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The effect of buffering of acetylsalicylic acid on dissolution, absorption, gastric pH and faecal blood loss

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Summary

A high-buffered experimental acetylsalicylic acid (ASA) tablet designed to be swallowed intact and a conventional low-buffered ASA tablet were compared in vitro with regard to dissolution and buffering and in vivo with regard to absorption, intragastric buffering and tendency to cause gastrointestinal bleeding.

The high-buffered tablet was dissolved in vitro within 3 min. In vivo the tablet raised the intragastric pH to a minimum value of 7 and reached a maximal plasma concentration after 20–30 min. The low-buffered tablet dissolved more slowly and did not raise the pH in vitro above 2. In vivo the tablet raised the intragastric pH to 4.5 and a maximal plasma concentration of salicylate was obtained after 90 min. The high-buffered tablet reduced the daily faecal blood loss by 50% compared to the low-buffered tablet.

It can be concluded that the high-buffered tablet was more rapidly dissolved and faster absorbed than the low-buffered tablet. The reduced gastrointestinal bleeding found with the high-buffered tablet is probably due to an adequate in vivo buffering.

Introduction

Ingestion of ordinary acetylsalicylic acid (ASA) tablets is known to cause gastric mucosal bleeding (Croft and Wood, 1967; Leonards and Levy, 1970; Arvidsson et al., 1975). Although the gastric mucosal damage depends on many factors, the most important variable appears to be gastric pH (Jabbari and Valberg, 1970; Bowen et

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al., 1977). Subjects ingesting large doses of buffering substances together with ASA demonstrate a reduced blood loss in comparison with subjects taking unbuffered ASA (Leonards and Levy, 1969a; Leonards and Levy, 1972). The protection provided by buffering is primarily due to an increase in the pH of the gastric contents, which minimizes the absorption of aspirin from the gastric lumen as well as the back-diffusion of acid through a damaged mucosal barrier (Davenport, 1965). Effervescent preparations, containing bicarbonate for buffering, may raise the intragastric pH to about 7 (Dotevall and Ekenved, 1976; Cooke and Hunt, 1970), and these preparations are also more rapidly absorbed than ordinary tablets (Ekenved and Elofsson, 1975; Leonards, 1963).

To our knowledge there is no ASA preparation commercially available with a buffering capacity comparable to that of effervescent ASA, which is designed to be swallowed intact without a preceding dissolution in water. Whether such a preparation could show similar properties to effervescent ASA regarding gastrointestinal tolerance and rate of absorption is an open question, as solid dosage forms seem to be more ulcerogenic than those taken as solutions or suspensions (Rainsford, 1978), probably because of local effects on the mucosa produced by undissolved ASA particles (Leonards and Levy, 1969b). Therefore the dissolution properties of such a preparation might be of importance not only for the rate of absorption but also for the gastrointestinal tolerance.

The aim of the present investigation was to study the in vitro and in vivo properties of a high-buffered ASA tablet designed for swallowing whole in comparison with a conventional low-buffered ASA tablet. In the in vitro studies the dissolution rates and the pH elevation effects were investigated. In the in vivo studies the rate of absorption, the buffering of the gastric contents and the gastrointestinal tolerance of these tablets were compared.

Materials and Methods

Test preparations

Two types of ASA preparation were studied.

(A) Low-buffered tablets (Magnecyl, ACO, Sweden), containing 500 mg acetylsalicylic acid and 70 mg MgO per tablet.

(B) High-buffered tablets (H 215-1-1, AB Hässle, Sweden) containing 325 mg acetylsalieylic acid, 525 mg $NaHCO_3$ and 75 mg Na_2CO_3 per tablet, and giving the formulation a buffer capacity per tablet of 6.1 mmol HCl at pH 5.0.

In vitro studies

Dissolution rate. Dissolution rate was studied using a modified Levy beaker (Johansson et al., 1971). The tablet was fixed in a wire-net basket and placed in 500 ml simulated gastric juice (USP XX) without enzymes at 37°C. The juice was agitated with a propeller (45 × 15 mm) at 40 rpm. Samples were withdrawn with a pipette after 1, 2, 3 and 5 min and filtered. The mean value of the amount of ASA

from 5 individual tablets was determined and calculated on the stated amount of ASA per tablet.

pH effects. The increase of pH against time was determined by placing one tablet in a mixture of 10 ml distilled water and 25 ml 0.1 M HCl at 37°C. The solution was agitated with a propeller (45 × 15 mm) at 40 rpm.

