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# Determination of baseline human nasal pH and the effect of intranasally administered buffers☆

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**Abstract**

The nose is becoming a common route of drug administration, however, little is known about the pH of the human nasal cavity. Local pH may have a direct effect on the rate and extent of absorption of ionizable compounds and hence this study was performed to investigate normal pH values and whether pH could be manipulated by various buffers. Twelve healthy volunteers participated in a study to measure pH in the anterior and posterior sites of the nasal cavity. Miniature pH electrodes were placed 3 cm apart in the nasal cavity and a baseline was recorded for 30 min once the pH had stabilized. One hundred microlitres of isotonic solution was sprayed into the nostril and the pH was measured for 4 h post-dose. The following five formulations were tested: formulation A — sodium chloride (0.9%) at pH 7.2; formulation B — sodium chloride (0.9%) at pH 5.8; formulation C — Sørensens phosphate buffer (0.06 M) at pH 5.8; formulation D — Sørensens phosphate buffer (0.13 M) at pH 5.8 and formulation E — formulation as (c) but adjusted to pH 5.0. Each formulation also contained saccharin sodium (0.5%) as a taste marker for nasal clearance. The time at which each subject detected the taste of saccharin was noted. The 30-minute baseline recording prior to administration of the nasal spray formulation demonstrates that there was both considerable intersubject and intrasubject variation in nasal pH. The average pH in the anterior of the nose was 6.40 ($+0.11$, $-0.15$ S.D.) when calculated from $H^+$ values. The pH in the posterior of the nasal cavity was 6.27 ($+0.13$, $-0.18$ S.D.). The overall range in pH was 5.17–8.13 for anterior pH and 5.20–8.00 for posterior pH. Formulation A caused the pH in the anterior part of the nasal cavity to reach a maximum of 7.06 in 11.25 min from the baseline of pH 6.14 ($P < 0.05$). The mean baseline pH was 6.5 for the posterior part of the nose which did not change over the recording period. Formulation B caused the anterior pH to increase from pH 6.60 to 7.25 within the first minute. This fell back to a mean pH of 7.07 over the first hour which was still significantly above the baseline. It remained at this value for

☆ Please note that AstraZeneca has no association with this work.

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the remainder of the recording period. The initial average posterior pH was 6.32 and again this did not significantly change over the recording period. Formulation C produced a sustained increase in anterior nasal pH from a baseline pH of 6.57–7.12. A small transient decrease was observed in the pH in the posterior of the nose but baseline pH of 6.6 was re-established within 15 min post dose. Formulation D significantly reduced anterior nasal pH from 6.30 to 5.87 by 30 min reaching a pH of 5.95 by 90 min where it remained for the remainder of the recording period. The posterior baseline pH was 6.3 and introduction of the pH 5.8 buffer caused a slow increase over 90 min to pH 6.6. Formulation E increased anterior pH from 6.1 to 6.7 for the remainder of the recording period. It had an insignificant effect on posterior nasal pH. The mean ($\pm$S.D.) time to taste saccharin for formulations A to E was $13.42 \pm 10.21$, $14.67 \pm 8.37$, $11.67 \pm 8.08$, $10.08 \pm 7.6$ $9.80 \pm 6.73$ min, respectively. There was no significant difference between the clearance times for the different formulations. In conclusion, average baseline human nasal pH is $\approx 6.3$. Nasal anterior pH can be decreased when buffers of 0.13 M and above are used. Mildly acidic solutions produce an increase in pH presumably due to reflux bicarbonate secretion. Posterior nasal pH was not altered by administration of any buffer except the 0.13 M buffer at pH 5.8. This produced a rise in posterior pH. 

*Keywords:* Nose; Nasal; pH; Human; Buffer; Circadian rhythm

## 1. Introduction

Topical intranasal drug delivery is primarily employed to treat allergies and infections that cause local irritation, sneezing and congestion. Increasingly, however, it is being used to deliver drugs systemically, particularly large molecules and peptides. Nasal drug delivery has several advantages over conventional routes of administration. It avoids gut enzymes, hepatic 'first-pass' metabolism and invasive procedures such as injections, but clearance of the formulations can be highly variable (Andersen et al., 1971, 1972).

