.4	55.5		
BMI	31.30	1.72	29.60	33.00		
time interval - minutes	237	79	158	315		
1984 + 1985 (n = 53)						
PS K - mmol/l	3.20	0.07	3.13	3.27		x
SP K - mmol/l	3.61	0.11	3.50	3.72	x	x
female:male ratio	5.6 : 1					

Table 10: number of subjects by diuretic and K group

	low K		high K	
drugs	n	%	n	%
nil	2	4	32	26
MF	6	11	10	8
MH	8	15	31	30

Table 8: features of high K group – pre-study serum K level >4mmol/l

variable	average	2 SEM	95% CI		significant* intra	inter
1984 (n = 61)						
PS K - mmol/l	4.44	0.09	4.38	4.53		x
SP K - mmol/l	4.14	0.12	4.03	4.26	x	x
n drugs	1.69	0.38	1.31	2.07		x
1985 (n = 61)						
PS K - mmol/l	4.39	0.07	4.32	4.47		x
SP K - mmol/l	4.23	0.13	4.10	4.36	x	x
n drugs	1.66	0.34	1.32	1.99		x
K compliance	1.02	0.20	0.82	1.22		
BP code	1.64	0.24	1.40	1.88		x
age - years	54.40	2.30	52.20	56.70		
BMI	30.70	1.76	28.90	32.40		
time interval - minutes	214	42	172	256		
1984 + 1985 (n = 122)						
PS K - mmol/l	4.42	0.06	4.36	4.47		x
SP K - mmol/l	4.19	0.09	4.10	4.27	x	x
female:male ratio	3.5 : 1					

Table 11: number of subjects by drug class and K group

	low K		high K	
drugs	n	%	n	%
nil	2	4	32	26
diuretic	15	28	43	35
diuretic + BB	21	40	34	28
diuretic + BB + VD	11	21	4	3

BB = β-blocker
VDA = vasodilator

Table 12: number of subjects by selected drugs and K group

	low K		high K	
drugs	n	%	n	%
nil	2	4	32	26
MF + reserpine	2	4	8	7
MH + reserpine	14	26	17	14
MH + sotalol	2	4	8	7
MH + sotalol + prazosin	9	17	1	1

Table 13 shows the relationship (odds ratio) between several drug combinations and dichotomised serum K values. Reserpine and sotalol when combined with MH were associated with low serum K levels. The addition of prazosin to MH and sotalol increased the relative rate by > 10 but the numbers in the latter cell was small

Table 13: relative rates for low serum K on high serum K

drugs	RR	95% CI	
non-drug	0.11	0.03	0.48
MF	1.43	0.49	4.16
MH	0.52	0.22	1.22
MF + reserpine	0.59	0.11	2.72
MH + reserpine	2.22	1.00	4.93
MH + sotalol	2.35	0.32	17.20
MH + sotalol + prazosin	24.80		

In table 14 serum K values stratified for <3.5mmol/l (low K) and ≥3.7mmol/l (normal K) in subjects on sotalol and prazosin are compared with the values in subjects not on these drugs. The data show associations of both drugs with low serum K values.

Table 14: number of subjects on MH with or without sotalol and prazosin in a low K group and in a normal K (≥3.7mmol/l)

	low K	normal K		low K	normal K
on sotalol	13	1	on prazosin	11	5
not on sotalol	1	3	not on prazosin	3	11

In table 15 the mean serum K values in subjects during the study period were compared with the latest values observed in the same subjects in the pre-study period. The analysis shows that the use of prazosin was associated with a significant reduction in serum K levels. Reserpine with both formulations of moduretic was associated with hypokalemia in both periods but the associations were not statistically significant in all instances.

Table 15: mean serum K values the same subjects during the study period compared with values in the pre-study period

drug	n	K mmol/l SP	95% CI		K mmol/l PS	95% CI	
nil	58	4.12	4.00	4.24	4.17	4.04	4.31
MH	64	4.03	3.89	4.16	3.97	3.84	4.10
MF	31	3.86	3.66	4.06	3.87	3.72	4.02
MH + R	52	3.81	3.67	3.95	3.86	3.73	3.98
MF + R	20	4.06	3.81	4.30	3.75	3.50	4.00
MH + S	8	3.86	3.46	4.27	3.94	3.68	4.19
MH + S + P	13	3.32	3.07	3.57	3.80	3.59	4.01

Some features of the subjects from the low K group who were on half-strength moduretic, sotalol and prazosin are shown in table 16. Their serum K values during treatment with half-strength moduretic, sotalol, and prazosin (MSP Rx) are compared with values found in the period immediately preceding the change (other Rx).