In vivo studies

Absorption

The studies were performed in 6 healthy male volunteers aged 22–27 years (mean age 24 years) and weighing 63–74 kg (mean weight 68 kg) using a randomized cross-over design. Each experiment started in the morning when the subjects had been without food and drink for at least 10 h. The doses of ASA administered were 1000 mg of the low-buffered preparation (2 tablets) and 975 mg of the high-buffered one (3 tablets). The tablets were swallowed together with 150 ml water at room temperature.

Absorption was studied by measuring plasma salicylic acid levels in venous blood samples drawn before ASA administration and at suitable intervals for 6 h. The concentration of salicylic acid in plasma was assayed by liquid–solid chromatography with UV-detection (Bogentoft et al., 1978). From the data obtained the rates of absorption and elimination were estimated by CSTRIP, a Fortran IV computer programme (Sedman and Wagner, 1976). Statistical comparisons were made by means of Student's paired *t*-test.

Effect on gastric pH

The study was performed according to a randomized cross-over design in 12 healthy male volunteers aged 20–27 years. The preparations were given in the same doses and in the same way as in the absorption studies. Gastric pH was studied by using the Heidelberg radiotelemetry capsule (Telefunken AG, F.R.G.) (Nöller, 1962). The recordings of gastric pH were performed in accordance with details previously described by Ekenved and Walan (1975).

Statistical comparisons of paired data were made by means of Sign test and Wilcoxon's signed rank test. Since pH is a logarithmic variable, the median was chosen as a measure of the central tendency.

Effect on gastric bleeding

Twelve healthy male volunteers aged between 27 and 43 years (mean age 33) with regular bowel habits were included in this cross-over study. None had any history of ASA intolerance, gastrointestinal disease, recent nose bleeding, anal fissure or haemorrhoids. Permission to use ^{51}Cr for labelling of erythrocytes was obtained from the Isotope Committee of Sahlgren's Hospital, Gothenburg.

The trial was carried out using a technique with ^{51}Cr-labelled erythrocytes as described by Arvidsson et al. (1975). The two preparations studied were administered in a randomized order over two separate 7-day periods. In brief, the gastrointestinal blood loss was quantified by determining the faecal excretion of ^{51}Cr over

the last 5 days of the treatments. Each treatment period was preceded by a control week without therapy for determination of the basal gastrointestinal blood loss. The dose of ASA studied was 1 g t.i.d. from day 1 to day 7 (at about 08.00, 13.00 and 17.00 h). The tablets were swallowed whole with half a glass of tap water. No recommendations were given regarding tablet intake in relation to food. Wine and spirits were not allowed during the study.

In order to study possible effects of the buffering on the pH of urine, samples of urine produced during the night were collected in the morning of day 7 during the ASA periods and day 5 of the control period. Furthermore one blood sample for salicylate determination was drawn on day 7 of both the treatment periods at about 08.00 h, before the morning dose.

Statistical analyses were performed by means of Wilcoxon's signed rank test for paired data.

Results and Discussions

In vitro studies

Dissolution rates and buffering properties of the preparations are shown in Fig. 1. The low-buffered preparation had a significantly lower dissolution rate than the high-buffered tablet. From the low-buffered tablet only 17% ASA was dissolved within 5 min, while the high-buffered tablet dissolved completely within 3 min.