A review of the medical literature reveals that there has been little, if any, scientific investigation into the pH characteristics of the human nasal cavity. This information is directly relevant to the delivery of drugs via the nasal route since local pH can significantly affect the rate and extent of absorption of ionizable compounds. This has been demonstrated in vitro and ex-vivo studies (Gibson and Olanoff, 1987). Buffering a solution to a target pH optimised for a particular drug should in theory, improve the absorption across the nasal epithelia.

The aims of this study were to determine baseline physiological pH of the nasal cavity in 12 healthy volunteer subjects and to investigate whether intranasally administered buffers could achieve and sustain a target pH within the nasal cavity. It was postulated that the pH of a solution may affect its clearance from the nasal cavity, hence this was also measured using the saccharin-taste test (Batts et al., 1991).

## 2. Materials

The formulations investigated were:

1. Sodium chloride (0.9%) adjusted to pH 7.2 with dilute sodium hydroxide + saccharin sodium (0.5%).
2. Sodium chloride (0.9%) adjusted to pH 5.8 with dilute hydrochloric acid + saccharin sodium (0.5%).
3. pH 5.8 Sørensens phosphate buffered solution (0.06 M) + saccharin sodium (0.5%).
4. pH 5.8 Sørensens phosphate buffered solution (0.13 M) + saccharin sodium (0.5%).
5. pH 5.8 Sørensens phosphate buffered solution (0.06 M) adjusted to pH 5.0 with dilute hydrochloric acid + saccharin sodium (0.5%).

No pharmacologically active agent was administered to the subjects during the trial. All formulations contained only components regarded as being inert and generally safe (GRAS status). Merck Sharp and Dohme Research Laboratories provided the five formulations, aseptically filled into amber glass vials. This study was originally initiated as part of a development program at Merck Sharpe and Dohme and the pH range used in this study was identified as the most appropri-

ate for nasal administration and drug stability for a particular development compound. It is thought that the osmolarity of the solutions could potentially effect the rate of nasal absorption (Ohwaki et al., 1987). The maximum strength pH 5.8 phosphate buffer system (0.13 M) was designed to be isotonic with physiological plasma. All other formulations were made isotonic by the addition of sodium chloride. The final osmolarity of each solution was checked using an osmometer (Advanced Instruments) operating on the principle of freezing point depression.

## 3. Methods

Twelve healthy volunteer subjects took part in the study, six males and six females within the age range 18–50 years. The exclusion criteria included the use of prescribed or over-the-counter medications which could influence the results of the study, current medical conditions which could influence the outcome of the study, participation in a clinical trial within the previous 3 months, habitual tobacco smoking and use of drugs of abuse.

Before entry into the study, the volunteers were given both written and verbal information concerning the nature of the trial. Volunteers were required to give written consent to participation on the trial. The study was carried out in accordance with the Declaration of Helsinki (Hong Kong amendment) and had approval from the Nottingham University Ethical Committee.

The study was performed as an open, randomized five-way cross-over. Subjects were requested to come to the department $\approx 30$ min before the investigation to allow their respiratory system to acclimatize to the conditions within the hospital. On the study day, the volunteers were seated and the patency of each nostril was ascertained visually. The most patent nostril was chosen for the study.