Table 16: serum K values of subjects on MH, sotalol and prazosin compared with values when not on these drugs

Interval in minutes	serum K (mmol/l) MSP Rx	other Rx	dose (mg) of sotalol	prazosin	n. drugs other Rx	BP
1070	2.5	3.2	80	2	2	4
75	2.9	3.7	80	4	0	2
270	3.1	3.4	80	6	3	2
220	3.2	3.8	160	4	6	2
220	3.2	3.8	160	4	6	2
210	3.3	4.0	80	10	2	3
238	3.3	4.0	80	10	3	3
215	3.3	3.9	80	2	3	3
135	3.4	3.2	160	4	3	4
335	3.4	3.9	80	2	5	4
120	3.6	4.2	160	4	8	4
145	3.8	4.1	160	10	4	3
240	4.2	4.2	160	2	4	2
average	3.32	3.8			3.77	2.92
95% CI	3.07 - 3.59	3.57 - 4.01				

In tables 17 and 18 the relationship between severe hypertension (BP code ≥3) and mild hypertension (BP code = 2) and serum K is shown.

Table 17: BP and K status

	severe HT	mild HT
low K	9	10
high K	11	28

Odds ratio = 2.29; 95% CI = 0.73 – 7.16

Table 18: BP in low K and high K groups when on and not on MH, sotalol, and prazosin combined

	on MH+S+P		not on MH+S+P	
	severe HT	mild HT	severe HT	mild HT
low K group	6	0	3	11
high K group	0	0	10	28

DISCUSSION

The numbers in most cells were too low for robust statistical analysis. The data nevertheless suggest that prazosin lowers serum K levels and that reserpine might also do so. Reserpine which dilates the afferent arterioles in the kidney may therefore like other vasodilators increase plasma renin activity and K loss. The role of sotalol in K homeostasis could not be assessed because of small numbers. It does not however appear to have been associated with a low serum K level but it also did not seem to protect against drug-induced renin secretion and consequent K loss. The use of an adequate dose of a K-wasting thiazide diuretic with a possibly inadequate dose of the K-sparing amiloride in MH in contrast with a possibly more effective dose of amiloride in MF may have contributed to the observed hypokalaemia. This interpretation assumed that K loss plateaus despite an increasing dose of thiazide diuretic but parallels the dose of amiloride, but the differences in serum K levels between the two formulations of moduretic were contradictory. A high K intake did not seem to protect against hypokalaemia in the affected subset of subjects.

The reduction in serum K levels may therefore have been a response to an increase in renin secretion and the consequent activation of the RAS system caused by a low Na diet and a thiazide diuretic especially when combined with prazosin or reserpine. Because activation of the RAS system is also associated with blood pressure elevation prazosin prescribed to subjects with hypokalaemia could aggravate rather than ameliorate hypertension and the subjects could be diagnosed as suffering from refractory hypertension. The obverse could also hold: hypertension refractory to drugs which increase renin secretion is associated with low serum K levels.

This inference was supported by the finding that pre-study hypokalaemia was more prevalent among subjects with severe and/or refractory hypertension. As the subjects recruited into the study were not drug-naive their K status and degree of hypertension when not on anti-hypertension agents are not known. It was therefore

not possible to tell whether the degree of hypertension, the RAS status, and the hypokalaemia in the pre-study period were drug-induced or not.

If the serum K level reflects the level of plasma renin activity and RAS status it can be used as a marker for the pathophysiology of a subject's hypertension and a guide to discriminating and definitive therapeutic intervention.

The clinic stopped using sotalol and prazosin as soon as the low serum K trend was noted. The study was done several months later. Due to circumstances beyond my control the observations were not shared or further investigated.

Lessons learned:

- Well-structured and maintained medical records and management protocols can facilitate monitoring of patterns and timely corrective action.
- Serum K can serve as a cheap proxy for renin status and as such can be used as a guide to the rational management of hypertension.

References

[1] http://www.effieschultz.com/files/pdf/2004_HT_guidelines.pdf. Item 11. Records. pages 26 – 28.

[2] http://www.effieschultz.com/files/pdf/2004_HT_guidelines.pdf. Item 13.2. General and non-drug measures. pages 31 – 44.