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URINARY pH AND PLASMA LEVELS OF SALICYLATE AFTER ADMINISTRATION OF DIFFERENT BUFFERED ACETYLSALICYLIC ACID FORMULATIONS

C. BOGENTOFT, G. DAHL AND A. MAGNUSSON

Research Laboratories, AB Hässle, Mölndal, Sweden

ABSTRACT

In a controlled cross-over study comprising eight healthy subjects of effervescent acetylsalicylic acid (ASA) and an experimental ASA formulation were compared with unbuffered ASA and placebo concerning effects on the urinary pH within a dosage interval after 2 days' medication with 3 g ASA daily. The effects on the urinary pH were related to the morning plasma salicylate concentrations observed.

Both the buffered formulations significantly increased the median pH of the period studied compared to unbuffered ASA, the effervescent by 1·5 units and the experimental by 0·6 units. Unbuffered ASA significantly decreased the median pH compared to placebo. Those subjects with the most acidic urine during placebo treatment showed the most pronounced pH elevations due to effervescent ASA. The plasma salicylate concentration was significantly lower with the effervescent formulation compared with unbuffered ASA, but there was no statistical difference between the experimental tablet and unbuffered ASA.

The variable effects on the urinary pH and the plasma salicylate concentrations induced by the two buffered preparations are explained by the different absorbabilities of the buffering agents included. The results presented are consistent with recommendations not to use bicarbonate-containing ASA formulations continuously when high plasma levels are desirable.

KEY WORDS Urinary pH Plasma kinetics Acetylsalicylic acid Buffering

INTRODUCTION

Ingestion of conventional acetylsalicylic acid (ASA) tablets causes increased gastrointestinal blood loss due to mucosal injury mainly in the stomach.[1–3] Although the extent of the mucosal damage depends on many factors, a prerequisite for damage induction appears to be a low gastric pH.[4, 5] Subjects ingesting large amounts of buffering substances together with ASA demonstrate a reduced blood loss in comparison with subjects taking unbuffered ASA.[6, 7] Buffering substances and conventional antacids may, however, also raise the pH

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of the urine.[8-10] Owing to the pH dependence of the renal clearance of salicylic acid,[11,12] alkalinization of urine may increase the elimination and thereby reduce plasma levels of salicylate at steady-state.[8,10,11]

Since different buffering systems might have variable effects on urinary pH, e.g. due to different absorption tendencies, effects on the pH of the urine and plasma salicylate levels cannot be predicted by *in vitro* studies alone. In the present investigation commercial and experimental ASA formulations with different buffering systems and buffering capacities were studied in comparison with unbuffered ASA and placebo regarding the effects on the urinary pH within a dose interval after 2 days' medication. The levels of salicylate in plasma on day 3 were also compared and related to urinary pH.

MATERIALS AND METHODS

Eight healthy subjects (including four females) aged 27–51 years (mean age 36 years) with no history of ASA intolerance participated. Before the study the subjects were informed verbally and in writing, of the purpose and performance of the study.

Test preparations

Table A: Effervescent ASA tablets (Bamyl®-S, AB Hässle, Sweden) containing 500 mg acetylsalicylic acid, 1250 mg $NaHCO_3$ and 500 mg citric acid per tablet. Each tablet comprising a buffering capacity of 80 ml 0·1 M HCl at pH 4·5.

Tablet B: Experimental ASA tablets (H 7571, AB Hässle, Sweden) containing 500 mg acetylsaclicylic acid, 400 mg $CaCO_3$, and 200 mg Na_2CO_3 per tablet. Each tablet comprising a buffering capacity of 91 ml 0·1M HCl at pH 4·5 and showing a 95 per cent solubility of ASA within 5 min, i.e. almost identical dissolution properties as tablet A.[19]

Tablet C: Conventional ASA tablets (Aspirin®, Bayer, Germany) containing 500 mg acetylsalicylic acid per tablet and without any buffering capacity at pH 4·5.

Tablet D: Placebo tablets containing 0·5 g lactose per tablet and without any buffering capacity.