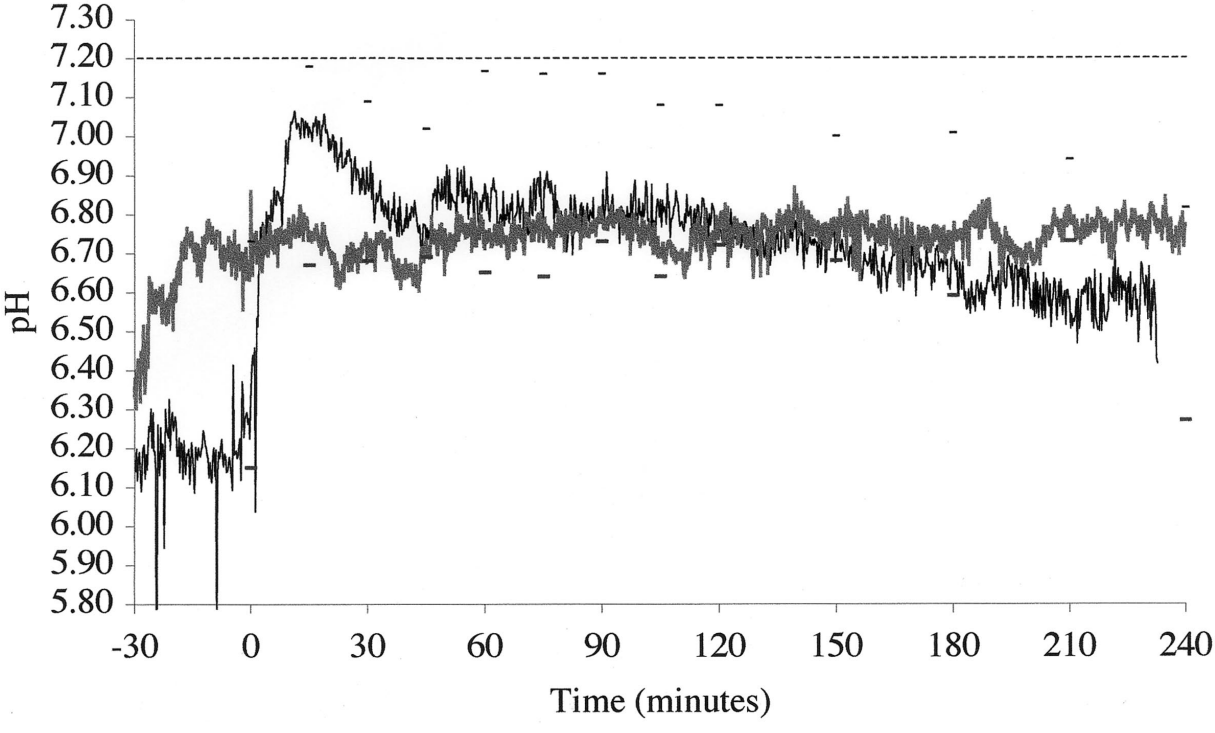


Fig. 1. The effect of sodium chloride (0.9%) at pH 7.2 on (formulation A) mean human nasal pH. Anterior pH is shown by the thin black line and posterior pH by the thicker grey line. Error bars are representative for all figures. (- - - -) indicates pH of buffer administered.

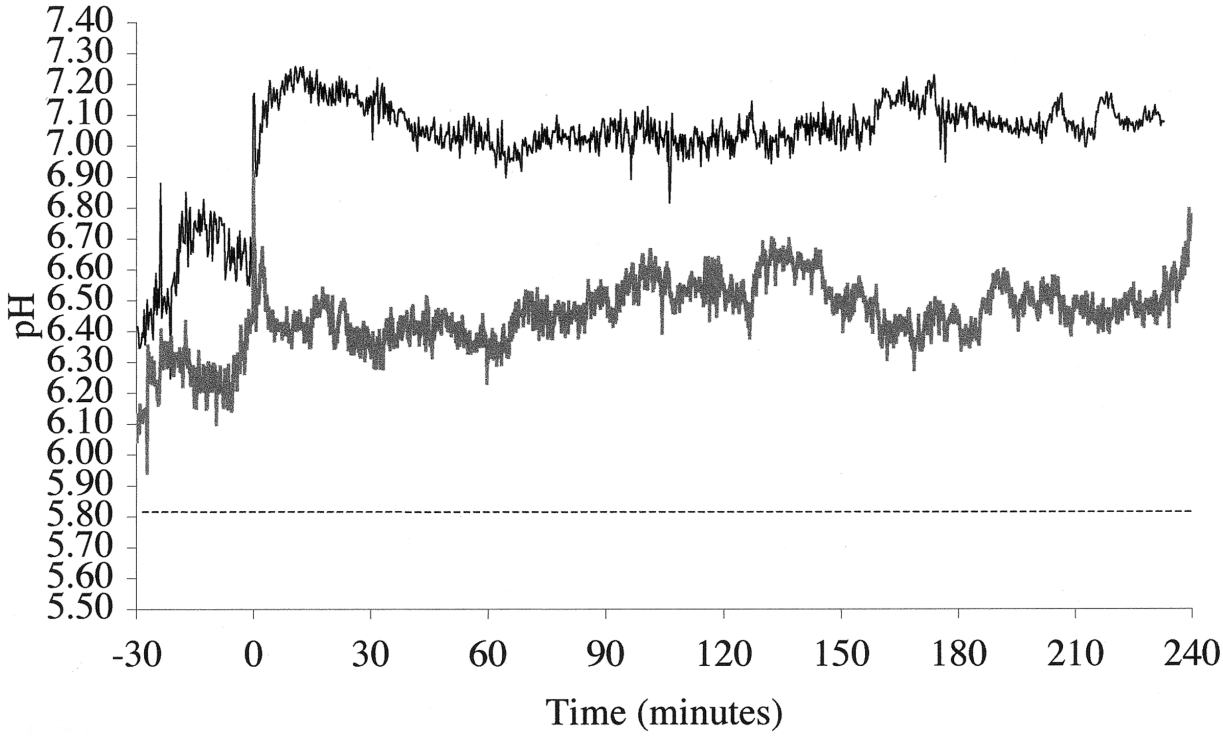


Fig. 2. The effect of sodium chloride (0.9%) at pH 5.8 (formulation B).

