

pH and salivary sodium bicarbonate during the administration protocol for methotrexate in children with leukemia

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ABSTRACT

Objective: To analyze the behavior of pH and sodium bicarbonate (NAHCO₃) in the saliva of patients with leukemia during the administration protocol for Methotrexate (Mtx). **Materials and Methods:** A controlled clinical essay was carried out on 23 patients between 4 and 18 years of age with high-risk Acute Lymphoblastic Leukemia. Sampling was carried out at T₀: basal condition; T₁: 12 hours after intravenous administration of sodium bicarbonate, before administering Mtx and T₂: 3 hours after administering Mtx, the time of maximum concentration. Chiron-Diagnostic 378® equipment was used to determine pH and sodium bicarbonate. The data was interpreted using Analysis of Variance at the 5% significance level. **Results:** The highest values of sodium bicarbonate were observed at T₂, with salivary pH levels remaining within neutrality ranges, diminishing slightly in T₁. **Conclusion.** In this study, the dose of sodium bicarbonate considered in the administration protocol of 3 g /m² Mtx, kept sodium bicarbonate levels in saliva at normal levels and pH neutral.

INTRODUCTION

The capacity of human saliva to stabilize acids is essential for maintaining pH in the oral environment above critical levels for hydroxyapatite to protect the teeth from demineralization. The system responsible for the buffering capacity of human saliva includes bicarbonate, phosphate and proteins (1), with the bicarbonate buffer system being the most important (2). It is believed that the transportation of bicarbonate to the salivary glands occurs via the changing mechanisms of bicarbonate/chlorine. The concentration of bicarbonate in the saliva is a consequence of the metabolic passage of CO₂ through the salivary glands (1). CO₂ is diffused freely through the epithelial boundary and, due to the presence of the protein carbonic anhydrase, acid neutralization by the salivary bicarbonate is facilitated (3).

The modification of the ecological equilibrium of the buccal cavity is related to the presence of systemic diseases or the administration of medication, all of which could produce qualitative changes in the saliva (4-6), among which pH and sodium bicarbonate (NAHCO₃) are worthy of mention (2).

Clinical and forensic research has demonstrated that the salivary concentration of a substance may be related to its concentration in blood; the substances may pass from the plasma to saliva through intercellular or intracellular transportation. The latter could be by active transportation or by passive diffusion, which will depend on molecular weight, lipidic solubility, degree of ionization and proteic load. The mechanisms whereby a substance is transferred to saliva have an important implication for their use in

diagnosing (7). In the case of a patient with cancer, the administration of acid substances such as Methotrexate in doses over 2 g/m², requires the administration of alkaline substances such as sodium bicarbonate before and during 72 hours in order to maintain hyperhydration and obtain alkaline diuresis, since the blood's most important tampon uses bicarbonate – a basic compound in equilibrium with carbonic anhydride, an acid compound.

The more acid penetrates the blood, the more bicarbonate and the less CO₂ are produced; on the other hand, the more the base penetrates the blood, the more CO₂ and the less bicarbonate are produced; in both cases, the effect on pH is minimized (8), which could cause variations in pH and sodium bicarbonate levels in the saliva. A previous study concluded that the administration of methotrexate or cyclophosphamide did not modify the salivary buffering capacity in pediatric patients with cancer (9); these considerations served as the basis for this study, the purpose of which was to analyze the behavior of sodium bicarbonate in the saliva of patients with high-risk acute lymphoblastic leukemia, the oncological treatment protocol of which uses high doses of Mtx.

MATERIALS AND METHODS

-Patients

The population was made up of the children and adolescents that attended the Oncohematological Unit of the Hospital de Especialidades Pediátricas (Hospital of Pediatric Specialties) (HEP), State of Zulia, Venezuela, between April 2004 and May 2005. The sample comprised 23 patients ranging from 4 to 18 years of age. Inclusion criteria: Patients must have been diagnosed with Acute Lymphoblastic Leukemia (ALL) in accordance with the French – American – British (FAB) (10), with indication to receive the Total XV Protocol of St Jude Children's Research Hospital, which includes the administration of high doses of methotrexate (3g/m²) and hyperhydration with sodium bicarbonate (12 mEq/m²), during the consolidation phase (day 44, day 51) and maintenance phase (weeks 10,20,24,31,39 and 47). Exclusion criterion: The presence of active carious cavities. This study was approved by the Ethics Committee of the HEP; each parent or guardian signed an agreement report once the purpose therefore was explained to him or her.

