subjects. It is desirable that the dosage schedule in intensive salicylate therapy be adjusted individually on the basis of the patient's predetermined salicylate elimination rate in order to prevent drug accumulation or gradual decline of drug concentration to subtherapeutic levels.

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Quinethazone, a new Oral Diuretic

GERALD SANDLER,* M.D., M.R.C.P.

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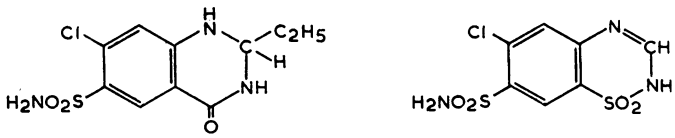
Quinethazone (Aquamox) is a recently introduced oral diuretic agent in which a cyclic carbamyl group has replaced the cyclic sulphamyl group present in the thiazides. It therefore differs basically from the thiazide diuretics in the absence of sulphur-1, 1-dioxide ring system from the benzothiadiazine molecule (Fig. 1).



QUINETHAZONE CHLOROTHIAZIDE

FIG. 1.—Chemical structure of quinethazone and chlorothiazide.

Several studies have established its effectiveness, which is similar to that of chlorothiazide (Ford, 1962 ; Seller *et al.*, 1962). Preliminary experimental observations suggested also that when quinethazone is used in combination with acetazolamide the natriuretic effect is enhanced but the urinary loss of potassium is reduced (Herken and Senft, unpublished observations, 1962).

It is the purpose of the present study to investigate the effectiveness of quinethazone as an oral diuretic both in normal subjects and in patients with congestive cardiac failure, and also to assess the effect of the combination of quinethazone and acetazolamide on the urinary loss of sodium and potassium in these patients.

Patients and Methods

Studies in Normal Subjects

The diuretic effect of quinethazone and acetazolamide alone and in combination was studied in four healthy adults (three male, one female) aged 25 to 27. During the investigations the subjects carried out normal hospital duties and took a normal diet with unrestricted fluid. The dose of quinethazone was 200 mg. and acetazolamide 500 mg. The drugs were given at 8 a.m., and subsequently two-hourly collections of urine were made for 10 hours. On the day preceding administration of each drug similar urinary collections were made to provide control levels of urinary volume and electrolyte excretion. A period of two days was allowed between administration of the different drugs. The order of the initial drug was varied so that each of three subjects respectively received quinethazone, acetazolamide, and a combination of quinethazone and acetazolamide to start. In addition these three subjects received chlorothiazide, 1 g., for comparison with the other drugs.

In the fourth subject fludrocortisone was used to increase urinary potassium excretion and so allow investigation of the effect of quinethazone and acetazolamide in inhibiting loss of potassium. Initially, fludrocortisone was given in a dose of 1.5 mg. at night and 1 mg. at 8 a.m. the next day, and two-hourly urine collections were made for 10 hours to provide control values of sodium and potassium excretion. Subsequently the same regime was adopted together with quinethazone alone and in combination with acetazolamide given with the morning dose of fludrocortisone. On each occasion a similar control collection was made on the day preceding drug administration. The volume of each specimen of urine was recorded and the content of sodium, potassium, and chloride estimated.

Clinical Studies

Clinical studies were carried out on 16 patients, and these were subdivided into three groups :

Group 1.—Six patients with rheumatic heart disease—four of whom had chronic congestive cardiac failure, and two who had never had cardiac failure (these two patients were being treated for subacute bacterial endocarditis at the time of study). The effects of single doses of 200 mg. of quinethazone and 500 mg. of acetazolamide, alone and in combination, were studied in this group.

Group 2.—Four patients with congestive cardiac failure due to rheumatic heart disease or cor pulmonale in whom quinethazone and acetazolamide were compared with chlorothiazide (1 g. dose).

Group 3.—Four out-patients with chronic congestive cardiac failure due to rheumatic heart disease or cor pulmonale in whom the effects of prolonged courses of quinethazone, 200 mg. daily, acetazolamide, 500 mg. daily, or chlorothiazide, 1 g. daily, were investigated.