Two miniature pH electrodes (Radiometer electrode, (Copenhagen) connected to a Novo Memolog solid state recorder (Vertec Scientic, Reading)) were taped together with their tips 3 cm apart. These were sterilized and calibrated as per the manufacturer's instructions. The electrodes were inserted into the most patent nostril with the anterior electrode sited immediately inside the nasal cavity and the posterior electrode 3 cm further into the cavity so that they were in contact with the nasal floor mucosa. The electrodes were held in place with a plastic clamp which was adhered to the nose. Once the pH was stable, a baseline was recorded for 30 min.

The buffer solutions were administered at room temperature. Before administration, the vial was opened and the contents transferred to a proprietary spray pump, also supplied by Merck Sharp and Dohme Research Laboratories. After priming, these pumps reproducibly delivered 100 μl of solution as a fine spray.

After baseline had been measured, the electrodes were removed and 100 μl of one of the formulations was sprayed into the nasal cavity. To administer the formulation, the nozzle was inserted into the nasal cavity to a depth of $\approx 1$ cm and the pump head actuated. The subject's head was always in the upright position. The subjects were requested to breathe normally through their nose after administration of the buffer. The electrodes were replaced into their original positions and the recording resumed for a further 4 h. The subjects were asked to report to the investigator the exact time at which they detected the taste of saccharin. The assignment to treatment group was randomized.

At the end of the recording period, a post study calibration check was performed on the pH probes and the data was transferred to an Apple Macintosh computer for analysis using the communication software package Red Ryder (Freesoft Company). All calculations were carried out

using a spreadsheet (Microsoft Excel™). As pH is a logarithmic scale, all data analysis was carried out on $H^+$ concentrations. The values were reconverted to the pH scale for ease of interpretation.

## 4. Results

### *4.1. Thirty minute baseline period prior to formulation administration*

The average pH in the anterior of the nose was 6.40 (+0.11, −0.15 S.D.) when calculated from $H^+$ values. The S.D. is not evenly spread due to conversion to the logarithmic pH scale. The pH in the posterior of the nasal cavity was 6.27 (+0.13, −0.18 S.D.). The overall range in pH was 5.17–8.13 for anterior pH and 5.20–8.00 for posterior pH.

### *4.2. Effect of the formulations on nasal pH*

Formulation A (pH 7.2 unbuffered saline solution) caused the pH in the anterior part of the nasal cavity to reach a maximum of 7.06 in 11.25 min (Fig. 1). This was a rapid and significant increase from the baseline of 6.14 ($P < 0.05$). The decay back to baseline was slow and the pH had only reached 6.5 by the end of the recording period. The mean baseline pH was 6.5 for the posterior part of the nose, which did not change over the recording period.

Formulation B (pH 5.8 unbuffered saline solution) caused the anterior pH to increase from pH 6.60 to 7.25 within the first minute (Fig. 2). This fell back to a mean pH of 7.07 over the first hour which was still significantly above the baseline. It remained at this value for the remainder of the recording period. The initial average posterior pH