-Saliva samples

Saliva samples were collected from the patients selected for the study during one of the cycles of the consolidation phase (day 44) or maintenance (weeks 10, 20, 24, 31 and 47). The saliva was collected with the patient sitting upright and relaxed, stimulating saliva production by their chewing a paraffin capsule at three times: T₀; basal condition, considered as the moment at which the administration of high doses of methotrexate has not been started; T₁: 12 hours after beginning the administration of intravenous sodium bicarbonate and before administering Mtx; and T₂: three hours after concluding the administration of Mtx, the time of maximum concentration (Table 1). In this study, ranges of pH will be considered within normal limits when values

are between 6.0 and 7.5 (1) and salivary sodium bicarbonate levels of 5.8611 ± 2.7248 mmol/l (11). Chiron-Diagnostic 378® equipment was used to determine pH and sodium bicarbonate, following the specifications of the manufacturer.

-Administering chemotherapy

Once authorized to receive high doses of Mtx, hyperhydration of the patient was begun with 12 mEq/m² of sodium bicarbonate before and during the 72 hours following the administration of Mtx, with dose distributed in a single injection of 500 mg/m², followed by 2.500 mg/m² diluted in dextrose at 5% for three hours, both indicated intravenously.

-Statistical analysis

The data was processed and analyzed with the Prisma Statistical Program, Version 4, using Analysis of Variance (ANOVA) at a 5% significance level in which the between-subjects factor was age and the in-subject factor the evaluation times.

RESULTS

The samples from 23 patients with ages ranging between 4 and 18 years were analyzed. The patients were classified into four age groups: ≤ 5 (10 patients), from 5-10 (4 patients), 10-15 (5 patients) and > 15 (4 patients).

-pH in saliva

The average values of pH in saliva (Figure 1) showed no significant differences between T₀, T₁ and T₂. However, there is a slight decrease during T₁.

Figure 2 shows that the highest levels of pH observed during the study were located in the 10-15-year group and the lowest in the >15 group; likewise, this group showed the least difference between the averages of pH levels reached in T₀, T₁ and T₂.

No significant differences were found upon relating pH levels during the different evaluation times and the age groups. On the other hand, in spite of the fact that higher pH levels were observed in the 5-10 and 10-15 age groups during the different evaluation times, no significant differences were detected between them.

-Sodium bicarbonate in saliva

The behavior of bicarbonate levels in saliva was similar to that of salivary pH during the different treatment phases. The statistical test showed no significant differences. In Figure 3, a higher level of salivary bicarbonate can be observed at T₂ with respect to the levels at T₀ and T₁. The concentration of bicarbonate in saliva (Figure 4) showed a slight increase for the 10-15 age group and a decrease for the <15 age group in the different treatment phases. Bicarbonate concentration at T₂ was above that observed at T₀ and T₁, except in the ≤5 age group, in which sodium bicarbonate concentration was slightly higher at T₀. The greatest difference in sodium bicarbonate concentration was observed in the 10-15 age group, between T₂ and the other evaluation times.

Table 1. Chemotherapy administration and times to collecting the saliva sample.