In groups 1 and 2 the drugs were given at 10 a.m. and urine was collected for 24 hours from this time and assessed for volume and content of sodium, potassium, and chloride.

* From the Royal Infirmary, Sheffield.

A preliminary 24-hour collection was made on the day preceding administration of each drug, and two days were allowed between different drugs. All patients took a normal diet with unrestricted fluids, and existing treatment with digoxin was continued throughout the period of study. Serum electrolytes, blood urea, haemoglobin, and packed-cell volume were estimated on the morning of the control day and the day after drug administration. All patients were weighed daily and regular clinical assessment of cardiac failure was also made. In group 1 the drug used to initiate treatment was varied to minimize differences in response which might result from increasing duration of rest in hospital.

Comparison of quinethazone and acetazolamide with chlorothiazide in group 2 was carried out in two ways. In two patients the comparison was based on the A B B A principle designed by Gold *et al.* (1960), and in the remaining two patients the procedure adopted was that used in group 1.

All patients in groups 1 and 2 were allowed several days in hospital before any diuretic was given, to enable stable conditions to be attained.

The effect of prolonged daily administration of quinethazone and acetazolamide was studied and compared with chlorothiazide in group 3, each course of treatment lasting two weeks. The patients were seen at fortnightly intervals and observations made on body weight, degree of dyspnoea, and degree of pulmonary and systemic oedema. Estimation of serum electrolytes, blood urea, serum uric acid, haemoglobin, and packed-cell volume were also carried out at each attendance. Normal diet and unrestricted fluid were allowed throughout the study. The various drugs were again used in turn to initiate treatment.

Chemical Procedures

All chemical estimations were carried out on the Technicon Autoanalyser. Sodium and potassium were assessed by flame photometry, chloride by the mercuric thiocyanate method of Zall, Fisher, and Garner (1956), blood urea by the modified carbamido-diacetyl reactions of Skeggs (1957) and Marsh, Fingerhut, and Kirsch (1957), and serum uric acid by the phosphotungstic method of Kern and Stransky (1937).

Results

Normal Subjects

The mean increase in urine volume and excretion of sodium, potassium, and chloride is shown in Table I. The results represent the difference between the control value on the day preceding drug administration and that obtained with the drug, and are expressed as a percentage increase above the control levels. The maximum diuretic effect of quinethazone occurred in two to six hours, and the percentage increase of urinary volume during this period was greater than in the corresponding period after chlorothiazide administration, although a greater diuresis was obtained with chlorothiazide over the whole 10-hour period. The action of quinethazone was less prolonged than that of chlorothiazide. The combination of quinethazone and acetazolamide produced a greater increase of urinary volume than either drug singly, this being largely the result of a simple summation effect of both drugs. The percentage increase in urinary volume with the combination was greater than with chlorothiazide over the whole 10-hour period and in every two-hourly period.

The percentage increase of sodium excretion with quinethazone exceeded that with chlorothiazide in every two-hour urine specimen, and the natriuretic effect was still evident at 8 to 10 hours. When quinethazone and acetazolamide were combined the excretion of sodium was considerably enhanced

