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The effects of drug therapy on urinary pH — excipient effects and bioactivation of methenamine

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Summary

The effect of ascorbic acid and potassium citrate on urinary pH is studied. It is shown that ascorbic acid is of questionable value for the acidification of urine and that effervescent tablets of the vitamin may in fact alkalinise urine. This may explain the contradictory literature data on the urine-acidifying properties of the acid. At therapeutic doses, potassium citrate mixture B.P.C. alkalinises urine sufficiently to interfere with the bioactivation of methenamine to formaldehyde. Since both potassium citrate mixture B.P.C. and methenamine are used to treat lower urinary tract infections, their concomitant use should be avoided.

Introduction

The effect of urine alkalinisation and acidification on the elimination of weak electrolytes is well known (Beckett et al., 1968; Beckett and Rowland, 1965). This knowledge has been used clinically. Urine acidification, for example, has been used to increase the rate of excretion of drugs such as weakly basic antimalarial drugs (Jailer et al., 1947), quinidine (Gerhardt et al., 1969), amphetamine (Beckett and Rowland, 1965) and sympathomimetic agents (Rappolt et al., 1979). Urine alkalinisation has on the other hand been used to solubilise cysteine in cysteinuria and uric acid in hyperuricemia. The elimination kinetics of weakly acidic drugs has also been altered by this approach either to minimise adverse effects or to optimise activity (Kostenbauder et al., 1962; Bailey, 1974, Brumfitt and Percival; 1962 and Murphy et al., 1965). Examples include reducing the renal toxicity of high dose methotrexate and inhibiting the crystallisation of insoluble sulphonamides in renal tubules.

Urine alkalinisation is also used as an end-point in the management of cystitis. Alkalinisation is claimed to minimise symptoms and to inhibit the growth of many of the micro-organisms involved. For this purpose potassium citrate mixture B.P.C. is widely used in general practice. Despite this there does not appear to have been a systematic study of its effect on urinary pH. This is particu-

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larly important since it is often used together with methenamine, a formaldehyde-releasing agent which requires activation in a low-pH environment (Miller and Phillips, 1970; Musher and Griffith, 1974; Musher et al., 1976; Naccarto et al., 1979; Gollamudi et al. 1981). Indeed to achieve this environment, high-dose ascorbic acid is often used with conflicting results.

This study was initiated in an attempt to gain some more information in this confused area of therapy.

Materials and Methods

Ascorbic tablets were obtained as conventional tablets (500 mg Macarthys, Essex, England) and as effervescent tablets (1 g Redoxon tablets. Roche Products Ltd, Welwyn Garden City, U.K.). Potassium citrate mixture B.P.C. was prepared fresh using BP-grade materials. Enteric-coated methenamide mandelate tablets (Mandelamine 500 mg tablets, W.R. Warner and Co. Ltd., Hampshire, U.K.) were used in all the studies. All the other reagents used were of laboratory grade or higher.

Subjects for study

Nine healthy male volunteers aged between 23 and 39 years participated in this study. All the volunteers were drawn from among postgraduate students and staff and all gave their informed consent. None of the subjects were on medication of any kind, including non-prescription drugs. Not all of the subjects participated in all of the studies.

Measurement of urinary pH

The pH meter was calibrated with buffer solutions of pH 4 and pH 10 at room temperature everyday. Urine samples were allowed to equilibrate with the room temperature before pH determination. Agitation of urine samples during pH determination was kept to a minimum to avoid any increase in pH due to loss of carbon dioxide (Marshall, 1922). pH of urine samples collected in the day time was determined within 3 h of collection. Urine samples collected in the evening were stored in the refrigerator overnight. All pH determinations were performed within 24 h of micturition. When 24-h pooled samples were required, individual urine samples collected were stored in the refrigerator immediately after pH determination.

Urine samples collected over a 24 h period, that is from the first sample collected in the morning to the last sample collected just before bed were pooled together for each subject. These will be referred to as the 24-h pooled samples. pH of the 24-h pooled samples were determined within the next 24 h.