Study design

The study had a randomized cross-over design. Each test preparation was taken for a period of 2 days at a dose of 2 tablets t.i.d. (at 8.00 a.m., 3.00 p.m., and 10.00 p.m.). The last dose was taken at 8.00 a.m. on day 3. Tablet A was dissolved in about 150 ml tap water before intake while tablets B, C, and D were swallowed whole together with the same amount of water. Owing to the different methods of administration and different appearances of the tablets,

strictly blind conditions could not be obtained. Samples of urine were collected before the start of medication (day 1) and every 2 h on the third day from 8.00 a.m. (before tablet intake) until 4.00 p.m. The 8.00 a.m. urine was not the overnight urine. The subjects were instructed to empty the bladder as completely as possible on the sampling occasions and not to urinate between these occasions. Determinations of pH were performed within 15 min after sampling with a glass electrode and a pH meter (PHM 64, Radiometer, Denmark) calibrated either at pH 4 and 7 or at pH 7 and 9. Samples of venous blood for salicylate determinations were drawn at 8.00 a.m. on day 3 before the tablet intake. The concentration of salicylate in plasma was assayed using a method of liquid–solid chromatography with u.v. detection of salicylic acid.[13]

Breakfast on day 1 was taken after the sample of urine had been collected at 8.00 a.m. Lunch on day 3 was taken between 11.30 a.m. and 12.00 noon. The subjects were instructed to keep their diet as similar as possible during the different periods. No other restrictions were put on food intake. In order to avoid carry-over effects at least 3 days free of medication separated the treatment periods. Compliance to medication was estimated by counting the tablets taken from each bottle.

Statistics

As pH is a logarithmic function the median was chosen as a measure of the central tendency of data. The statistical comparisons of urinary pH values were performed using Wilcoxon's signed rank test. For comparisons of the plasma salicylate levels Student's *t*-test for paired data was utilized. Spearman's rank correlation test was used for correlation determinations.

RESULTS

According to the tablet count compliance to medication was complete throughout the whole study. Median values of urinary pH before treatment and during the third day are shown in Figure 1.

With effervescent ASA significantly higher ($p < 0{\cdot}05$) urinary pH compared to the experimental ASA tablet and conventional ASA was obtained on all sampling occasions on day 3 (Figure 1). All subjects showed median pH for the study period (Table 1) above 7·0 and the group median was 7·4. In comparison to this the experimental ASA tablet and the conventional tablet gave median values 0·9 and 1·5 pH units less, respectively. The most pronounced pH elevations with the effervescent tablet were obtained by those subjects having the most acidic urine due to placebo ($R_s = -0{\cdot}976$; $p < 0{\cdot}01$). All subjects were found to have lower plasma concentrations of salicylate during treatment with the effervescent formulation compared to the conventional tablet (Table 2) and the mean level was reduced by 44 per cent from 0·635 mmol/l^{-1} to 0·360 mmol l^{-1} ($p < 0{\cdot}01$). No significant correlation between the individual pH

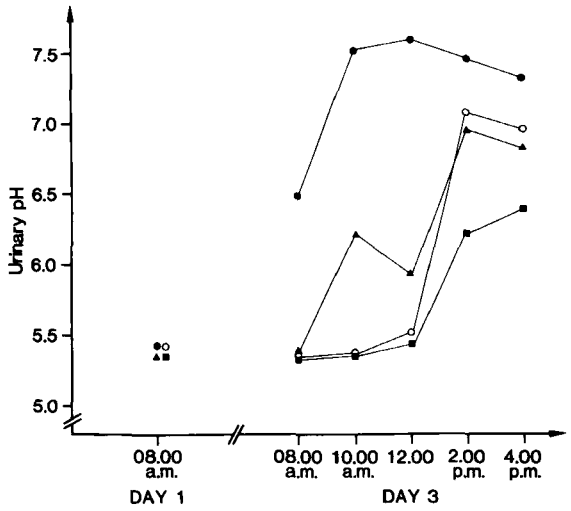

Figure 1. Urinary pH values with the different ASA formulations and placebo on the five sampling occasions on day 3. ●=effervescent ASA; ▲=experimental ASA; ■=conventional ASA; ○=placebo

elevation of urine and the corresponding reduction in plasma concentration compared to conventional ASA was found, however.