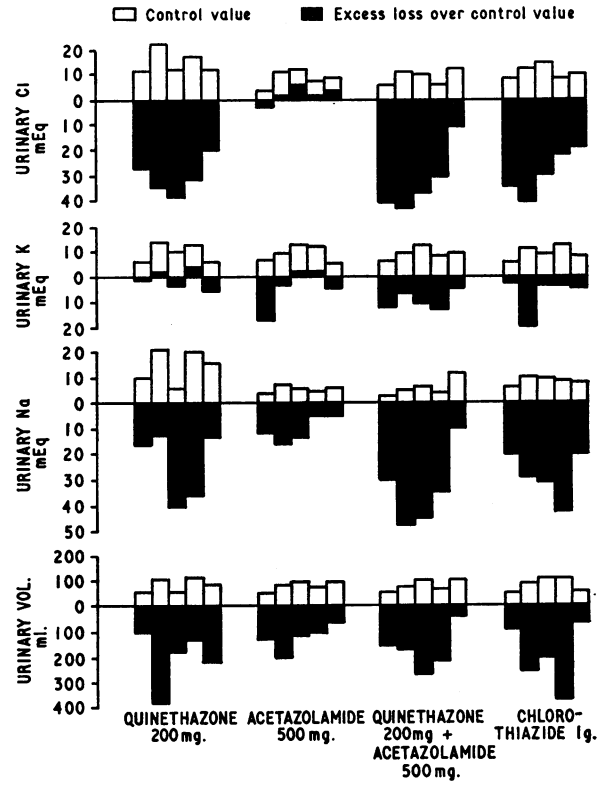


FIG. 2.—Urinary excretion of water, sodium, potassium, and chloride produced by quinethazone, acetazolamide, and chlorothiazide in a normal subject.

at every phase, but again this was largely the result of a simple summation effect of the two drugs. There was little difference between quinethazone and chlorothiazide in the percentage increase of urinary potassium excretion over the 10-hour period, although fluctuating differences occurred during the various two-hour collections. The addition of acetazolamide to quinethazone produced a threefold to fourfold increase in potassium excretion beginning within two hours of giving the drugs. The percentage increase of

TABLE I.—*Mean Changes in Urinary Volume and Sodium, Potassium, and Chloride Excretion in Three Normal Subjects (Results Expressed as a Percentage Increase Above Control Values)*

Drug	Mean Changes in Volume						Mean Change in Loss of Na^+						Mean Change in Loss of K^+						Mean Change in Loss of Cl^-					
	2-hourly Specimens					Total 10 hr.	2-hourly Specimens					Total 10 hr.	2-hourly Specimens					Total 10 hr.	2-hourly Specimens					Total 10 hr.
	1	2	3	4	5		1	2	3	4	5		1	2	3	4	5		1	2	3	4	5	
Quinethazone 200 mg. ..	113	227	60	−44	13	25	424	262	667	244	167	310	106	18	47	12	74	38	371	249	306	163	194	248
Acetazolamide 500 mg. ..	237	108	138	256	37	118	590	362	256	202	359	324	472	120	25	51	164	103	68	−0·5	−22	−0·2	−11	−15
Quinethazone 200 mg. Acetazolamide 500 mg.	319	258	179	186	163	186	1,091	1,151	657	548	319	684	327	148	85	60	116	124	453	232	187	234	174	238
Chlorothiazide 1 g.	142	144	26	41	72	73	391	273	305	179	127	239	100	146	27	−2	15	41	295	202	112	95	80	155

chloride excretion was most pronounced with quinethazone alone, exceeding that produced both by chlorothiazide and by the combination of quinethazone and acetazolamide. Like sodium loss, chloride excretion was most marked in the first six hours, but the action was sustained over the whole 10-hour period.

The detailed results obtained in one of the normal subjects are shown in Fig. 2. The control levels of water, sodium, and potassium excretion follow approximately similar patterns at different periods of the study, confirming the validity of comparison of the different drugs. The maximum excretion of sodium occurred within four to six hours of giving quinethazone, and loss of chloride and water followed approximately the pattern of sodium excretion. Chlorothiazide resulted in a similar pattern of excretion of water, sodium, and chloride to quinethazone, but potassium loss was less marked with quinethazone in this subject.

Fig. 3 shows the effect of fludrocortisone in enhancing potassium excretion in a normal subject. Quinethazone, either alone or in combination with acetazolamide, increased the potassium loss still further throughout the whole 10-hour period.