Control of subjects and sample collections

No restrictions were made on the diet, fluid intake and physical activities of the subjects. The subjects were, however, advised to maintain their usual dietary habits throughout the study period and to avoid deviation from the normal, especially in the consumption of food and drinks that are known to affect the urinary pH. These include citrus fruits and juices, large quantities of milk, cheese, plums, prunes and cranberries.

Micturition was according to natural urge and was not scheduled except in studies investigating postprandial alkaline tides and circadian rhythms or where indicated. The total volume of urine at each voiding was collected in separate containers and the exact time of micturition recorded. The pH was determined immediately or the urine was stored in the refrigerator and determined within 24 h. Such storage did not significantly alter the pH readings (< 0.05 pH unit).

Study of urinary postprandial alkaline tide

Hourly urine samples were collected from two subjects (subjects 2 and 4) for two days each to monitor urinary pH profile throughout the day. Control of study and pH determinations were as stated in previous sections.

Study of circadian rhythm of urinary pH

Urine samples from subject 4 were collected for 30 days.

Study of effects of potassium citrate mixture B.P.C. ascorbic acid tablets B.P. and effervescent ascorbic acid tablets (Redoxon) on urinary pH

Seven subjects (subjects 1–7) participated in a

4 treatment cross-over study. For reasons unrelated to the drugs, one subject (subject 7) dropped out after 2 treatments.

The treatment, dose, dosage frequency were as laid out in Table 1.

During each treatment period, except for treatment A, subjects received drugs for a total of 7 days. The first dose was taken from Friday. Urine samples were collected from the third day (Sunday) onwards. Each treatment period ended on the seventh day (Thursday) evening unless otherwise indicated.

Between each treatment there was a break of one week to allow for recovery from the effects of prior treatment.

Study of urinary pH and urinary formaldehyde levels in subjects receiving methenamine mandelate with and without the coadministration of plain ascorbic acid tablets B.P. and potassium citrate mixture B.P.C.

4 subjects (subjects 1, 2, 4 and 5) participated in this 3-treatment sequential trial. Dose and dosage frequency for each treatment were as stated in Table 2.

The trial protocol was as laid out in Table 3.

1.5 g of methenamine mandelate tablets were taken as stat dose at 13.00 h on Sunday; thereafter 1 g was taken at 18.00 h and 23.00 h. For the next 4 days (Monday–Thursday) the dose was as stated in Table 2.

Ascorbic acid tablets (plain) B.P. and potassium citrate mixture B.P.C. were taken for 6 days from Saturday to Thursday during their respective treatment periods.

Urine samples were collected from the day after the first dose of methenamine (i.e. from Monday) until Thursday.

To facilitate the analysis of urinary formaldehyde levels the first 4 urine samples of the day were collected at scheduled time intervals. Micturition was scheduled at 08.00, 12.00, 14.30 and 17.00 h. All subsequent samples for the day were not scheduled and micturition was according to the natural urge.

Urinary formaldehyde levels were determined for the first 4 samples of the day. The first samples were analysed within 3 h of micturition and the next 3 samples were all analysed within half an h of micturition. 10% of each volume of urine sample were used to obtain the 24-h pooled sample.

Determination of urinary formaldehyde levels

A colourimetric method was used for the determination of urinary formaldehyde levels. The method used was an adaptation of earlier procedures (Chrastil and Wilson, 1975; Gollamudi et al. 1979) 2.5 ml of urine were diluted to 50 ml with distilled water. 15 ml of the diluted solution was shaken vigorously for 3 min with 1 g of mercuric chloride. The solution was then filtered through Whatman no. 1 filter paper. The filtrate was shaken a second time with 1 g of mercuric chloride and again filtered. One ml of the filtrate was then transferred to a stoppered boiling tube, mixed thoroughly with 1 ml of tryptophan 0.1% reagent followed by one ml of concentrated sulphuric acid 98% w/v and 0.2 ml of ferric chloride 1% reagent. The resulting solution was heated in a water bath maintained at 70 °C for 90 min and allowed to cool to room temperature.

