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THE INFLUENCE OF ORALLY ADMINISTERED ALKALI AND ACID ON THE RENAL EXCRETION OF QUINACRINE, CHLOROQUINE AND SANTOQUINE¹

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Haag and Larson (1) demonstrated in 1942 that in the case of nicotine the extent of urinary excretion of a chemical may be related to the reaction of urine. They emphasized the importance of taking into consideration the dissociation constant of a drug and the relative reabsorbability of the free and dissociated base. Extending these studies to the urinary excretion of quinine in man, Haag, Larson and Schwartz (2) found in 1943 that the urinary output could be doubled by passing from an alkaline to an acid urine and they ascribed the difference to greater resorption of quinine from the urinary tract when the urine is alkaline.

In connection with studying the behavior of newer antimalarial drugs in man, the extent of the influence of urinary acid-base balance upon renal excretion was re-examined. Parallel studies by Emerson and Dole (3) indicated that renal clearance of quinacrine is subject to 100-fold variations due principally to 2 variables, the urinary pH and the renal plasma flow. Work conducted at the same time by the Army Malaria Research Unit at Oxford (4) emphasized the striking parallelism between urinary excretion of quinacrine and ammonia. They found that the ratio of urinary quinacrine to urinary ammonia is directly proportional to the plasma quinacrine concentration. Trager and Hutchinson (5) in 1946 similarly found the urinary excretion of quinacrine to be closely correlated with the urinary excretion of ammonia.

The present investigation was designed to ascertain the effect of oral ingestion of alkali and acid upon the renal excretion of this general type of organic compound. The substances selected

for study were quinacrine, chloroquine (SN-7618), and santoquine (SN-6911).

METHODS AND MATERIALS

The patients utilized in this study were from the middle and older age groups. No restriction was placed on the diet or upon water intake during the observations and the patients were permitted the freedom of the ward. All drugs were administered orally and according to a single general dosage pattern. A high initial dose was administered during the first 24 hours and this was followed by the serial administration of smaller maintenance doses. Several days were allowed to elapse for the stabilization of the plasma drug concentration before observations were begun.

Alkali was administered orally in the form of sodium bicarbonate at a total daily dose of 20 grams. This was given in doses of 2.5 grams at 2-hour intervals during the day for 7 doses and once during the night. Acid was administered orally in the form of ammonium chloride at a total daily dose of 8 grams. The dosage schedule was the same as for the bicarbonate, each dose being 1.0 gram.

Plasma and urine estimations were performed by methods developed by Brodie. Quinacrine was determined fluorometrically by the single extraction procedure using ethylene dichloride (6); the alkaline wash was used in the urine determinations but not in the plasma determinations. The ethylene dichloride extract was made acid with trichloroacetic acid (Masen [7]). Santoquine was estimated by the colorimetric procedure depending upon a salt formation with methyl orange (Brodie *et al* [8]).

The recently developed specific method (1947) for the analysis of chloroquine (9), involving the use of heptane and alkaline washes, was not yet available at the time of the present study. The procedure used involved the extraction of chloroquine with ethylene dichloride at pH 11, followed by the return of the drug to dilute acid. The acid solution was buffered at pH 9.5 and subjected to ultra-violet irradiation for a 1-hour period. Concentration was estimated by measurement of fluorescence generated by the irradiation. This procedure includes in the measurement interfering degradation products of chloroquine which are found in plasma to the extent of 20 to 50 per cent. However, it is quite specific for urine since only negligible amounts of these degradation products appear in urine.

¹ This work was carried out under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and New York University.

Urine pH was determined in all cases on freshly voided urine samples using a glass electrode. No precautions were taken to maintain CO_2 tensions in the transfer of fluid. Consequently the data on urinary pH must be taken as close approximations rather than precise estimations of the pH of bladder urine. During the period of alkali administration the urinary pH rose to values between 7.5 and 8.0; during the acid period the pH fell to values of 4.0 to 5.0.

RESULTS

Quinacrine

The experimental data obtained on 4 patients receiving maintenance doses of 0.2 and 0.3 grams of quinacrine dihydrochloride are summarized in Table I. The amounts and concentrations noted are expressed in terms of free base. The control values for the renal excretion of quinacrine varied from 1 to 3 per cent of the daily dose. Excretion was reduced to 0.07 to 0.3 per cent of the daily dose during alkalization and increased to 2 to 6 per cent during acidification. There was in individual cases a 14- to 25-fold increase in going from one state to the other. As is to be expected, such a change is not reflected in the plasma quinacrine concentration since the extent of renal excretion in relation to the oral dose is low in all cases. The plasma level of quinacrine remained roughly constant in 1 patient who was at equilibrium before the observations were begun, and