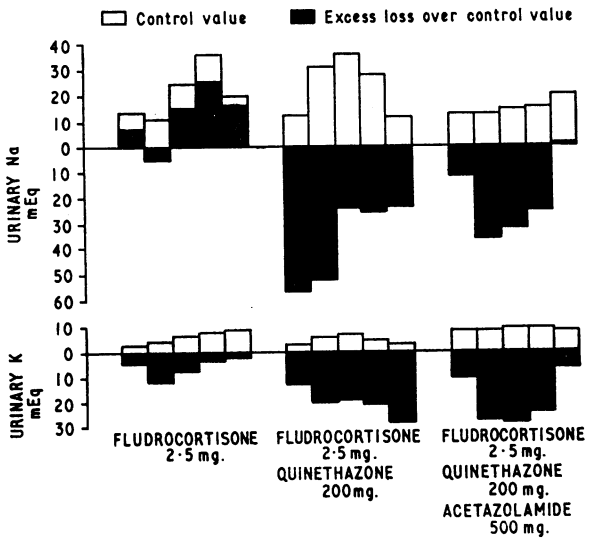


FIG. 3.—Effect of quinethazone alone and in combination with acetazolamide on urinary loss of sodium and potassium produced by fludrocortisone in a normal subject.

Clinical Studies

Group 1.—Table II shows the effects of quinethazone and acetazolamide in the six patients with rheumatic heart disease, four of whom had chronic congestive cardiac failure. In these four patients quinethazone proved an effective diuretic, and the combination of quinethazone and acetazolamide increased urinary volume but the effect was less than the sum of the effects of the individual drugs. The percentage increase of sodium excretion with quinethazone was almost three times greater than the control value, and the addition of acetazolamide increased sodium excretion but again did not produce a complete summation effect. Potassium excretion was enhanced by quinethazone, though to a less extent than sodium excretion, and the combination of quinethazone and acetazolamide increased the potassium excretion considerably. Chloride loss with quinethazone was less marked than sodium loss.

An effective diuresis also occurred with quinethazone in the two patients in group 1 with compensated rheumatic heart disease; but, although excretion of sodium was increased, this was considerably less marked in relation to the control values than in the patients with congestive failure. Acetazolamide was more effective than quinethazone in promoting loss of water and sodium in these two patients, and was even more effective than the combination of acetazolamide with quinethazone. The increased loss of potassium produced by quinethazone exceeded that of sodium, but it is of interest that in one of the two patients in this group (Case 5) the addition of acetazolamide resulted in an even smaller loss of potassium than occurred on the preceding control day.

Group 2.—Comparison of quinethazone with chlorothiazide in four patients with congestive cardiac failure showed no consistent differences between the two drugs. Fig. 4 compares the effects of quinethazone with chlorothiazide in a patient with cor pulmonale using the A B B A principle. In this patient there were no obvious differences between the drugs in excretion of sodium and water, while potassium excretion was greater with quinethazone, but in two other patients in this group potassium loss was greater with chlorothiazide. The combination of quinethazone and acetazolamide, compared similarly with chlorothiazide, was more effective in promoting loss of water and sodium, but the excretion of potassium was also enhanced and exceeded that with chlorothiazide (Fig. 5). The mean urinary sodium/potassium excretion ratio in all the in-patients with cardiac failure was 2.1/1 with quinethazone compared with 1.2/1 with chlorothiazide in the four patients in whom chlorothiazide was used (group 2). The combination of quinethazone and acetazolamide resulted in an increase in the ratio to 2.6/1.

In both groups 1 and 2 no consistent changes were seen in the levels of serum sodium, potassium, chloride, bicarbonate, and blood urea; nor did the haemoglobin and packed-cell volume vary significantly. There was also no significant

TABLE II.—*Changes in 24-hour Excretion of Water, Sodium, Potassium, and Chloride with Quinethazone and Acetazolamide Alone and in Combination*