TABLE 1

Treatment, preparations and dosage regimen

Treatment	Drug	Dose/dosing time (h)
A	no drug	–
B	Ascorbic acid tablets B.P.C. (plain) 500 mg	2 g 3 times a day 08.00, 15.30, 23.00
C	Effervescent ascorbic acid (Redoxon) tablets 1 g	2 g 3 times a day 08.00, 15.30, 23.00
D	Potassium citrate mixture B.P.C.	10 ml 4 times a day 08.00, 13.00, 18.00, 23.00

TABLE 2

Treatment, preparations and dosage regimens (methenamine)

Treatment	Drugs	Dose/dosing time (h)
E	Methenamine mandelate tablets (Mandelamine) 500 mg	1 g 4 times a day 08.00, 13.00, 18.00, 23.00
F	Methenamine mandelate tablet (Mandelamine) 500 mg + plain ascorbic acid tablets B.P.C. 500 mg	1 g 4 times a day 08.00, 13.00, 18.00, 23.00 2 g 3 times a day 08.00, 15.30, 23.00
G	Methenamine mandelate tablets (Mandelate) 500 mg + potassium citrate mixture B.P.C.	1 g 4 times a day 08.00, 13.00, 18.00, 23.00 10 ml 4 times a day 08.00, 13.00, 18.00, 23.00

TABLE 3

Trial protocol (methenamine)

Subjects	Week/treatment		
	1	2	3
1	E	G	–
2	E	G	–
4	E	F	G
5	E	F	–

Codes as in Table 2.

The absorbance of the solution was determined spectrophotometrically at 575 nm. A blank correction was obtained by carrying distilled water through the assay procedure. The correction for background absorbance by urine constituents was carried out by measuring absorbance of drug-free urine samples from the same subjects collected while they were not on methenamine. Each subject provided 2 days of drug-free urine samples for the correction of background absorbance.

A calibration curve was obtained by carrying known concentrations of aqueous formaldehyde solutions (20, 50, 100, 150, 200, 250, 300, 350 and 400 μg/ml) through the assay procedure. Preliminary study showed that methenamine was completely removed by the treatments with mercuric chloride. Addition of methenamine did not influence the slopes of the formaldehyde calibration curve. Addition of drug-free urine for the formaldehyde calibration curve was also found to be inconsequential when the appropriate blank corrections were made.

Calibration curves were constructed on 5 different occasions and the reproducibility of the slopes is shown by the close agreement in the results. The mean and the S.D. were 0.00734 and 0.000119 absorbance units/μg/ml, respectively. A standard solution of 100 μg/ml of formaldehyde was carried through the assay procedure everyday as a control. All analyses were performed in triplicate.

Statistical analysis of results

Statistical analysis of the pH values were performed after conversion to hydrogen ion (H^+) concentrations in order to avoid errors introduced by averaging the negative logarithmic values (Ayres et al., 1977).

Statistical analysis of results was performed with each subject acting as his own control.

F-test for analysis of variances and *t*-test for analysis of means were performed (Moore et al., 1972). Where the variances were significantly different and the number of samples was less than 30, the analysis of means was performed by the method advised by Dixon and Massey (Daniel, 1978).

Results and Discussion

Although circadian rhythms have been reported for urinary pH (Rijberg, 1943; Barnett and Blume, 1938) preliminary studies carried out in this study showed (Figs. 1 and 2) that day to day variations is large and intersubject variability is high. When extensive data were collected for long periods of time (30 days and 240 urine samples) a consistent pattern emerged (Fig. 3). However, it can be seen

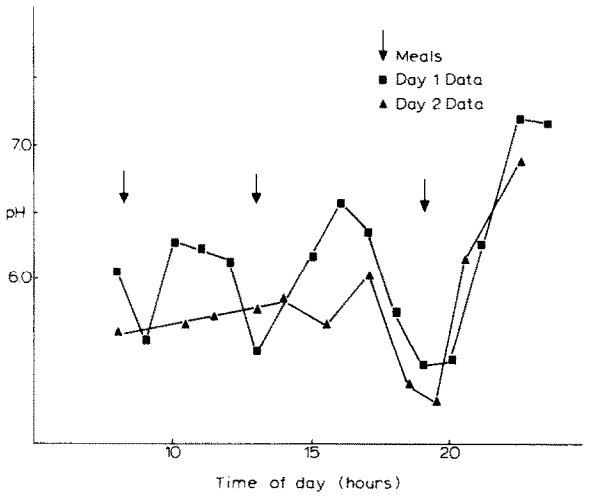


Fig. 1. Variation in urinary pH throughout the 24-h day. Subject 2.

