THE EFFECT OF URINARY pH ON THE ELIMINATION OF QUININE IN MAN

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Recently it was reported from this laboratory that in human smokers urinary nicotine elimination is markedly affected by the pH of the urine (1). In brief, it was found that when the urine was alkaline only one-fourth as much nicotine was eliminated as when the urine was acid. This difference was explained on the basis of greater nicotine resorption through the urinary mucosa from an alkaline urine, the alkalinity increasing the proportion of alkaloidal base, the form in which, presumably, the alkaloid is most efficiently resorbed.

Because the pK_a value of quinine is so similar to that of nicotine (8.3 vs. 8.07, fig. 1), it was thought that the elimination of quinine might behave in a manner similar to that of nicotine. This possibility seems especially interesting in view of the observations of Gnilosirova-Guryea (2) on the importance of alkaline diets during quinine therapy, and Sinton's (3) recommendation of alkalies as useful adjuvants to quinine in the treatment of malaria. Accordingly, we have made the following studies on the effect of changes in urinary pH on the urinary elimination of quinine in man.

EXPERIMENTAL. The subjects were male medical students in apparent good health. No restrictions were placed on their habits, except that they were requested to keep their urine volume as constant as possible during the experimental periods.

For the purpose of acidifying the urine 1 gram of ammonium chloride was given orally four times a day; for alkalizing the urine 4 grams, more or less, of an effervescent alkaline preparation was given six times a day. No difficulty was encountered in maintaining the urine acid. With some individuals alkalinization was difficult, and with one subject it was impossible to maintain the pH above 6.94 satisfactorily. pH determinations were made with a glass electrode.

One-half gram quinine (as the sulfate) was administered orally in capsules when the urine had reached the desired pH, and two consecutive 24 hour samples of urine were collected. The subjects continued to take the acidifying or alkalizing drugs during the entire period. In some subjects a 24 hour control specimen of the urine was also collected immediately before administration of the quinine.

Quinine determinations were made by the fluorimetric method of Kelsey and Geiling (4) on ether extracts of the urine. In three experiments in which 10 mg. of quinine was added to 100 cc. of urine the average recovery was 98%. Specimens of urine from four subjects prior to receiving quinine were entirely negative for quinine by this method.

A second series of quinine determinations was made on the urine without extraction and purification. Control experiments showed that if properly diluted (1:100–1:200) the average recovery amounted to 92% of the quinine added. When four samples of urine from subjects not taking quinine were tested by this technic fluorimetric readings were obtained, indicating the presence of from 0 to 4 mg. equivalent of quinine for a 24 hour sample.

RESULTS AND DISCUSSION. Table 1 gives the results obtained on ether extracts of urine, and shows that about twice as much quinine was eliminated when the urine was acid as when the urine was alkaline. This indicates to us that quinine is more actively resorbed from the urinary tract when the urine is alkaline than when it is acid. The elimination values as a whole fall within the

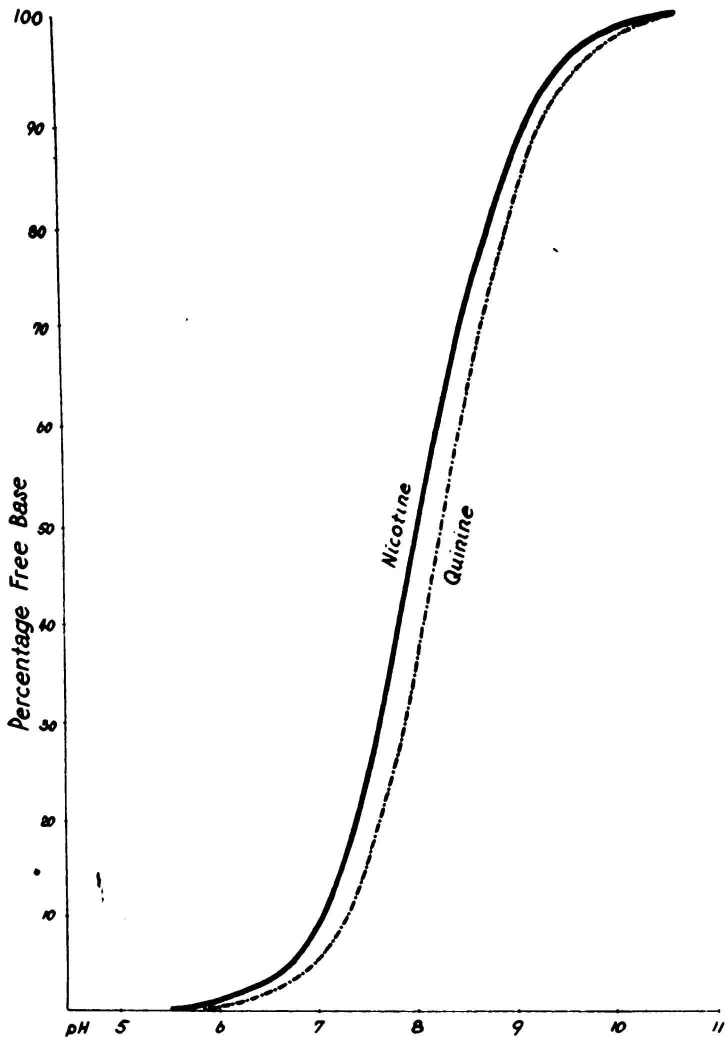

FIG. 1. EFFECT OF pH ON THE PERCENTAGE OF NICOTINE AND QUININE PRESENT AS THE ALKALOIDAL BASE

The above curves were constructed from values obtained using the formula $pH = pK_a + \log \frac{base}{salt}$. The pK_a value used for quinine was that obtained by Sir S. Rickard Christophers (Ann. Trop. Med., **31**: 43, 1937). The pK_a value used for nicotine was obtained by us by electrometric titration.

range reported by other investigators (5). Subject No. 10 was unable to elevate his urinary pH above 6.94; nevertheless, there was a slight difference between the quinine elimination at this pH and at pH 5.06.

