Evaluation of Expected Ventilatory Response to Metabolic Acidosis in Severely Ill Patients

Marco Marano¹, Deepak Jain²*, HK Aggarwal³, Francesco Izzo⁴

Abstract

Introduction: Winters’ formula (pCO₂=1.5*HCO₃+8) is used worldwide to predict the ventilatory response to metabolic acidosis, namely to predict the pCO₂ value complying with reduction of serum bicarbonate concentration (HCO₃). This equation was obtained half a century ago in mostly pediatric subjects. Subsequently different and inconsistent rules have been suggested. The study was done to verify the reliability of Winters’ formula in severely ill patients with respect of other modern and commonly used formulas.

Methods: We applied Winters’ formula and some other formulas to a dataset of arterial gas analysis from 29 severely ill malaria patients (about half of them requiring ICU or hemodialysis). The expected pCO₂ value was computed by each formula and the root mean square error (RMSE) was measured. Beyond predicting the expected pCO₂ value, expected range of values was also computed (as expected value ± each own error) and agreement with the best fit equation (± its error) was assessed.

Results: In this dataset featured by metabolic acidosis of moderate degree (mean pH 7.2, mean HCO₃: 15.3 mmol/l) a strong positive linear relationship between pCO₂ and HCO₃ was found (R squared =0.97). The best fit linear equation was in form of pCO₂ = 1.28*HCO₃+11.55. Winters’ formula exhibits the lowest RMSE (1 mmHg) and shows the better agreement (Cohen’s kappa=0.7) with the best fit equation.

Conclusions: Winters’ formula can still profitably used to compute the expected pCO₂ value and in turn to infer mixed (metabolic plus respiratory) acid-base disorders in severely ill patients.

Introduction

Metabolic acidosis is commonly encountered acid-base disturbance in clinical settings. The hallmark is decreased serum bicarbonate concentration (HCO₃) and low pH. As compensatory tool, triggered by low pH and sensed by central chemoreceptors, alveolar ventilation increases and arterial partial pressure of carbon dioxide (pCO₂) decreases, thus alleviating pH derangement. The degree of ventilatory response to metabolic acidosis, namely the amount of pCO₂ reduction was assessed 50 years ago by Winters and coworkers in critically ill patients.³ They provided the basic formula to compute the expected value of pCO₂ complying with the decreased HCO₃. Although obtained in mostly pediatric subjects and a long time ago, their equation is still relevant worldwide.³ However, other researchers suggested different and inconsistent rule-of-thumb serviceable in less severe acidosis.³⁶ Moreover Winters’ formula has been recently associated with high error-in-prediction in cases of metabolic acidosis of small degree.⁶⁻⁷ As recent evidence on performance of Winters’ rule is lacking, we tried to gain further insights on this issue by interrogating gas analysis dataset from patients with severe malaria. It is well known that etiology of the acidosis does not affect the magnitude of the ventilatory response, but degree of severity does, so we looked for patients virtually experiencing moderate to severe metabolic derangement.

Materials and Methods

We retrospectively analyzed data of patients presenting to a tertiary healthcare center Pt. B. D. Sharma PGIMS, Rohtak, Haryana, India fulfilling the modified WHO criteria of severe malaria.³ These patients had their blood gas analysis assessment at time of in-hospital admission. Patients older than 18 years with uncomplicated metabolic acidosis were screened from data sheet/records. Inclusion criteria were pH<7.38; HCO₃ < 22 mmol/l and pCO₂ < 38 mmHg according to well-acknowledged rule³. Moreover we selected only patients with arterial oxygen saturation >90% especially to exclude lung failure. Finally, arterial blood gas analysis from 29 severely ill adult patients were analyzed. In this dataset, the relationship between pCO₂ and HCO₃ was evaluated by the best fit equation method and the inaccuracy of the predicted value of pCO₂ in respect of the one actually measured was computed as root mean square error (RMSE). Furthermore, the R squared coefficient of correlation (between pCO₂ and HCO₃) was obtained. Afterwards, some rules found in the literature to compute the pCO₂ value fitting the HCO₃ reduction in metabolic acidosis, were applied and RMSEs pertaining to each formula were computed.