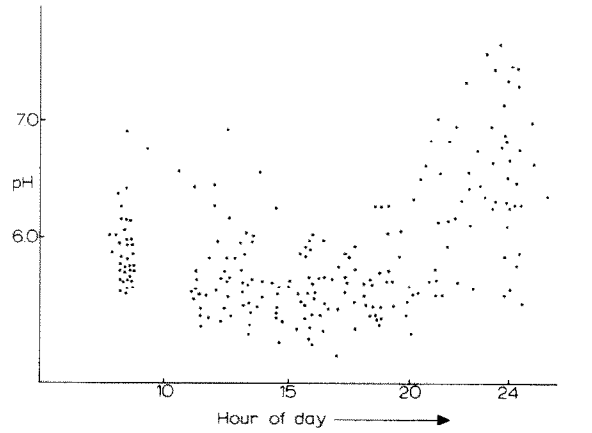


Fig. 2. Variation in urinary pH throughout the 24-h day. Subject 2.

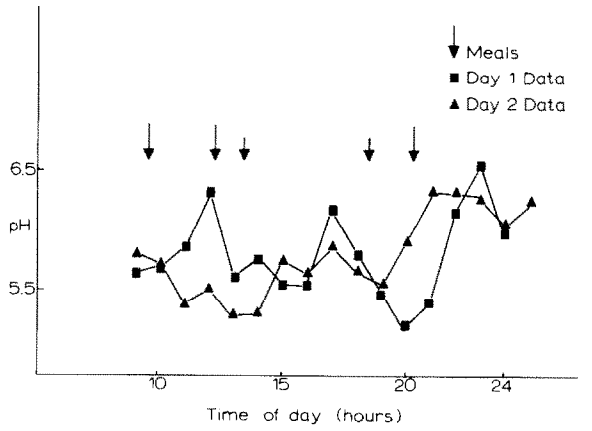


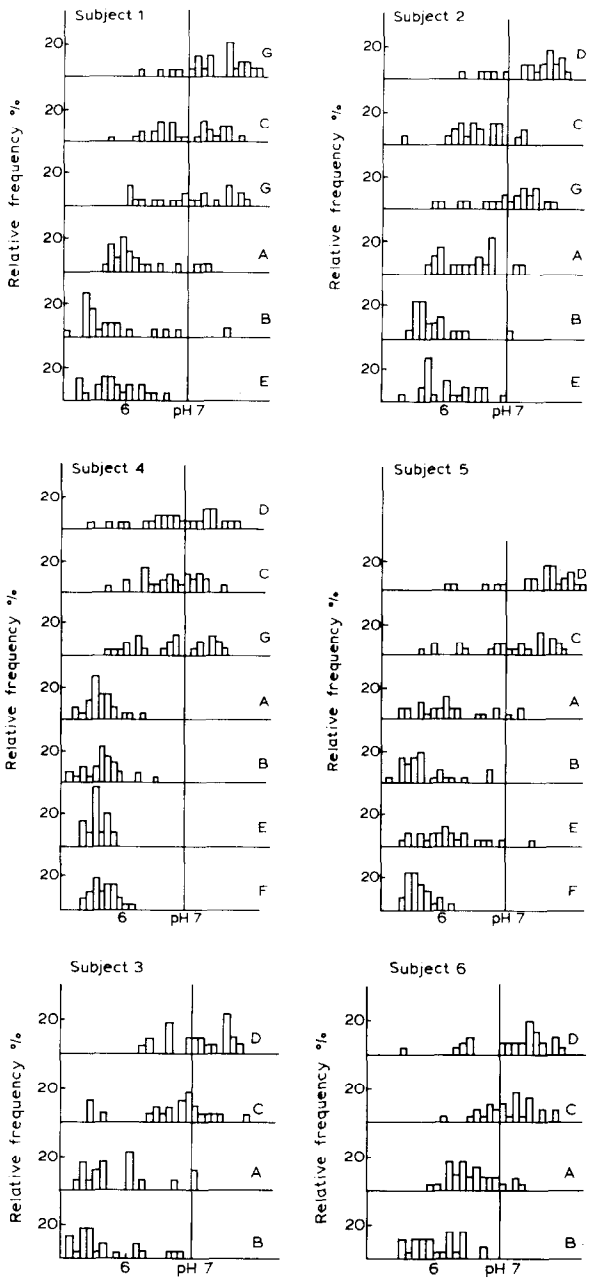
Fig. 3. Urinary pH–time profile. Subject 4.