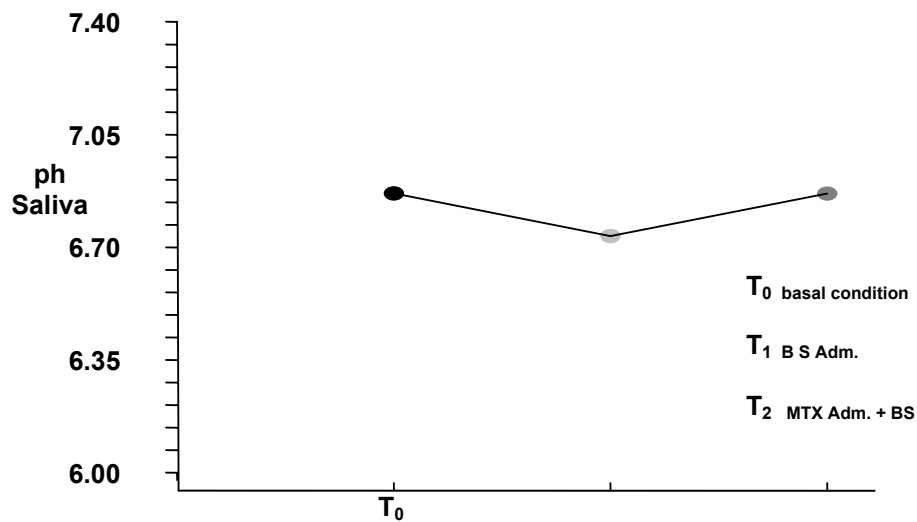
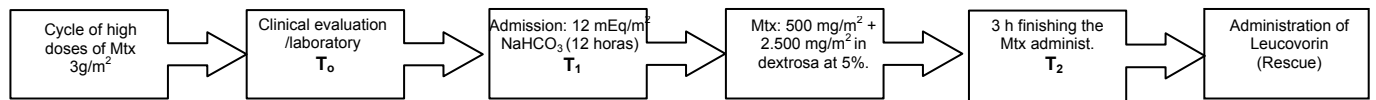


Fig. 1. Salivary pH according to times of evaluation.

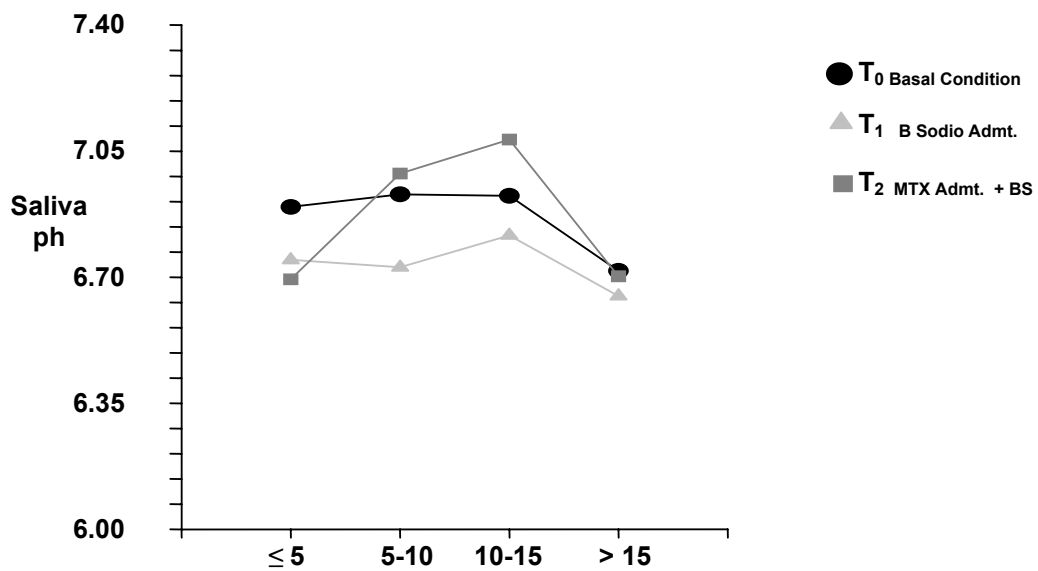


Fig. 2. Salivary pH according to age groups.

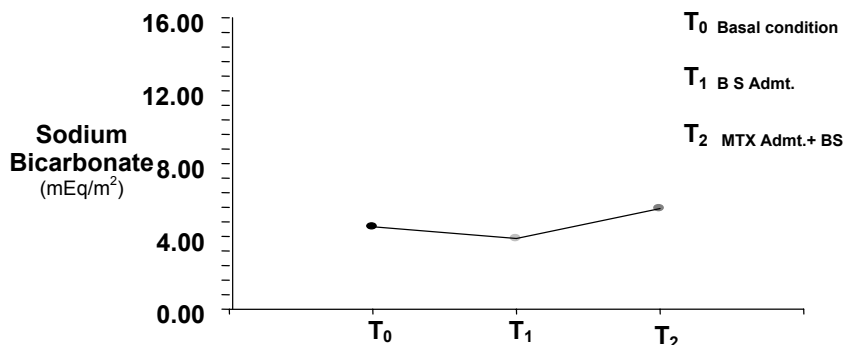


Fig. 3. Salivary sodium bicarbonate according to times of evaluation.