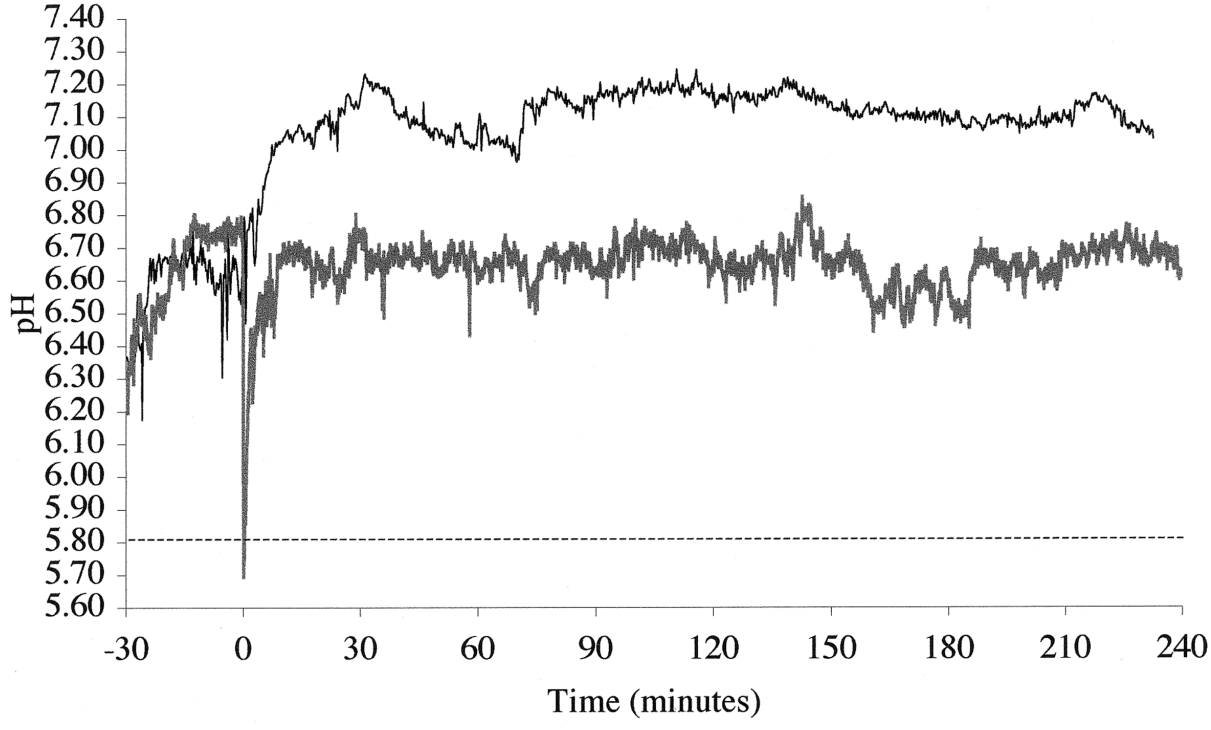


Fig. 3. The effect of Sørensens phosphate buffer (0.06 M) at pH 5.8 (formulation C).