that at any given time of day the variability in urinary pH was so high that single time measurements do not appear satisfactory for monitoring the effects of ingested agents on this parameter. Postprandial alkaline tides as previously reported by Elliot et al. (1959), Rijberg (1943) and Vaziri et al. (1980) also appear inconsistent (Figs. 1 and 2). Therefore, for all subsequent studies all urine samples were collected and each individual subject acted as his own control. The mean urinary pH calculated from the pH of all the individual urine samples was not significantly different from the pH of the 24-h pooled samples thus suggesting that the buffer capacity of the urine samples was not significantly different from each other.

Effects of potassium citrate mixture B.P.C. and ascorbic acid

Potassium citrate mixture B.P.C. is widely used as a urine-alkalinising agent for the symptomatic relief of cystitis. Yet, there is little documented evidence in the literature on the magnitude of the pH change. One study using 4 g sodium citrate 4 times daily showed that this sodium salt increased urinary pH (Muller and Van Rijssen, 1977). The mechanism by which citrate alkalinises urine is unclear but increased potassium intake leads to a secondary fall in hydrogen ion concentration in response to increased secretion of potassium ions in the distal renal tubules (Mudge, 1980). Fig. 4 shows that potassium citrate mixture did in fact increase urinary pH at the dose given in all of the subjects studied. A mean pH increase of more than one unit over the control value was observed using both sample mean and 24 hour pooled samples (Table 4).

In contrast to potassium citrate, ascorbic acid is used to acidify urine. The literature however is highly confusing. Barton et al. (1981) and Hetey et al. (1980) for example concluded that ascorbic acid was ineffective as a urine acidifier. The first group of authors used i.v. ascorbic acid (2 g single dose) while Hetey et al. (1980) used 1 g 4 times daily without specifying the dosage form. McDonald and Murphy (1959) on the other hand reported that ascorbic acid was effective for this purpose. Furthermore Muiznieks (1978) reported that pure ascorbic acid was more effective than



CODES A Control
B Plain ascorbic acid tablets (2g 3 times daily)
C Effervescent ascorbic acid tablets (2g 3 times daily)
D Potassium citrate mixture BP (10ml 3 times daily)
E Methenamine tablets (1g 4 times daily)
F Methenamine tablets (1g 4 times daily) + plain ascorbic acid tablets (2g 3 times daily)
G Methenamine tablets (1g 4 times daily) + Potassium citrate mixture BP (10ml 4 times daily)