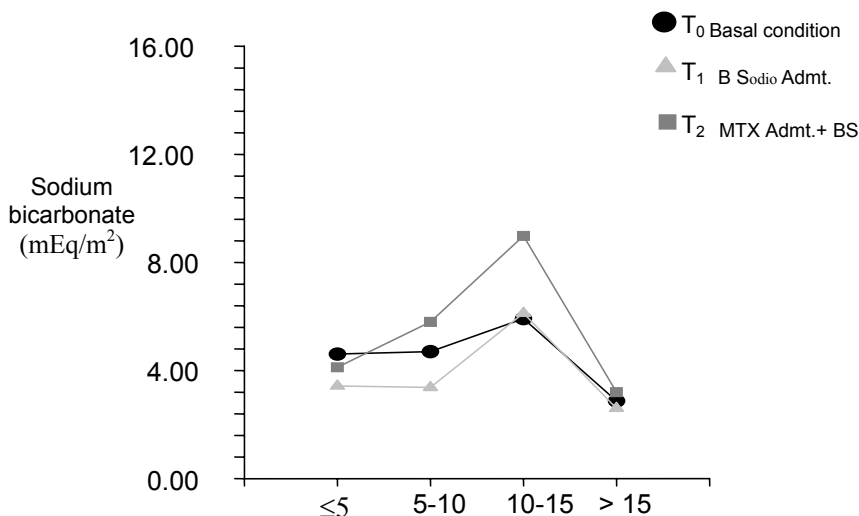


Fig. 4. Salivary sodium bicarbonate according to age groups.

DISCUSSION

The administration of Mtx produced no variations in pH and salivary sodium bicarbonate, differing from Olofsson et al (4), Ertugrul et al (5) and Al-Nowaiser et al (6), which could in this case be explained by the use, during the administration protocol of the cytostatic agent, of an optimum dose of sodium bicarbonate, thus maintaining levels of sodium bicarbonate within normal ranges and neutral pH in the saliva.

Contrary to expectations, the lowest values of pH and salivary bicarbonate were observed during the administration of the bicarbonate (T₁), when chemotherapy administration was started. It is possible that, at central level, the action of psychological (12) or psychopathological (13) factors such as stress or anxiety –not considered in this study– could have caused a decrease in the salivary flow rate, which is very closely related to bicarbonate concentration (14). Although this study did not evaluate the salivary flow rate, it may be considered that the emotional aspect and not chemotherapy was probably responsible for this result, since chemotherapy may cause alterations that are usually temporary and less severe than those produced by radiotherapy as reported by Valicena and Escalona (15), who suggest that chemotherapy

may produce changes in salivation, with total saliva presenting modifications in composition or decreasing slightly. The increase in pH levels and bicarbonate during T₂ could be related to bicarbonate concentrations in the blood, probably due to the continuous infusion received during 48 hours, time enough to allow the passage of sodium bicarbonate from the blood to the saliva (16).

The levels of pH at T₀ decreased as the age of the patients under evaluation increased. The presence of local factors such as dental caries, plaque level and gingivitis could have influenced our findings; Zambrano et al (17) point out that these factors increase with age, which produces qualitative changes in the microbial flora of the saliva and induces a decrease in salivary pH.

It is thereby concluded that the dose of sodium bicarbonate considered in the administration protocol of 3 g /m² of Mtx, kept the levels of sodium bicarbonate within normal ranges and neutral pH. It would be pertinent to continue with studies that could include measuring saliva flow rate and considering health-disease conditions in the mouth as variables moderating the parameters evaluated here, as well as the relationship between the values of pH and sodium bicarbonate in blood and saliva.

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