Case No.	Sex and Age	Diagnosis	Increase in Volume			Increase in Na^+ Loss			Increase in K^+ Loss			Increase in Cl^- Loss		
			Q	A	Q + A	Q	A	Q + A	Q	A	Q + A	Q	A	Q + A
		Group 1 Decompensated Patients												
1	F 62	R.H.D.	320	−45	350	33·2	39·6	172·4	33·4	14	52·7	66	13	110·3
2	M 59	R.H.D.	540	1,265	1,530	−74	107	74	−15	72	19	133	−13	102
3	F 59	R.H.D. (with ascites)	400	40	570	53	27	135	18·8	14	35	126·2	−10	127
4	F 59	R.H.D.	225	275	350	4·5	2·3	4·7	−7·3	17·7	70·4	19·7	−22·7	59·2
Mean		Vol.-ml. Electrolytes-mEq	370·2	383·7	700	14·3	44·0	96·0	7·5	29·4	44·3	86·2	−8·2	99·6
		% Increase Above Control	52	47	79	270	106	339	141	85	261	158	−9	278
		Group 1. Compensated Patients												
5	M 16	R.H.D., S.B.E.	725	700	870	56·1	108·1	187·8	48·8	6·2	−23·5	148	2	87
6	F 18	R.H.D., S.B.E.	290	1,520	960	32·3	157·7	39·1	3·4	57·5	15·4	64·5	84	158
Mean		Vol.-ml. Electrolytes mEq	507·5	1,110	915	44·2	132·9	113·4	26·1	31·8	−4·0	106·2	43	122·5
		% Increase Above Control	44	106	67	41	199	117	69	43	−13	91	54	81

Q = Quinethazone. A. = Acetazolamide. R.H.D. = Rheumatic heart disease. S.B.E. = Subacute bacterial endocarditis.

change in the clinical state or body weight in response to a single dose of any diuretic drug.

Group 3.—Table III shows the clinical and biochemical results of a two-weeks course of 200 mg. of quinethazone and 500 mg. of acetazolamide alone and in combination, and compares the effects with a similar course of chlorothiazide 1 g. daily. All four patients had required previous maintenance therapy with conventional diuretics for a period of at least several months. Body weight was lowest in every case with the combination of quinethazone and acetazolamide, but

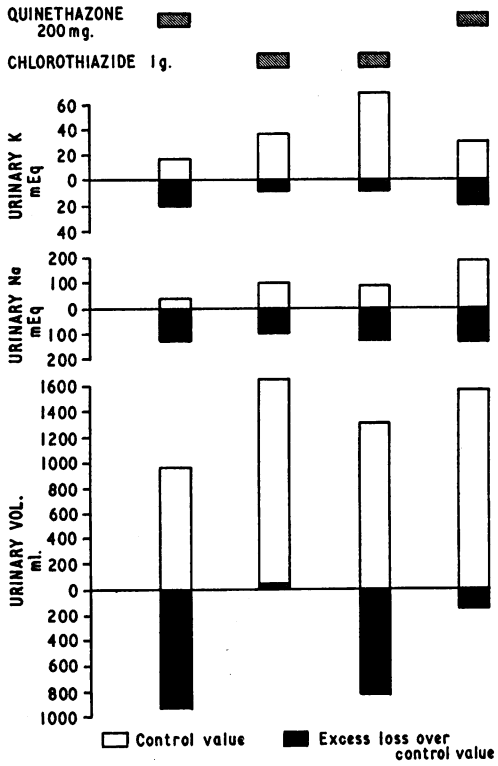


FIG. 4.—Comparison of urinary loss of water, sodium, and potassium with quinethazone and with chlorothiazide in a patient having cor pulmonale.

there was no correlation with the degree of dyspnoea or oedema. Blood urea, however, rose by an average of 45% compared with the control level in three of the four patients when the combination was used, and the serum uric acid was also highest when both drugs were used together. In addition the greatest fall in serum potassium occurred with combined quinethazone and acetazolamide in three of the four patients, the average fall being 28% compared with the control level, but there were no clinical manifestations of hypokalaemia.

There were no consistent changes in serum levels of sodium, chloride, or bicarbonate, or in the haemoglobin or packed-cell volume.