We have tested Winters’ formula that reads pCO₂=1.5* HCO₃+8,¹ the very simple formula (2,6,7) (pCO₂= HCO₃ +15);²⁶⁷ Fulop’s rule stating that the expected pCO₂ value is equal to the 2-digit numbers to the right of the

¹Senior Consultant, Hemodialysis Unit, Maria Rosaria Clinic, Pompei, Italy; ²Senior Professor, Department of Medicine, ³Senior Professor & Head Department of Medicine II, Division of Nephrology, Pt. B.D. Sharma University of Health Sciences, Rohtak, Haryana; ⁴Consultant, Hemodialysis Unit, Maria Rosaria Clinic, Pompei, Italy; ⁵Corresponding Author
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pCO₂ value, that is a single number, can be computed from the expected HCO₃⁻ concentration or the pH using the following equations:

\[ \text{pCO}_2 = 1.28 \times \text{HCO}_3^- + 11.5 \]

where \( \text{pCO}_2 \) is in mmHg and \( \text{HCO}_3^- \) is in mmol/l. This equation is obtained by applying a superimposing respiratory disorder to a metabolic acidosis.

The best fit linear equation linking pCO₂ and HCO₃⁻ is curvilinear. This is because the relationship between pH and pCO₂ is not linear, and the ventilation response along the full range of severity of metabolic acidosis that eluded inclusion/exclusion criteria. Moreover, it has not been emphasized enough that simple rules have been proposed and validated for this purpose. Remarkably, these simple rules have not only been shown to be effective but also to minimize the error associated with different equations.

<table>
<thead>
<tr>
<th>Name of rule</th>
<th>Equation</th>
<th>RMSE (mmHg)</th>
<th>K Cohen agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winters’ rule</td>
<td>( \text{pCO}_2 = 1.5 \times \text{HCO}_3^- + 8 )</td>
<td>1</td>
<td>0.69</td>
</tr>
<tr>
<td>Very simple formula</td>
<td>( \text{pCO}_2 = \text{HCO}_3^- + 15 )</td>
<td>1.39</td>
<td>substantial</td>
</tr>
<tr>
<td>Common practical rule</td>
<td>( \text{pCO}_2 = 1.2 \times \text{HCO}_3^- + 11.2 )</td>
<td>1.72</td>
<td>moderate</td>
</tr>
<tr>
<td>Fulop’s rule</td>
<td>( \text{pCO}_2 = (\text{pH}-7) \times 100 )</td>
<td>9.7</td>
<td>moderate</td>
</tr>
</tbody>
</table>

**Discussion**

Winters’ formula has been used over half a century to predict the fall of pCO₂ intended to minimize the pH derangement during metabolic acidosis. However, over the years other simple rules have been proposed and validated for this purpose. Remarkably, it has not been emphasized enough that other formulas, such as Winters’ formula, can correctly predict the ventilation response along the full range of severity of metabolic acidosis.

As shown in Table 1 Winters’ formula applied to this dataset exhibited the lowest RMSE (1 mmHg). The very simple formula and the common practical rule showed a slightly higher RMSE (1.39 and 1.72 mmHg, respectively). Finally, an RMSE close to 10 mmHg was associated with Fulop’s rule. Due to this very large error, the latter formula was no longer taken into account hereafter.

As said, all but seven data points fell within the range best fit equation ± 1 RMSE. As shown in Table 1, Winters’ formula applied to this dataset exhibited the lowest RMSE (1 mmHg). The very simple formula and the common practical rule showed a slightly higher RMSE (1.39 and 1.72 mmHg, respectively). Finally, an RMSE close to 10 mmHg was associated with Fulop’s rule. Due to this very large error, the latter formula was no longer taken into account hereafter.