With the buffered experimental tablet, significantly raised pH values of urine ($p<0{\cdot}05$) compared to conventional ASA were obtained on all sampling occasions on day 3 except the first at 8.00 a.m. and the last at 4.00 p.m. (Figure 1). As with the effervescent tablet the median pH of the study period was

Table 1. Individual medians of urinary pH on the five sampling occasions on day 3

Subject No.	Median pH Effervescent ASA	Experimental ASA	Conventional ASA	Placebo
1	7·52	6·22	5·74	5·36
2	7·32	6·89	5·94	6·40
3	7·29	6·28	5·24	5·50
4	7·34	5·90	5·64	5·78
5	7·56	6·68	5·86	6·30
6	7·32	6·38	6·11	6·98
7	7·69	6·98	5·94	6·56
8	7·64	7·25	5·98	6·84
Group median	7·43*†	6·53*	5·90	6·35

*$p<0{\cdot}05$ vs. conventional ASA.
†$p<0{\cdot}05$ vs. placebo.

Table 2. Individual values of morning salicylate concentration in plasma 8.00 a.m. day 3 at a dosage of 3 g ASA daily

Subject No.	Plasma salicylate concentration Conventional ASA	Effervescent ASA	Experimental ASA
1	0·189	0·058	0·136
2	0·512	0·117	0·666
3	0·263	0·196	0·225
4	1·004	0·626	0·888
5	0·978	0·513	0·517
6	0·765	0·575	0·809
7	0·885	0·411	0·825
8	0·481	0·385	0·526
Mean	0·635*	0·360	0·574*
S.E.M.	0·113	0·076	0·099

*$p < 0{\cdot}05$ vs. effervescent ASA.

significantly raised ($p < 0{\cdot}05$) compared to conventional ASA (Table 2). However, no significant correlation between the individual pH elevations and the corresponding pH values during placebo treatment was found. With the experimental tablet a mean plasma concentrations of 0·574 mmol l^{-1} was obtained (Table 2). This was about 10 per cent lower but not statistically different from that obtained with the conventional tablet. It was, however, significantly higher than that obtained with the effervescent tablet ($p < 0{\cdot}01$).

During treatment with conventional ASA no significant differences in urinary pH compared to placebo were obtained on the different sampling occasions, although the values especially on the last two occasions studied tended to be lower (Figure 1). The median pH of the period (Table 2) was, however, significantly lower ($p < 0{\cdot}05$).

DISCUSSION

Urinary pH affects the kinetics of elimination for drugs that are either weak bases[14, 15] or weak acids.[16, 17] The renal clearance of unmetabolized salicylic acid is only one of the different pathways by which salicylate is eliminated from the body. This way, however, contributes to the total urinary excretion to an increasing degree with higher plasma levels due to the saturation kinetics of salicylic acid metabolism,[17] and with increasing alkalinity of urine.[18]

Up to pH 7 the clearance of salicylic acid increases slowly and rather linearly, but at pH values above 7 this increase becomes exponential.[12] At sustained pH values above 7 significant effects on the elimination rate and the plasma concentration could therefore be expected.

The results presented here show that both the different buffered tablets increased the urinary pH although the increase with the experimental tablet was of considerably smaller magnitude. Only the effervescent tablet, however, gave rise to a significantly reduced salicylate concentration in plasma. This result seems relevant since only the effervescent preparation brought about sustained urinary pH values in the range above 7·0. Recently, however, a urinary pH increase comparable to that obtained with the experimental ASA tablet was reported to affect the plasma levels of salicylate.[11] This deviation from our results could, however, be explained by the relatively small number of subjects included and by the low plasma levels achieved, as the effects on the salicylate levels become more pronounced the higher the blood concentration.[11]

Although it contained a slightly higher buffering capacity than that of the effervescent tablet, the experimental ASA tablet gave rise to significantly less pronounced effects on urinary pH. This can probably be explained by the different absorption tendencies of buffering systems used. For the effervescent bicarbonate buffer it is to be expected that the buffer remaining unreacted with the acid in the stomach will eventually be absorbed in the intestine, while the corresponding part of the carbonate buffer of the experimental tablet will be only marginally absorbed.

Effervescent ASA is an excellent ASA formulation for short-term use because of good gastrointestinal tolerance[3,6] and rapid absorption.[19,20] Effervescent formulations of ASA are in any case seldom recommended for long-term treatment in, for example, rheumatic diseases when high plasma concentrations of salicylate are desirable. The results of this study are fully consistent with that statement. For long-term treatment a buffering system similar to that of the experimental tablet should be preferable due to the reduced tendency to give lower plasma levels. Whether this type of buffering will also improve the gastrointestinal tolerance in a similar way to that shown with bicarbonate containing formulations has, however, not been studied.

The alternative for long-term treatment is therefore still enteric-coated formulations of ASA.

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