Discussion

Preliminary studies of quinethazone (Aquamox) have demonstrated its effectiveness in patients with cardiovascular or renal disease, and in patients with both compensated and decompensated heart disease (Seller *et al.*, 1962 ; Ford, 1962),

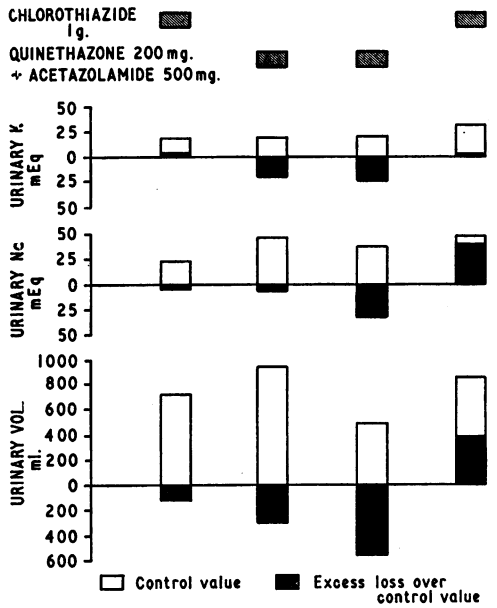


FIG. 5.—Comparison of urinary loss of water, sodium, and potassium with chlorothiazide and a combination of quinethazone and acetazolamide.

the most effective dose being 200 mg. (Seller *et al.*, 1962). In the present study an effective diuretic action has been produced by quinethazone in normal subjects, although the total diuretic effect over a 10-hour period was less marked than with chlorothiazide. Sodium and chloride excretion, on the other hand, were greater with quinethazone than with chlorothiazide, the loss of both ions continuing for at least 10 hours, but little difference in potassium excretion was found between the two drugs. When the urinary potassium was increased by fludrocortisone in a normal subject, neither quinethazone alone nor the combination of quinethazone and acetazolamide

TABLE III.—*Clinical and Biochemical Results in Out-patients (Group 3) with Prolonged Daily Use of Quinethazone and Acetazolamide, and Chlorothiazide*

Case No.	Sex and Age	Diagnosis	Drug	Clinical				Biochemical—Serum Values						P.C.V. %
				Weight kg.	Dyspnoea	Oedema		Na^+ mEq/l.	K^+ mEq/l.	Cl^- mEq/l.	HCO_3^- mEq/l.	Urea mg/100 ml.	Uric Acid mg./100 ml.	
						Pulmonary	Systemic							
9	F 62	R.H.D.	Q	45·4	–	+	–	138	4·4	84	—	43	2·6	43
			A	47·0	–	–	–	136	4·6	103	20·7	43	4·5	38
			Q+A	43·2	–	+	–	136	4·7	95	27·5	53	5·7	43
			C	44·5	–	+	–	125	5·2	97	24·4	41	3·1	45
10	M 54	Cor pulmonale	Q	83·4	+	–	+	136	3·3	100	—	70	7·6	39
			A	81·5	+	+	–	131	4·1	107	17·6	75	5·2	41
			Q + A	80·0	+	+	–	131	3·0	99	22·4	98	5·5	42
			C	81·8	+	–	–	129	4·4	99	20·3	87	6·5	42
11	M 54	R.H.D.	Q	85·4	–	+	–	136	4·9	99	—	36	—	—
			A	86·8	–	–	–	131	3·7	110	15·8	36	4·2	44
			Q+A	84·1	–	–	–	129	2·7	95	25·3	41	6·7	51
			C	86·6	–	–	–	131	3·6	100	27·1	34	5·2	40
12	F 70	R.H.D.	Q	48·8	–	–	+ +	128	4·2	99	22·3	26	2·4	35
			A	53·1	–	–	+ +	134	4·6	109	21·5	32	3·5	33
			Q + A	48·6	–	–	+	134	3·1	96	24·9	55	4·4	33
			C	50·6	–	+ +	+ +	134	4·5	97	23·5	34	3·5	35

was successful in conserving potassium, and in fact produced an even greater urinary loss. The addition of acetazolamide to quinethazone enhanced the diuretic and natriuretic effect of quinethazone in the three normal subjects by a simple summation effect between two drugs, and a concurrent increase of potassium excretion was also produced.