sodium ascorbate. The present study gives some indication of the reasons for the wide discrepancies reported by previous authors. Firstly, very different dose regimens were used in the different studies and urine sample protocols were also very different. In a number of the studies the dosage form is not even specified (e.g. Nahata et al. 1977; Travis et al., 1965; Murphy et al., 1965; Hetey et al., 1980). The sampling protocols and experimental methods also appeared inadequate in a number of studies in that inherent variability as seen in Figs. 1 and 2 were not taken into sufficient account. Nitrazine paper was used for end-point measurement in some relatively recent papers (Naccarto et al., 1979 and Murphy and Zelman, 1964). The data in Fig. 3 show that the formulation determines the effect of ascorbic acid on urinary pH. Effervescent ascorbic acid tablets generally increased urinary pH while plain ascorbic acid tablets had the opposite effect. This is more clearly seen in Table 4. Some of these changes were, however, small in that in two of the subjects on plain ascorbic acid and some on effervescent ascorbic acid, the change observed did not attain statistical significance at the $P < 0.05$ level (Table 5). All effervescent ascorbic acid tablets are formulated with a base which includes an alkaline carbonate. The formulation used in this study contains 1 g of sodium bicarbonate. Bicarbonates are known to alkalinise urine (Beckett, 1965; Bennett, 1978; Jailer, 1947; Kostenbauder et al., 1962) and it is apparent that at the ratios used in the effervescent formulations the bicarbonate overwhelms the weak acidifying properties of ascorbic acid and tartaric acid which are also present in the product. In a number of the studies using 1-g tablets it is almost certain that effervescent formulations were used since the bulk properties of ascorbic acid are such that 1 g tablets are bulky

Fig. 4. Effect of drug treatment on urinary pH. A, control; B, plain ascorbic acid tablets (2 g, 3 times daily); C, effervescent ascorbic acid tables (2 g, 3 times daily); D, potassium citrate mixture B.P.C. (10 ml 3 times daily); E, methenamine tablets (1 g, 4 times daily); F, methenamine tablets (1 g, 4 times daily) + plain ascorbic acid tablets (2 g, 3 times daily); G, methenamine tablets (1 g, 4 times daily) + potassium citrate mixture B.P.C. (10 ml, 4 times daily).

TABLE 4

Effect of methenamine mandelate treatment alone or in combination with other agents on urinary pH.

Subject	Control			Ascorbic acid tablets BP			Ascorbic acid effervescent tablets			Potassium citrate mixture B.P.C.		
	n	$\bar{x} \pm$ S.D.	$\bar{p}$H	n	$\bar{x} \pm$ S.D.	$\bar{p}$H	n	$\bar{x} \pm$ S.D.	$\bar{p}$H	n	$\bar{x} \pm$ S.D.	$\bar{p}$H
1	24	1.0036 ± 0.6553	6.00	23	2.7679 ± 1.9874	5.56	24	1.0036 ± 0.6553	6.00	31	0.2287 ± 0.3432	6.64
2	19	0.5971 ± 0.5105	6.22	22	1.8742 ± 0.9804	5.73	19	0.5971 ± 0.5105	6.22	22	0.5343 ± 0.9030	6.27
3	18	2.2369 ± 1.8060	5.65	22	3.1001 ± 2.2333	5.51	18	2.2369 ± 1.8060	5.65	24	0.6509 ± 1.1627	6.19
4	27	2.5773 ± 1.2867	5.59	31	2.5858 ± 1.7825	5.59	27	2.5773 ± 1.2367	5.59	28	0.3027 ± 0.4113	6.52
5	27	1.3757 ± 1.3107	5.86	25	2.5811 ± 1.7193	5.59	27	1.3757 ± 1.3107	5.86	26	0.2940 ± 0.5112	6.53
6	31	0.3355 ± 0.2389	6.47	26	1.1423 ± 0.8484	5.94	31	0.3355 ± 0.2389	6.47	28	0.1093 ± 0.1313	6.96

n = number of urine samples; $\bar{x}$ = mean of hydrogen ion concentration $\times 10^6$; S.D. = standard deviation; pH = pH corresponding to $\bar{x}$.

and generally conventional formulations of 1 g ascorbic acid are not commercially available. From the present study it can be concluded that the use of effervescent formulations would invalidate any study investigating the urine-acidifying activity of ascorbic acid. A number of authors have, on the basis of limited data, indicated that this may be a problem (Roy, 1977; McLeod and Nahata, 1978) but it would appear that their caution has gone unheeded.

Effect of methenamine mandelate alone and in combination with ascorbic acid or potassium citrate mixture B.P.C.