While it has been shown that the oral administration of alkalies apparently facilitates absorption of quinine from the gastrointestinal tract (6), this in itself could not account for a decreased urinary elimination; rather one would expect the reverse.

We believe that the reason relatively greater resorption from the urinary tract occurs with nicotine in the case of smokers than with quinine in the present experiments is due largely to two factors. First, there is a difference between the pK_a values of nicotine and quinine which may be favorable to greater resorption of nicotine. Secondly, in the case of the quinine administration, the drug was given in one single large dose, whereas, with nicotine, its intake, and hence

TABLE 1

Percentage of ingested quinine in ether extracts of urine

SUBJECT	ALKALINE URINE							ACID URINE						
	First 24-hour sample			Second 24-hour sample				First 24-hour sample			Second 24-hour sample			
	pH	Volume	Amount excreted	pH	Volume	Amount excreted	Total amount excreted	pH	Volume	Amount excreted	pH	Volume	Amount excreted	Total amount excreted
		cc.	*per cent*		*cc.*	*per cent*	*per cent*		*cc.*	*per cent*		*cc.*	*per cent*	*per cent*
1	7.20	2,140	9.4	7.22	2,380	1.5	10.9	5.80	2,100	14.0	5.38	1,200	1.9	15.9
2	7.47	1,535	6.5	7.61	1,300	1.6	8.1	5.48	1,915	18.9	5.19	1,660	2.6	21.5
3	7.72	2,350	9.2	7.65	1,720	1.1	10.3	5.17	3,115	13.7	5.21	1,540	1.4	15.1
4	7.47	1,315	4.5	7.21	1,735	0.7	5.2	5.19	1,665	13.2	4.99	1,515	1.5	14.7
5	7.69	1,835	5.9	7.37	1,415	0.9	6.8	5.09	3,935	10.1	5.19	2,120	3.4	13.5
6	7.30	1,620	7.4	7.62	1,025	1.0	8.4	5.05	1,610	19.5	5.14	1,275	3.0	22.5
7	7.60	1,675	9.3	7.80	1,825	1.7	11.0	5.09	1,900	15.3	5.13	1,830	1.9	17.2
8	7.38	2,065	8.7	7.59	1,570	1.9	10.6	5.02	1,890	13.6	4.94	1,073	1.1	14.7
9	7.57	1,250	6.2	7.60	1,165	2.7	8.9	5.14	925	17.7	4.97	755	3.4	21.1
Averages...	7.49	1,754	7.45	7.52	1,570	1.45	8.9	5.22	2,117	15.1	5.12	1,441	2.25	17.4
10*	6.94	1,485	9.8	6.21	790	2.7	12.5	5.21	1,500	12.0	5.06	872	2.1	14.1

* See text.

its elimination, in the case of smokers, was gradual during a period of many hours.

On averaging the 48 hour values obtained on unextracted urine the fluorescent equivalent of 25.7% of the administered quinine was found in the urine when it was maintained alkaline, and 29.2% when it was maintained acid. Comparison of these figures with those gotten on extracted urine indicates that after quinine administration there occurs in the urine a fluorescent quinine metabolic product (or products) that is not extractable with ether. In view of this it may be well to reserve judgment as to the exact identity of the fluorescent material in the ether soluble fraction of such urine. At present, the possibility that the latter fraction may include ether soluble fluorescent metabolic products of quinine in addition to unchanged quinine has not been eliminated. However, due to the lack of suitable methods of proven specificity for the determination of quinine in biological materials we have tentatively assumed that the ether soluble fraction represents unchanged quinine.

While the subjects of these tests were requested to keep their urinary volume reasonably constant during the experimental periods, they did not always do this too well. However, comparison of the total urinary volumes (48 hr.) of the nine subjects while the urine was maintained alkaline and while it was maintained acid, showed no statistically significant differences. Further evidence that variations in urinary volume of the magnitude encountered was not an important deciding factor in these excretion studies may be adduced from the results obtained in 2 subjects in whom the urinary volume was deliberately varied (table 2).

TABLE 2

Relationship between urinary volume and quinine excretion following the oral administration of 500 mg. quinine

SUBJECT	LOW URINE VOLUME			HIGH URINE VOLUME		
	pH	Urine	Quinine eliminated first 24 hours	pH	Urine	Quinine eliminated first 24 hours
		cc.	mg.		cc.	mg.
1	5.80	2,100	70	5.45	4,290	58.9
11	5.15	1,030	65	5.50	3,870	69.7

SUMMARY

When quinine was given in a dose of 500 mg. orally to human subjects, it was found that the extent of urinary elimination was related to the pH of the urine. When the urine was maintained alkaline one-half as much quinine, on an average, was eliminated as when the urine was acid (8.9 vs. 17.4%). This difference is assumed to be due to greater resorption of quinine from the urinary tract when the urine is alkaline than when the urine is acid.

Although the amount of quinine "saved" to the patient is small on alkalinization of the urine, this saving plus the advantages of an alkaline regime suggested by clinical investigators on the basis of other types of observations, seem to recommend further consideration of the use of alkalies in the quinine therapy of malaria.

These experiments again indicate the importance of considering the possible influence of urinary pH in quantitative studies on the urinary excretion of certain chemicals.

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