The effectiveness of quinethazone in congestive cardiac failure, whether due to rheumatic heart disease or chronic lung disease, was also confirmed in the present study. The diuretic and natriuretic action of quinethazone was less marked than that of chlorothiazide, but no consistent difference was evident between the two drugs in respect of potassium excretion. However, a more favourable sodium/potassium excretion ratio was found with quinethazone than with chlorothiazide, and similar results were reported by Seller *et al.* (1962). The combination of quinethazone and acetazolamide was considerably more effective than with quinethazone alone in promoting loss of water and sodium, but the excretion of potassium was also greatly increased. There was no evidence to suggest that in congestive cardiac failure the combination of quinethazone and acetazolamide produced a natriuretic effect greater than the sum of the individual effects, or that the combination favourably influenced potassium loss.

The diuretic effect of quinethazone was not confined to decompensated rheumatic heart disease as it was evident also in the three young patients with rheumatic heart disease and subacute bacterial endocarditis who had never been in cardiac failure. The addition of acetazolamide to quinethazone in one of these compensated patients provided the only instance in the present study where a favourable effect was produced on potassium excretion.

Prolonged daily use of quinethazone was satisfactory in controlling clinical manifestations of cardiac failure in outpatients though no better than chlorothiazide. The combination of quinethazone and acetazolamide was more effective in controlling body weight than either quinethazone alone or chlorothiazide, but the combination also produced the most unfavourable effect on the levels of serum potassium, blood urea, and serum uric acid. No gastro-intestinal side-effects, skin rashes, or haematological complications were encountered with quinethazone given for two weeks, and there were no clinical features of gout with the combination of quinethazone and acetazolamide.

The site of action of quinethazone is not known with certainty, but is thought to be at the renal tubular level where it depresses tubular resorption of sodium (Seller *et al.*, 1962). The increase in the diuretic and natriuretic effect of quinethazone produced by the addition of acetazolamide is probably due to the complementary action of a drug causing loss of sodium and chloride and one producing loss of bicarbonate. Although no toxic side-effects were seen with the combination in the present study, the use of the combination may be limited by the potential hazards of acetazolamide, which include the production of hyperchloraemic acidosis that may aggravate the acidosis already existing with chronic respiratory insufficiency or chronic renal failure, hypokalaemia due to excessive urinary potassium loss, and a number of allergic reactions (Reisner and Morgan, 1956).

Summary

The effects of quinethazone (Aquamox), a new oral diuretic, which is neither a thiazide derivative nor a mercurial compound, have been studied in four normal subjects, in patients with chronic congestive cardiac failure due either to rheumatic heart disease or to chronic lung disease, and in two patients with compensated rheumatic heart disease who had never been in cardiac failure. In addition the effect of combining acetazolamide with quinethazone has been investigated and a comparison has been made between quinethazone and chlorothiazide.

In the normal subjects a single dose of 200 mg. of quinethazone proved an effective diuretic, and the natriuretic action exceeded that with 1 g. of chlorothiazide. Potassium excretion was similar with quinethazone and chlorothiazide. The addition of 500 mg. of acetazolamide to quinethazone enhanced the diuretic and natriuretic action by simple summation of the effects of the two drugs, but a concurrent increase in potassium excretion was also produced.

The effectiveness of a single dose of 200 mg. of quinethazone was confirmed in eight in-patients with congestive failure, although the loss of water and sodium was less than with 1 g. of chlorothiazide ; potassium loss was again similar with the two drugs. A good response was also obtained with quinethazone in the two patients with compensated rheumatic heart disease. Combination of acetazolamide with quinethazone enhanced water loss and both sodium and potassium excretion.

Prolonged daily use of 200 mg. of quinethazone was as effective as chlorothiazide in the clinical control of four outpatients with congestive cardiac failure. Although body weight was lowest with the combination of quinethazone and acetazolamide, unfavourable effects on serum potassium and blood urea were seen. The potential hazards of acetazolamide are pointed out which may limit the use of the combination.

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