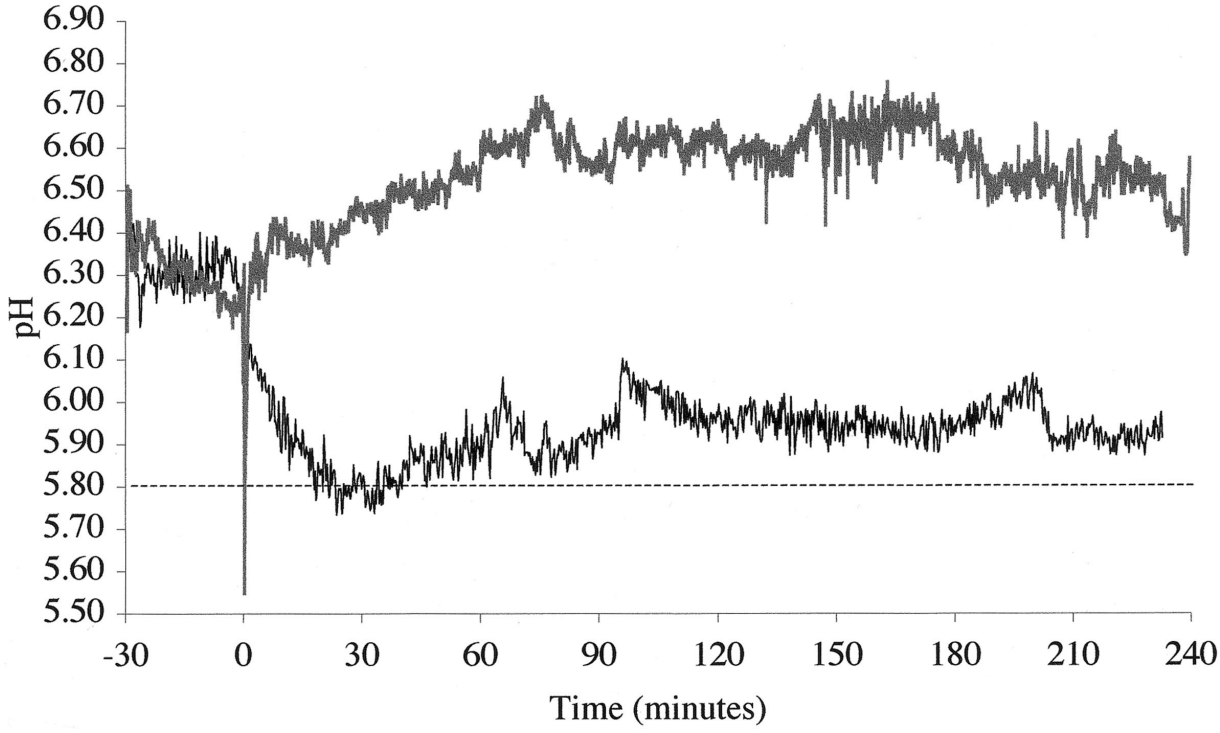


Fig. 4. The effect of Sørensens phosphate buffer (0.13 M) at pH 5.8 (formulation D).

was 6.32 and again this did not significantly change over the recording period.

Formulation C (pH 5.8 isotonic 0.06 M phosphate buffer) produced a sustained increase in anterior nasal pH from a baseline pH of 6.57–7.12 (Fig. 3). A small transient decrease was observed in the pH in the posterior of the nose but baseline pH of 6.6 was re-established within 15 min post dose.

Formulation D (pH 5.8 isotonic 0.13 M phosphate buffer) significantly reduced anterior nasal pH from 6.30 to 5.87 by 30 min reaching a pH of 5.95 by 90 min where it remained for the remainder of the recording period (Fig. 4). The posterior baseline pH was 6.3 and introduction of the pH 5.8 buffer caused a slow increase over 90 min to pH 6.6.

Formulation E (pH 5.8 isotonic 0.06 M phosphate buffer, adjusted to pH 5.0) increased anterior pH 6.1–6.7 for the remainder of the recording period (Fig. 5). It had very little effect on posterior nasal pH.

### *4.3. Saccharin-taste time*

The mean ($\pm$S.D.) time to taste saccharin for formulations A–E was $13.42 \pm 10.21$, $14.67 \pm 8.37$, $11.67 \pm 8.08$, $10.08 \pm 7.6$ and $9.80 \pm 6.73$ min, respectively. There was no significant difference between the clearance times for the different formulations.

## 5. Discussion

None of the formulations appeared to significantly affect the clearance time as measured by the saccharin-taste test. These values compare with other values reported in the literature for this test e.g. $11.2 \pm 6.3$ min with a range from 6 to 25 min (Ridley et al., 1995).

The effect of altering nasal pH on the absorption of certain drugs has been studied in animals and animal models by other groups. To date, enhanced absorption of vasopressin by a reduc-

tion in pH has been demonstrated in rats (Morimoto et al., 1991), but the rat tracheal cilia model shows that decreased pH has an adverse effect on ciliary beat frequency (Su and Po, 1994). Reduction in nasal pH has also been demonstrated to result in lower blood glucose levels in dogs treated with intranasal insulin (Hirai et al., 1978). No studies have been previously reported in which buffers have been administered to man in an attempt to alter nasal pH.

This study shows that baseline nasal pH is 6.4 in the anterior of the nose and 6.27 in the posterior of the nose. This is in agreement with a previous study which measured the pH of nasal secretions in adults and children (Chien et al., 1989). The ranges were 5.5–6.5 and 5.0–6.7, respectively, however, pH does vary with air temperature, sleep, emotions and food ingestion (Chien et al., 1989).

Administration of 100 μl of isotonic saline solutions of pH 7.2 and 5.8 and low strength (0.06 M) buffers of 5.8 and 5.0 all succeeded in increasing the pH in the anterior part of the nose. Although this was expected with the pH 7.2 saline, which was of higher pH than baseline, this was surprising for the buffers and saline of a pH lower than baseline. It can be postulated that the introduction of a slightly acidic buffer into the nose may have triggered a reflex increase in mucus production in response to a perceived irritant. Stimulated nasal mucus is rich in bicarbonate, which would explain the observed increase in pH (Chien et al., 1989). The pH of the posterior section of the nasal cavity is more difficult to influence. It is possible that there was insufficient volume of buffer used in this study to penetrate far enough back into the nose or the pattern of drainage from the nasal cavity was such that the buffer did not come into contact with the electrodes, or the buffer capacity was exhausted by the time the formulation reached this area.

