The Effect of Acetazolamide* on Arterial Carbon Dioxide Tension in Respiratory Acidosis: A Preliminary Report

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Carbon dioxide retention in hypoventilation resulting from bronchitis or bronchopneumonitis leads to respiratory acidosis. Non-compensated acidosis modifies the blood pH, thereby altering the acid base balance. It is not unusual to find respiratory acidosis in patients with chronic respiratory insufficiency. Cournand¹ reported the successful treatment of emphysematous patients with hypercapnia using either artificial respiration or a carbonic anhydrase inhibitor such as acetazolamide. Several investigators, including Nadel² and Taymor et al³ found that acetazolamide lowers the carbon dioxide tension in the arterial blood. They reached this conclusion by determining the pH and total carbon dioxide content of the arterial blood, using the Henderson-Hasselbalch equation. This study was undertaken to evaluate the significant results of this therapy in Chile. Therefore, we have determined the carbon dioxide tension in the arterial blood both before and after administration of acetazolamide to patients with respiratory acidosis.

Method

Following a half hour rest period in a supine position, the oxygen and carbon dioxide tension of blood drawn from the radial artery, were determined in four patients with chronic pulmonary disease (silicotuberculosis, bronchial asthma, bronchiectasis, emphysema, pulmonary heart disease): complicated by acute bronchitis or bronchopneumonitis. The blood was extracted with a Luer-lok syringe, with heparin in the dead space. It was then equilibrated with a bubble of alveolar air, (the composition of which was controlled in a Haldane chamber) in a Roughton-Scholander apparatus,⁴ at a temperature of 37.5°C. In these studies we followed the technique of Riley et al.⁵ Plasma electrolytes were also controlled by direct technique in a Lange flame photometer. Benedict and Tissot spirometers were used to measure pulmonary volume and ventilatory capacity, respectively. Values corrected to BTPS are expressed as percentages of the predetermined levels.⁶ Diureas and weight of patients were controlled. A Singer and Hastings nomogram was used to measure the pH of arterial blood, with values of carbon dioxide arterial tension, hematocrit, and Fenn's diagram for calculation of arterial carbon dioxide content, when this was not determined in a Van Slyke apparatus.

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²Kindly supplied as Diamox by Lederle Laboratories, Pearl River, New York.
³Professor of Tuberculosis & Respiratory Diseases, School of Medicine, University of Chile.
### TABLE I
BLOOD STUDIES AND MAXIMUM BREATHING CAPACITY OF FOUR PATIENTS WHO RECEIVED ACETAZOLAMIDE

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Date</th>
<th>Sex</th>
<th>Age</th>
<th>CO₂ Arterial Pressure mm. Hg.</th>
<th>O₂ Arterial Pressure mm. Hg.</th>
<th>Arterial Content CO₂ Vol. per cent</th>
<th>Arterial Blood pH</th>
<th>Hematocrit</th>
<th>H⁺</th>
<th>Sat. per cent</th>
<th>MBC (a)</th>
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<tr>
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<td>F</td>
<td>60</td>
<td>67</td>
<td>78</td>
<td>52</td>
<td>7.36</td>
<td>42</td>
<td>437</td>
<td>94</td>
<td>60</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>94</td>
<td>57</td>
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<tr>
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<td>6.30.56</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.40</td>
<td>400</td>
<td>94</td>
<td>57</td>
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</tr>
<tr>
<td>2</td>
<td>6.19.56</td>
<td>F</td>
<td>61</td>
<td>52</td>
<td>51</td>
<td>55</td>
<td>7.32</td>
<td>46</td>
<td>478</td>
<td>80</td>
<td>31</td>
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<td></td>
<td></td>
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<td>7.34</td>
<td>457</td>
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<td></td>
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<td>80</td>
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<td></td>
<td></td>
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<td>7.40</td>
<td>400</td>
<td>95</td>
<td>50</td>
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<tr>
<td>3</td>
<td>6.11.56</td>
<td>M</td>
<td>65</td>
<td>57</td>
<td>57</td>
<td>60</td>
<td>7.24</td>
<td>575</td>
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<td></td>
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<td></td>
<td>437</td>
<td>93</td>
<td>+ *</td>
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<tr>
<td>4</td>
<td>8.1.56</td>
<td>M</td>
<td>58</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>7.26</td>
<td>550</td>
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<td>20</td>
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<td>7.29</td>
<td>513</td>
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<td>20</td>
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<td></td>
<td>8.6.56</td>
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<td></td>
<td></td>
<td></td>
<td>7.42</td>
<td>387</td>
<td>94</td>
<td>74</td>
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</table>

H⁺ concentration of hydrogen ions 10⁻⁸ molecules per liter

* saturation percentage of arterial oxihemoglobin

MBC maximum breathing capacity: percentages of predetermined value expressed in ml. (BTPS)

(a) see Table III

$ treatment discontinued. Normal CO₂ arterial pressure resulted from a second course of therapy

* clinical estimate of pulmonary ventilation.
FIGURE 1: Evolution of the PaO₂ and PaCO₂ after initiation of treatment with acetazolamide. (Patient No. 4).