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each valid to predict the ventilatory response to definite reductions of HCO3: the more severe the metabolic acidosis and the higher the slope of the linear equation. Accordingly, the key point in investigating the ventilatory response to metabolic acidosis is the amount of HCO3 reduction or, in other words, the degree of severity of acidosis, whatever is the cause of acidosis.3,5

Study population in Winters’ group was featured by metabolic acidosis of severe degree: mean HCO3 was close to 10 mmol/l and all values were below 16 mmol/l.1 In a recent study of metabolic acidosis with HCO3 close to 10 mmol/l, the magnitude of ventilatory response was similar.9 But one cannot assume that Winters’ formula works well in patients with less severe acidosis or, in other words, it cannot be regarded as always and anywhere valid rule, as is currently considered.2

In most of dialysis patients investigated in the recent decades, the degree of severity of acidosis was mild with HCO3 closer to 20 mmol/l rather than to 10 mmol/l10. In this population, rules other than Winters’ formula are more effective: the common practical rule and by the expected pCO2 value (in that case SE=1.11 mmHg) leading to 4.4 mmHg range. Supports of the common practical rule empirically defined such limits as ±5 mmHg leading to a wider range of 10 mmHg.3 More recently, one of this study’s author, reported a 6.7 mmHg range associated with both the common practical rule and the very simple formula by using 2 RMSEs, instead of empirical numbers.7

As an original line of research, Fulop investigated the chance of computing the expected pCO2 value from the pH number.7 In a large series of patients with HCO3 slightly over 10 mmol/l, his two digit rule was able to correctly predict pCO2 only in the half of instances, although he also resorted to the wide range of ±5 mmHg. Indeed, efficacy of this rule is poor. Overall, many different and inconsistent rules exist and it is unclear which rule should be used. In addition, suitability of Winters’ formula surprisingly seems to be undermined.

With purpose to gain further insight in this field, we selected severely ill patients with Malaria aiming to mirror Winters’ analysis. In these patients parasitized erythrocytes pack the microcirculation and impair oxygen delivery. Anaerobic glycolysis leads to lactic acidosis with multi-organ involvement. Renal tubular injury and kidney failure further contribute to metabolic acidosis whose severity strongly affects the morbidity and mortality rates11. However, despite the adverse clinical outcomes featuring our population, the degree of acidosis was not as severe as in Winters’ population and had moderate to severe acidosis. In these patients, the best fit linear equation looks like to the common practical rule, virtually sharing the same slope (Table 2), but equations’ similarity doesn’t allow to select the best formula and errors pertaining to differrent formulas must be checked. Thus, Winters’ formula - associated with the lowest error (Table 1) - turned out to be the best formula to rule out superimposed respiratory disorders in the patients with not so severe acidosis also.

As a further point of investigation, we also looked for the lower and the higher limit of compensation, at which mixed disorders occur. Winters’ and coworkers estimated these as 2 standard errors (SE) above and below the expected pCO2 value (in that case SE=1.11 mmHg) leading to 4.4 mmHg range. Supports of the common practical rule empirically defined such limits as ±5 mmHg leading to a wider range of 10 mmHg.3 More recently, one of this study’s author, reported a 6.7 mmHg range associated with both the common practical rule and the very simple formula by using 2 RMSEs, instead of empirical numbers.7

In the present investigation many efforts have been made to build a dataset of pure, uncomplicated, metabolic acidosis, indeed pCO2 and HCO3 were strongly related with R squared approaching the unit. The RMSE associated with Winters’ formula was exactly 1 mmHg, which, besides being an useful clinical threshold, corresponds to a very low error. By using two RMSEs upon and below the expected pCO2 value, the range pertaining to uncomplicated metabolic acidosis amounted to 4 mmHg, the narrowest ever found.

We also assessed the agreement between different formulas (± each own RMSE) to rule out respiratory acid-base disorders. As shown in Table 2, Winters’ formula was featured by the highest agreement with the best fit equation.

The retrospective nature of our analysis is main weakness of this study. However, we resorted to dataset from prospective trial which excluded patients with diseases other than severe malaria causing metabolic acidosis. In addition, we further applied well-acknowledged inclusion criteria. Ventilation impairment for reasons other than metabolic acidosis might have biased the database despite our efforts to rule out lung diseases and some patients might have experienced circulatory failure as well as glycolytic abnormalities. However, great homogeneity and robustness of our data is witnessed by the close relationship between pCO2 and HCO3 leading to R squared close to the unit.

In conclusion, although obtained a long time ago, Winters’ formula still profitably allows to predict both the expected pCO2 value and the range of pCO2 values pertaining to uncomplicated metabolic acidosis. Hence, this formula seems suitable to rule out respiratory acid-base disorders superimposing metabolic acidosis.

References