The high-buffered tablet increased the pH significantly more than the low-buffered

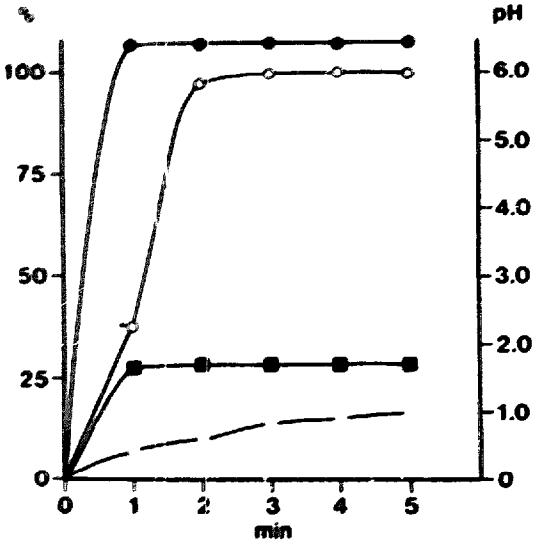

Fig. 1. In vitro dissolution of ASA in simulated gastric juice (USP XX) without enzymes: ○, high-buffered tablet; □, low-buffered tablet. pH increase against time in 100 ml water+25 ml 0.1 M HCl: ●, high-buffered tablet; ■, low-buffered tablet.

tablet and gave a pH maximum of 6.45 after 2 min compared to 1.75 after 10 min for the low-buffered tablet.

In vivo studies

Absorption

Mean levels of plasma salicylate are shown in Fig. 2. The high-buffered tablet was absorbed very fast with a mean maximal plasma level 20–30 min after administration, compared to 90 min for the low-buffered preparation. This difference was statistically significant ($P < 0.05$). At 20 and 30 min the plasma levels of the high-buffered tablet were significantly higher ($P < 0.05$) than for the low-buffered tablet. The opposite situation was found from 180 min onwards, when the low-buffered formulation showed significantly higher plasma levels ($P < 0.05$). The average half-life of absorption for the high-buffered preparation (9 min) was significantly shorter ($P < 0.05$) than that of the low-buffered (24 min). In the case of the elimination half-life no significant difference was found.

The rate of absorption for high-buffered tablets was as fast as that observed with high-buffered effervescent tablets (Ekenved and Elofsson, 1975; Leonards, 1963). This indicates that the in vivo dissolution of the high-buffered tablet was very rapid. The slower absorption from the low-buffered tablet is probably due to a slower in vivo dissolution but a slower gastric emptying could also have contributed, since it has been shown that buffering with sodium bicarbonate increases the rate of gastric emptying (Dotevall and Ekenved, 1976; Cooke and Hunt, 1970).

Effect on gastric pH

Median values of gastric pH during 30 min after administration are shown in Fig. 2. Four to 16 min after administration high-buffered ASA induced a significantly higher pH than the low-buffered preparation ($P < 0.02$). High-buffered ASA

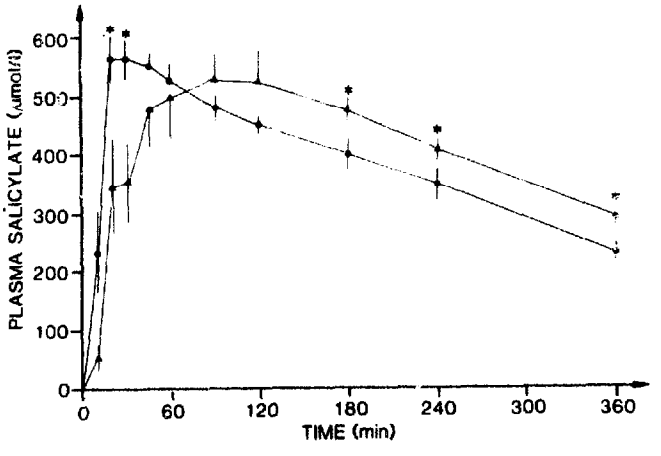

Fig. 2. Plasma salicylate (mean ± S.E.M., μmol/l) after administration of 1 g ASA to 6 fasting subjects. ▲, low-buffered ASA tablets; ●, high-buffered ASA tablets; *, $P < 0.05$.

raised the pH to values above 5 significantly faster than low-buffered ASA ($P < 0.01$). Within 2–3 min after administration pH was 5 or higher in all 12 subjects taking the high-buffered preparation in comparison with none taking the low-buffered. The median of the maximum pH after administration was 7 for the high-buffered tablet, which was significantly ($P < 0.01$) higher than that (4.5) of low-buffered ASA. Furthermore, the high-buffered preparation kept the gastric pH above 5 for significantly longer periods ($P < 0.05$) than did the low-buffered (18 min compared to 0 min).