FIGURE 2: Upper figure: pH Arterial blood. Lower figure: Arterial carbon dioxide content. (Patient No. 4). See text.
**TABLE II**
CORRELATION BETWEEN ELECTROLITOGRAF, WEIGHT AND SYMPTOMATOLOGY OF PATIENT NO. 1 BEFORE AND AFTER INITIATING ACETAZOLAMIDE THERAPY.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Date</th>
<th>K</th>
<th>Na</th>
<th>Cl</th>
<th>Alkaline Reserve</th>
<th>Weight Kilos</th>
<th>Cyanosis</th>
<th>Stertor</th>
<th>Dyspnea</th>
<th>Mental Symptoms</th>
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<td>3.3</td>
<td>145</td>
<td>102</td>
<td>28.0</td>
<td>78</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>Confusional state</td>
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<tr>
<td></td>
<td>6.21.56</td>
<td>4.87</td>
<td>125</td>
<td>95</td>
<td>20.27</td>
<td>71</td>
<td>++</td>
<td>+</td>
<td>—</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>6.30.56</td>
<td>3.02</td>
<td>137</td>
<td>95</td>
<td>23.8</td>
<td>72</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Normal</td>
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<tr>
<td></td>
<td>7.12.56</td>
<td>*2.06</td>
<td>125</td>
<td>99</td>
<td>15.38</td>
<td>74</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Normal</td>
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</tbody>
</table>

The electrolitographic values are expressed in mEq./L.

*alterations in repolarization of electrocardiogram

**TABLE III**
MODIFICATIONS IN VENTILATION AFTER ADMINISTRATION OF ACETAZOLAMIDE

<table>
<thead>
<tr>
<th>Date</th>
<th>Vital Capacity</th>
<th>Ventilation (L/min/m²)</th>
<th>Ventilation (L/min/m²)</th>
<th>Frequency</th>
<th>Maximum Breathing Capacity</th>
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<tr>
<td></td>
<td>Per cent of Predetermined Value</td>
<td>At Rest</td>
<td>At Exercise</td>
<td>At Rest</td>
<td>At Exercise</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>6.14.56</td>
<td>Control</td>
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<td>4.3</td>
<td>7.2</td>
<td>32</td>
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<tr>
<td>6.30.56</td>
<td>Diamox</td>
<td>46</td>
<td>5.9</td>
<td>11.1</td>
<td>24</td>
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<tr>
<td>7.12.56</td>
<td></td>
<td>47</td>
<td>6.6</td>
<td>16.6</td>
<td>23</td>
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<td>Patient No. 2</td>
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<td></td>
<td>63</td>
<td>8.9</td>
<td>12.6</td>
<td>19</td>
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</table>
Acetazolamide was administered in doses of 500 mg. daily for three days, with therapy suspended on the fourth day. This regimen was continued until the carbon dioxide arterial tension was restored to normal average levels. Total dosage of acetazolamide ranged from three to seven grams. Hemograms were done to detect possible bone marrow depression as reported by Underwood. Prior to acetazolamide therapy, subjects had been treated with antibiotics, mucolytics and bronchodilators over a period of not less than eight days, with no significant clinical response.

Results

Table I shows the fluctuations in the different values, both before and during acetazolamide administration. The significant decline in carbon dioxide arterial tension toward average normal values is apparent, as well as that in the saturation values of the oxihemoglobin arterial blood pH. The change in maximum breathing capacity and the reduction of total carbon dioxide concentration are also worthy of mention.

Table II sets forth controls for patient No. 1, in whom were noted the decrease in alkaline reserve as well as the tendency to reduction of the potassium and sodium ions. This, together with the decrease of cyanosis, headache and confusion, may be correlated with the values shown in Table I. The decrease in potassium in this case was so great that it led to modifications in the electrocardiogram, with changes in repolarization which reversed when treatment was discontinued.