The buffering capacity of the lower strength buffer (0.06 M) was probably not sufficient to overcome the secreted bicarbonate. Doubling the

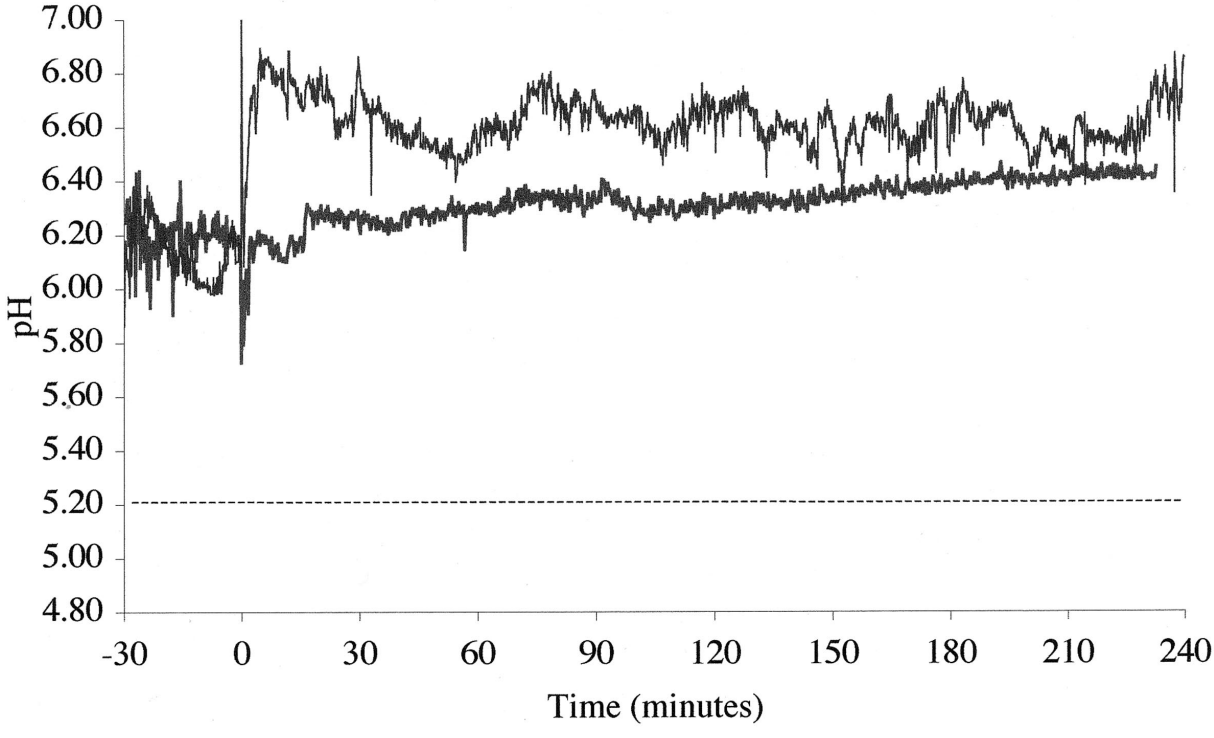


Fig. 5. The effect of Sørensens phosphate buffer (0.06 M) at pH 5.0 (formulation E).

buffer concentration, as in formulation D, produced a decrease in anterior nasal pH from 6.34 to 5.8. The decline from baseline started immediately after administration of the buffer and reached a minimum $\approx 25$ min later. Although the pH began to increase, baseline still had not been achieved 4 h post administration.

Only the stronger 0.13 M buffer (formulation D) affected the posterior pH. As the anterior pH began to rise, then the posterior pH also rose. Again it is possible that this was due to reflex bicarbonate secretion in response to the buffers low pH which was cleared backwards towards the nasopharynx.

In conclusion, baseline human nasal pH is 6.3. Nasal anterior pH can be decreased when buffers of 0.13 M strength and above are used. Acidic solutions produce an increase in pH presumably due to reflux bicarbonate secretion. Posterior nasal pH was not altered by administration of any buffer except the stronger 0.13 M buffer at pH 5.8. This produced a rise in posterior pH.

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