Methenamine is available both as conventional (Hiprex) and as enteric-coated tablets (Mandelamine). The base is usually formulated as the hippurate or mandelate in order to reduce the need to acidify urine for activation of the methenamine to formaldehyde. In one study the hippurate was reported to produce high urinary levels of formaldehyde more promptly than the mandelate but no attempt was made to dissociate the effect of the enteric coating from the effect of a change in counterion (Seneca and Peer, 1969). Conclusions about the relative efficacy of the different salts must therefore be drawn in this light. In the present study only the enteric-coated formulation was used. The results shown in Fig. 4 and Table 6 show that any lowering in urinary pH by methenamine mandelate was small and addition of plain ascorbic acid tablets did not significantly

TABLE 5

Statistical analysis of the effect of treatment on urinary pH

Subject	Plain ascorbic acid tablets Change in mean urinary pH		Effervescent ascorbic acid tablets Change in mean urinary pH		Potassium citrate mixture B.P.C. Change in mean urinary pH	
	All samples	24-h pooled samples	All samples	24-h pooled samples	All samples	24-h pooled samples
1	−0.44	−0.37	+0.64	+0.79	+1.11	+1.28
2	−0.49	−0.69	+0.05 *	+0.15 *	+0.87	+0.98
3	−0.14 *	−0.16 *	+0.63	+0.75	+1.21	+1.45
4	0 *	−0.04 *	+0.93	+1.07	+0.82	+1.19
5	−0.27	−0.52	+0.68	+0.86	+1.13	+1.43
6	−0.53	−0.45	+0.49	+0.61	+0.27	+0.77

All the pH changes are significant at the $P < 0.05$ level except for those marked *. For explanation of sample description and dosage schedules see Materials and Methods.

TABLE 6

Effect of methenamide mandelate treatment alone or in combination with other agents on urinary pH

Subject	Control			Methenamine mandelate tablets			Methenamine mandelate + ascorbic acid tablets plain			Methenamine mandelate + potassium citrate mixture B.P.C.		
	n	$\bar{x} \pm$ S.D.	$\bar{p}$H	*n*	$\bar{x} \pm$ S.D.	$\bar{p}$H	*n*	$\bar{x} \pm$ S.D.	$\bar{p}$H	*n*	$\bar{x} \pm$ S.D.	$\bar{p}$H
1	24	1.0036 ± 0.6553	6.00	22	2.1364 ± 1.7190	5.67				22	0.2516 ± 0.3193	6.60
2	19	0.5971 ± 0.5105	6.22	22	1.2233 ± 1.0688	5.91				22	0.2230 ± 0.3650	6.65
4	27	2.5773 ± 1.2867	5.59	24	2.7598 ± 0.9695	5.58	25	2.2639 ± 1.0382	5.65	24	0.3940 ± 0.4796	6.40
5	27	1.3757 ± 1.3107	5.86	23	1.2901 ± 1.1956	5.89	25	2.6119 ± 0.9903	5.58			

TABLE 7

Statistical analysis of the effect of methenamine administration alone or in combination with other agents on urinary pH

Subject	Methenamine mandelate tablets		Methenamine mandelate tablets + ascorbic acid tablets plain		Methenamine mandelate tablets + potassium citrate mixture B.P.C.	
	All samples	24-h pooled samples	All samples	24-h pooled samples	All samples	24-h pooled samples
1	−0.33	−0.23 *	–	–	0.93	1.32
2	−0.31	−0.22 *	–	–	0.74	0.86
4	−0.03 *	−0.01 *	+0.09 *	+0.1 *	0.84	0.91
5	−0.03 *	−0.11 *	−0.31 *	+0.3 *	–	–

All the pH changes are significant at the $P < 0.05$ level except for those marked *. For explanation of sample description and dosage schedules see Materials and Methods.

TABLE 8

Comparison of urinary formaldehyde levels during treatment with methenamine mandelate alone and in combination with potassium citrate mixture B.P.C.