TABLE II

The influence of orally administered alkali and acid on the renal excretion of chloroquine (SN-7618)

Patient	Si.	Wo.	Ke.	Al.	Ch.
Drug intake	200 mgm. per day	400 mgm. per day	400 mgm. per day	400 mgm. per day	400 mgm. per day
	Urinary excretion	Urinary excretion	Urinary excretion	Urinary excretion	Urinary excretion
	milligrams per 24 hours				
Control period	113 104 75	30 105 99	133 84 119	62 110 103	110 60
NaHCO_3 20 grams daily for 3 days	47 24 41	55 26 17	53 34 37	136 79 61	60 27 30
NH_4Cl 8.0 grams daily for 3 days	119 188 137	54 75 114	119 208 205	147 192 317	103 80

increased as a more or less linear function of time in the 2 who had not as yet achieved an equilibrium plasma quinacrine concentration.

Chloroquine

The experimental data obtained on 5 patients receiving 0.2 or 0.4 grams of chloroquine daily are summarized in Table II. The daily excretion, in terms of percentage of the daily dose, was high in all patients as compared to quinacrine. This varied in the case of chloroquine, from 15 to 50

TABLE I

The influence of orally administered alkali and acid on the renal excretion of quinacrine

Patient	Wr.		Wo.		Ni.		Na.	
Drug intake	300 mgm. per day		200 mgm. per day		200 mgm. per day		200 mgm. per day	
	Urinary excretion	Plasma level	Urinary excretion	Plasma level	Urinary excretion	Plasma level	Urinary excretion	Plasma level
	mgm. per 24 hrs.	µg. per L.	mgm. per 24 hrs.	µg. per L.	mgm. per 24 hrs.	µg. per L.	mgm. per 24 hrs.	µg. per L.
Control period	2.92 7.47 5.98	81	4.63 3.7	54	1.93 0.80	23 31	7.14 4.38 9.3	50 54
NaHCO_3 20 grams daily for 3 days	1.32 0.9 0.98		1.73 0.66 0.54	40 59	0.33 0.27 0.13	48 55	2.1 0.79 0.42	87 97
NH_4Cl 8.0 grams daily for 3 days	5.85 13.6 13.9		6.65 8.25	48	0.14 1.8 3.2	67	5.4 10.3 12.1	102

per cent in the control periods; was reduced to 7 to 20 per cent during alkalization and was increased to 20 to 90 per cent during acidification.

Santoquine

Observations on santoquine were limited to a single individual. However, they were designed to stress the effects of changes in the renal excretion of drug upon the maintenance of the plasma santoquine concentration while on a constant drug intake. Each phase of alkali and acid administration was of 5 days' duration and 2 complete cycles of alkali-acid treatment were obtained (Table III).

TABLE III

The influence of orally administered alkali and acid on the renal excretion of santoquine (SN-6911)

Patient McK.

Drug intake: 400 mgm. per day

	Urinary excretion	Plasma concentration
	mgm. per 24 hrs.	micrograms per liter
Control period	154 107 202 190	410 400
NaHCO ₃ 12.0 grams daily for 5 days	36 77 56 82	630
NH ₄ Cl 6.0 grams daily for 5 days	90 384 290 249 266	738 685 418
NaHCO ₃ 20.0 grams daily for 5 days	199 49 37 60 40	432 775 1010
NH ₄ Cl 8.0 grams daily for 5 days	166 181 191 149 183	881 343 324

It should be noted that a large portion of the daily dose of santoquine is excreted in the urine. This was perhaps more in the patient utilized than is usual. During the control period average renal excretion accounted for 41 per cent of the daily dose. This was decreased to an average of 16 per cent during the first alkalization and increased to an average of 64 per cent during the

first acidification. Similar results were obtained during the second cycle.

As is to be expected in such a circumstance, the plasma santoquine concentrations reveal a cycle which can be correlated with the intervals of low and high renal excretion. During the alkaline phase of low drug excretion, the plasma level slowly rose; during the acid phase of high excretion, the plasma level fell.

DISCUSSION

It is apparent from the data that the renal excretion of the anti-malarial drugs is dependent upon a series of variables in addition to the concurrent plasma concentration. These variables are of sufficient importance in the determination of the renal drug excretion, that the latter may not be used directly as an approximation method to estimate the general level of the plasma drug concentration.

The refinement introduced by the British workers (4) involving the simultaneous measurement of urinary ammonia and quinacrine does permit of an indirect determination of plasma quinacrine from measurements on urine alone. It appears to us that ammonia excretion may be governed by urinary acid-base balance in a manner similar to the other weak organic bases, such as the anti-malarial drugs. The ammonia measurement provides an index of variation in urinary acid-base balance. By taking the quinacrine concentrations in relationship to ammonia excretion, the Oxford workers were able to eliminate the variable of pH. Trager and Hutchinson (5) seem to ascribe a causal role to ammonia in promotion of urinary excretion; it appears far more likely that ammonia and quinacrine excretions are concomitantly altered in a similar manner by urinary changes in hydrogen ion concentration.