FIGURE 3: Diuretic effect of Acetazolamide (Patient No. 4).
Figure 1 shows the evolution of carbon dioxide and oxygen arterial tension in patient No. 4, after initiation of treatment with acetazolamide. Figure 2 gives the variations registered in the arterial blood pH, which showed an increase, and of the arterial carbon dioxide content, which decreased. In this patient there was an obvious diuretic effect, as may be noted in Figure 3. Maximum breathing capacity values appear in Figure 5, shown as percentages of the predetermined values, both before and after acetazolamide. (See Table III).

Discussion

In the presence of increased carbon dioxide tension, the body calls on the different mechanisms which tend to increase the bicarbonate, thus avoiding an abrupt acidification of the pH. Of these compensating mech-

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**FIGURE 4:** Evolution of electrolitogram in Patient No. 1 after initiation of treatment with acetazolamide.
FIGURE 5: Maximum Breathing Capacity values shown as percentage of the predetermine values (Ml., B.T.P.S.) before and after acetazolamide treatment.
M.A.—Patient No. 1; E.F.—Patient No. 2; A.C.—Patient No. 4
In black; before treatment values.

FIGURE 6: Linear correlation between the carbon dioxide arterial pressure, and the concentration of hydrogen ions in arterial blood in patients with respiratory acidosis and its evolution in time with acetazolamide treatment. The whole line represents the equation.
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We would first mention the purely physiochemical which affect the blood and tissues, with participation of the various buffer systems, especially those which also act on the hemoglobin and protein. To these mechanisms are added the diffusion of cellular bicarbonates, plus the transfer of the chloride and phosphate ions, lactates and exchange of sodium and potassium ions.8 Taymor et al.9 have shown that renal reabsorption of the bicarbonate radical (HCO₃⁻) is in direct proportion to the carbon dioxide arterial pressure.

Thus, it appears that the initial action on the respiratory center is governed by Gray's equation.9 However, this stimulating action does not prevail in pronounced hypercapnia, particularly if increased carbon dioxide arterial pressure is added to the inhibiting effect of the increased bicarbonate levels on the respiratory center.10, 11 We have found there is a lineal correlation (r:0.789) between the carbon dioxide arterial pressure, and the concentration of hydrogen ions in arterial blood, an equation similar to that described by Gray.9 (See Figure 6).12

\[
H^+ = 0.68 \text{ CO}_2 \text{ arterial pressure } +13.6
\]

These findings, together with the hypoventilation manifested by pa-
tients with hypercapnia, lead us to believe that the modifications of the buffer properties in the blood and tissues produce a depressing action on the respiratory center. If we add the intra-extracellular ionic modifications which lead to alterations of the membrane potential, we might explain the lack of response of the respiratory center to stimuli to which it ordinarily reacts. The hypoxia factor will act in much the same manner, as it leads to a modification of the ventilatory response. In continued carbon dioxide retention, at the expense of the hypoventilation produced by physiochemical changes in the respiratory center, and the effects it may sustain from the fluctuations of the bicarbonates as well as the obstructive mechanisms of the bronchioli, we find that arterial blood pH will reach a new level in accordance with the Henderson-Hasselbalch equation. In Figure 7 we have attempted to show these various changes. At this point acetazolamide acts on the bicarbonates, first in the blood and tissue buffer systems (direct action on the respiratory/center?), progressively reestablishing the sensitivity of the respiratory center, thus permitting pulmonary elimination of the carbon dioxide. This, together with the renal mechanisms affected by this carbonic anhydrase inhibitor, eliminates the bicarbonate ions.

SUMMARY

The decrease in carbon dioxide arterial tension after initiation of treatment with acetazolamide in respiratory acidosis occurring in the decompensation stage of chronic respiratory insufficiency, is demonstrated.

RESUMEN

1. Se demuestra el descenso de la PaCO2 después de iniciar el tratamiento con Diamox en la acidosis respiratoria producida en la etapa de descompensación de la insuficiencia respiratoria crónica.

2. Se discuten los mecanismos de acción.

RESUME

1. On demoptre la descente de la PaCO2 après avoir commencé le traitement avec le Diamox dans l'acidose respiratoire produite pendant la décompensation de l'insuffisance respiratoire chronique.

2. On discute les mécanismes d'action.

ZUSAMMENFASSUNG

Nachweis der Abnahme der arteriellen CO2-Spannung nach Einleitung der Behandlung mit Diamox bei respiratorischer Acidose, wie sie auftritt im Stadium der Dekompensation einer chronischen, respiratorischen Insuffizienz.

REFERENCES


3 Taymor, R. C., Minor, J. B. and Friedberg, Ch. K.: “Influence of Carbonic Anhydrase