Thus it can be concluded that only high-buffered ASA seems to possess the properties required for adequate in vivo buffering of ASA, i.e. increasing the pH above 5 when less than 5% of the ASA is in a non-ionized absorbable form ($pk_a = 3.5$). Whether the buffering properties of the high-buffered preparation are sufficient to prevent absorption of ASA from the stomach cannot be answered by this study. It is very important in this connection to know whether the pH elevation achieved is maintained as long as ASA remains in the stomach. This was not studied here, but in other studies of high-buffered effervescent ASA preparations it was found that only about 6–12% of the administered ASA dose remained in the stomach when the pH fell below 5 and furthermore significantly reduced absorption of ASA from the stomach was found (Dotevall and Ekenved, 1976; Cooke and Hunt, 1970).

Effect on gastrointestinal bleeding

Stool collection and compliance to the medication was estimated by regular interviews. One subject (No. 1) admitted having missed one stool collection on

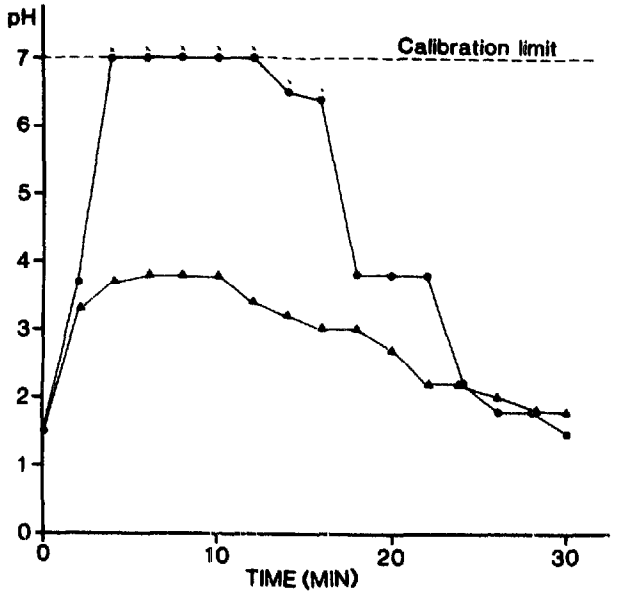

Fig. 3. Intragastric pH, median values, measured by the Heidelberg capsule technique, after administration of 1 g ASA to 12 fasting subjects. ▲, low-buffered ASA tablets; ●, high-buffered ASA tablets; ×, $P < 0.02$.

low-buffered ASA. The mean daily bleeding during this period was therefore calculated on the basis of 4 days' stool collection. Another subject (No. 7) admitted a deviation from the treatment schedule as he had missed the last dose on the sixth day of medication. This deviation, however, should not have significantly affected the results as a bleeding can only exceptionally be detected in faeces within as short a period as 24 h, since the transit time in healthy subjects is normally longer than 40 h (Becker et al., 1978; Burkitt et al., 1972). The ASA-induced bleeding was determined by subtracting the bleeding during the control period from that during the treatment period. Individual ASA-induced bleeding is shown in Fig. 4. The median values during the control and treatment periods were 0.7 and 4.9 ml/day, respectively, for the low-buffered preparation and 0.5 and 2.8 ml/day for the high-buffered ASA preparation. The increase in bleeding during ASA treatment was