Urine sample	Methenamine mandelate		Methenamine mandelate and potassium citrate mixture B.P.C.		Statistical comparison of formaldehyde levels
	pH	Mean urinary formaldehyde level ± S.D. (μg/ml)	pH	Mean urinary formaldehyde level ± S.D. μg/ml	
Subject 1					
08.00 h	5.78	279 ± 43	6.71	80 ± 51	S
12.00 h	6.03	59 ± 30	7.57	24 ± 6	NS *
14.30 h	5.51	57 ± 27	7.37	26 ± 6	NS *
17.00 h	5.54	50 ± 20	6.51	17 ± 8	S
Subject 2					
08.00 h	5.98	106 ± 57	6.30	48 ± 33	NS **
12.00 h	5.90	58 ± 25	7.26	21 ± 3	S
14.30 h	6.01	43 ± 21	7.08	16 ± 4	NS *
17.00 h	5.73	47 ± 20	6.86	6 ± 7	S
Subject 4					
08.00 h	5.80	209 ± 54	6.19	89 ± 42	S
12.00 h	5.63	81 ± 22	6.36	40 ± 21	S
14.30 h	5.42	69 ± 14	6.29	28 ± 8	S
17.00 h	5.44	73 ± 17	6.59	28 ± 14	S

S = statistically significant, $P < 0.05$; pH = mean urinary pH (with prior conversion to hydrogen ion centrations). The 08.00-h samples were analysed between 2 to 3 h after micturition.

* $0.1 > P > 0.05$. ** $0.2 > P > 0.1$.

improve the results. This is in agreement with data presented in Table 5 which showed some lowering in pH using plain ascorbic acid. The pH drop was not statistically significant in at least two of the subjects.

Analysis of the data from the potassium citrate/methenamine treatment showed a significant rise in pH in all 3 subjects (Table 7). Clearly addition of methenamine mandelate to the treatment did not alter the direction of the pH changes induced by the potassium citrate mixture. If an increase in pH follows such treatment, will this then lead to a clinically significant drug–drug interaction? There seems to be some divergence of opinion on this. One data sheet (Hiprex, 1986) advises against the concomitant use of potassium citrate mixture with methenamine hippurate treatment while no other (Mandelamine 1984) makes mention of this. Echoing manufacturer's advice, some compendial references also make the same confusing distinction (e.g. Martindale, 1982) under hexamine hippurate and mandelate. Others do not make any such mention for either compoumd (British National Formulary, 1986). Most standard texts (Griffin and D'Arcy, 1975; Hansten, 1985) on adverse drug interaction also do not make any recommendation on this subject although Stockley (1981) indicated that an interaction should be expected. To explore this aspect further, the generation of formaldehyde in urine following administration of methenamine mandelate with and without potassium citrate mixture was investigated. The data reported in Table 8 demonstrate that in all 3 subjects, there was an overall decrease in formaldehyde levels when the alkalinising mixture was administered together with methenamine mandelate.

Conclusion

Several conclusions can be drawn from the results of this study. Firstly, any circadian rhythm or postprandial tide which may characterise human urinary pH is so variable (Figs. 1 and 2) that over reliance on fixed time sampling for monitoring the effect of treatments on this parameter is unjustified unless a very large number of such samples is collected. Collection of all urine samples enable the effects of treatment to be identified using a relatively small number of subjects.

The formulation of ascorbic acid determines whether it increases or decreases urinary pH (Fig. 4). The use of effervescent products increases pH thus producing a result which is opposite to that which is clinically desirable when methenamine therapy is administered. At an oral dose of 2 g 3 times daily, plain ascorbic acid tablets produce only a marginal decrease in urinary pH (Fig. 4). The value of concomitant use of ascorbic acid with methenamine salts must therefore be questioned although it is possible that in clinical infections this may not necessarily be true. However, unless evidence to the contrary is provided it does not appear justifiable to complicate methenamine therapy with coadministration of ascorbic acid particularly since high doses of the latter are used.

Potassium citrate mixture is an effective urine alkaliniser (Fig. 4). Concomitant administration with methenamine leads to interference with activation of the prodrug and reduced urinary formaldehyde levels are observed. Such coadministration should be avoided in clinical practice. Since both agents are used in the management of lower urinary tract infections, vigilance by health practitioners is warranted. This particularly applies to general practice in the United Kingdom since both agents are available without prescription (Li Wan Po, 1982).

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