The experimental data are interesting for yet another reason. It must be assumed that at least a portion of the drug eliminated by the kidneys is excreted by a process other than glomerular filtration. This follows from a consideration (in the case of quinacrine) of the extent to which it is bound to the non-diffusible constituents of plasma (some 80 to 90 per cent of the total) and the observed rates of excretion. The mechanism responsible for such tubular excretion as occurs ap-

pears to be quite different from those responsible for the tubular excretion of such substances as phenol red, creatinine, diodrast, etc. The latter manifest considerable stability whereas this does not obtain for the tubular excretion either of quinacrine or of chloroquine and santoquine.

Data are not available with which to define the mechanisms involved though there is sufficient to warrant certain reasonable speculations. It is suggested that a small portion of the excreted anti-malarial drug is filtered at the glomerulus, the amount determined by the glomerular filtration rate, and the concentration of unbound drug in plasma water. A second portion is considered to be added to this in the proximal segment by a process of active tubular excretion similar to the conventional processes considered above. The combined filtered and secreted drug is presented to the distal segment of the nephron in concentrated form due in part to the reabsorption of water in the proximal tubule and loop of Henle. In the distal segment, a process of adjustment of hydrogen ion concentration takes place followed by equilibration of drug across the tubular membrane. The data are in keeping with the assumption that free base is more freely diffusible across the cells of the distal segment than the mono-acidic and diacidic salts of the drugs studied. Such being the case there may be expected to be net gain or loss of drug depending upon the relation between the hydrogen ion concentration of the tubular urine and that of peritubular fluid (*ca.* 7.34). Alkalinization of the tubular urine would increase the proportion of drug in the form of free base and in this way would promote reabsorption; acidification would counteract reabsorption by reducing the proportion of free base. A somewhat similar mechanism has been suggested to cover the renal tubular excretion of neutral red in the amphibian kidney (10).

The observation of Trager and Hutchinson (5) that the plasma quinacrine level rose soon after oral ingestion of large doses of ammonium chloride, would seem to provide another basis for the altered urinary excretion. The elevation in plasma level observed in their experiment is of brief duration and is in keeping with the increased plasma levels observed in dog experiments (11) in which acute acidosis was produced by CO_2 administra-

tion. The plasma quinacrine measurement in the present study revealed no significant changes in level since by design the blood sampling and ammonium chloride administration were timed to elicit only sustained changes. The promotion of urinary excretion of quinacrine by ammonium chloride appears to us not to be secondary to plasma drug elevation but rather a direct result of the acid urine counteracting drug reabsorption in the tubules.

Relatively large changes in excretion rate are expected to be reflected in changes in the plasma drug level on a constant regimen of oral dosage only when the absolute rate of excretion of the substance is high. This phenomenon is brought out strikingly in the patient receiving santoquine. During the acid periods drug excretion amounted to as much as 50 to 75 per cent of the orally administered dosage. The effective dosage was thereby reduced to $\frac{1}{2}$ or $\frac{1}{4}$ of the actual administered dose. During the alkaline period, the per cent of drug excretion was small, namely 20 per cent of the ingested dose. Under these circumstances, the effective oral dose was as high as 80 per cent of the actual administered dosage.

Quinacrine excretion, though markedly altered by acid-base changes, remains in all circumstances such a small percentage of the orally administered dosage that changes in renal elimination would not be reflected in the maintained plasma level. The changes in drug excretion, from 0.2 per cent during the alkaline period to 4 per cent in the acid period, would not reduce the effective oral dosage to an appreciable extent. The actual measurements on quinacrine plasma levels in the present experiment showed no cyclic fluctuation in acid and alkaline phases as were observed with santoquine.

One therapeutic implication of the above results is obvious. When toxicity is encountered during the administration of certain anti-malarial drugs, acidification of the urine by ammonium chloride would promote renal excretion of the drug. Effectiveness of such therapy should be good only with drugs of high excretion rate such as chloroquine and santoquine. With a drug like quinacrine which is excreted in the urine to only a slight degree even upon acidification, such therapy should have little value.

SUMMARY

1. The oral administration of ammonium chloride increases the renal excretion of quinacrine, chloroquine and santoquine in individuals on a constant maintenance dose of the drugs. Sodium bicarbonate given in a similar manner causes a retention of these drugs.

2. Changes in renal excretion are reflected in changes in plasma level only when the absolute rate of excretion of the substance is high.

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