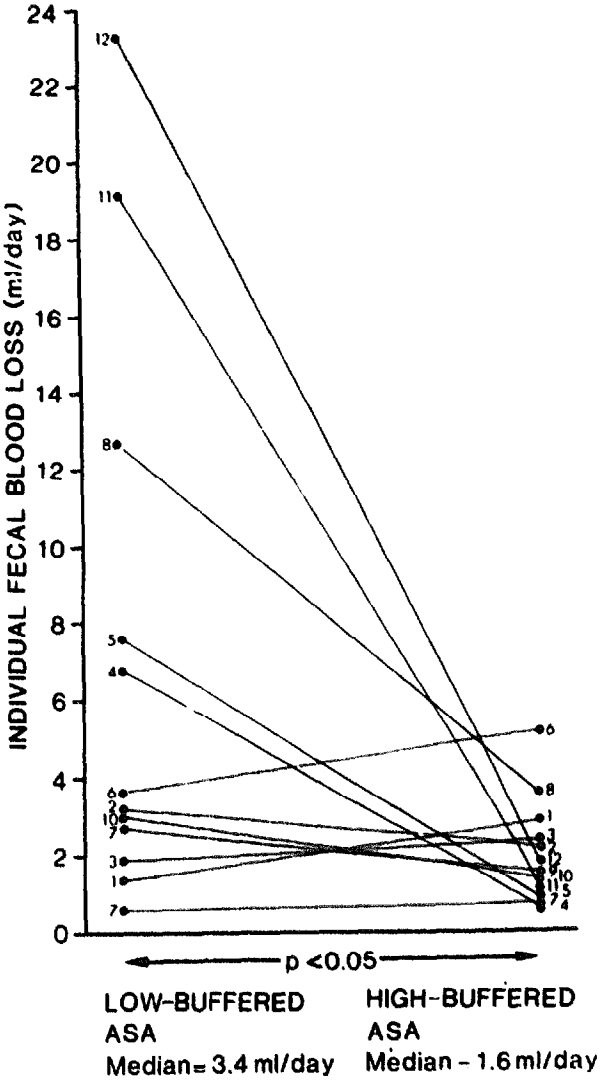

Fig. 4. Individual ASA-induced daily faecal blood loss (ml) in 12 subjects receiving 3 g ASA daily.

TABLE I

URINE pH (MEDIAN AND RANGE) AND MORNING PLASMA SALICYLATE CONCENTRATION (MEAN ± S.E.M., μmol/l) ON DAY 7 IN 12 SUBJECTS DURING TREATMENT WITH 1 g ASA t.i.d.

	Urine pH	Plasma concentration
High-buffered tablets	5.90 * (5.18–6.60)	91 *** (±26)
Low-buffered tablets	5.46 ** (4.96–6.12)	177 (±57)
Control	5.62 (5.26–6.34)	–

* $P<0.01$ vs low-buffered tablets.
** $P<0.05$ vs control.
*** $P=0.08$ vs low-bufferd tablets.

significant for both formulations ($P < 0.01$). However, the median bleeding induced by the high-buffered preparation was only about 50% of that from low-buffered ASA. This bleeding reduction was significant ($P < 0.05$) and was very similar to that found with a high-buffered effervescent ASA preparation (Arvidsson et al., 1975). This result indicates that a high-buffered ASA tablet designed to be swallowed intact can increase the gastrointestinal tolerance of ASA to a similar extent as an effervescent ASA formulation.

Mean values of salicylate concentration in plasma and urine pH during the different treatment periods are shown in Table 1. Urine pH was significantly higher with high-buffered than with low-buffered ASA ($P < 0.01$). The increase of about 0.4 pH units obtained with the high-buffered preparation might have contributed to the almost significantly lower plasma levels of salicylate ($P = 0.08$) during treatment with the high-buffered preparation. A pH-elevation of similar magnitude has recently been shown to significantly reduce steady-state plasma levels of salicylate (Hansten and Hayton, 1980). A significantly reduced pH compared to the control period was also obtained with the low-buffered tablet ($P < 0.05$). This effect could be caused by excreted salicylate and its metabolites.

Conclusions

The high-buffered ASA tablet studied here was found to be more rapidly dissolved in vitro and to be absorbed faster than a conventional low-buffered ASA tablet. The high-buffered tablet gave rise to less gastrointestinal bleeding than the low-buffered tablet, probably due to adequate in vivo buffering.

Furthermore, the high-buffered preparation led to a lower plasma concentration of salicylate at steady-state, probably due to effects on the rate of salicylate excretion induced by raising of the urinary pH.

On the basis of these results, it can be concluded that the high-buffered ASA preparation studied here, although swallowed whole as a tablet, has properties closely resembling those of high-buffered effervescent ASA.

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