The Veterinary Journal 200 (2014) 152–156

Contents lists available at ScienceDirect

The Veterinary Journal

journal homepage: www.elsevier.com/locate/tvjl

The central role of chloride in the metabolic acid–base changes in canine parvoviral enteritis

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ARTICLE INFO

Article history:
Accepted 24 January 2014

Keywords:
Canine parvovirus
Strong ion model
Henderson–Hasselbalch method

ABSTRACT

The acid–base disturbances in canine parvoviral (CPV) enteritis are not well described. In addition, the mechanisms causing these perturbations have not been fully elucidated. The purpose of the present study was to assess acid–base changes in puppies suffering from CPV enteritis, using a modified strong ion model (SIM). The hypothesis of the study was that severe acid–base disturbances would be present and that the SIM would provide insights into pathological mechanisms, which have not been fully appreciated by the Henderson–Hasselbalch model.

The study analysed retrospective data, obtained from 42 puppies with confirmed CPV enteritis and 10 healthy control dogs. The CPV-enteritis group had been allocated a clinical score, to allow classification of the data according to clinical severity. The effects of changes in free water, chloride, L-lactate, albumin and phosphate were calculated, using a modification of the base excess algorithm. When the data were summated for each patient, and correlated to each individual component, the most important contributor to the metabolic acid–base changes, according to the SIM, was chloride ($P < 0.001$). Severely-affected animals tended to demonstrate hypochloraemic alkalosis, whereas mildly-affected puppies had a hyperchloraemic acidosis ($P = 0.007$). In conclusion, the acid–base disturbances in CPV enteritis are multifactorial and complex, with the SIM providing information in terms of the origin of these changes.

Introduction

Assessment of acid–base status is frequently used in veterinary critical care cases, because it can be used to detect early physiological derangements, alerting clinicians to the possibility of decompensation, as well as providing treatment directives (Hopper, 2012). Traditionally, the Henderson–Hasselbalch (HH) technique has been used, when assessing plasma acid–base disturbances, which involves measuring two variables, namely carbon dioxide tension (pCO_2) and bicarbonate (HCO_3^-) concentration (Constable, 2000). A change in either of these will invoke a compensatory response in the other, to maintain a constant plasma pH (Constable, 2000). The reciprocity of this relationship may obfuscate interpretation of a mixed or non-compensated disorder, where it is unclear to what extent pCO_2 and HCO_3^- have changed due to the primary disorder, or due to compensatory mechanisms (Constable, 2000; Sirker et al., 2002). Calculations based on the standard base excess (titratable acidity or alkalinity) and the anion gap have been used in conjunction with the HH model, in an attempt to abrogate this problem (Siggaard-Andersen et al., 1960; Siggaard-Andersen and Fogh-Andersen, 1995).

The strong ion model (SIM), also known as Stewart's strong ion model, is an alternative method, used in assessment of acid–base disturbances (Fencl and Leith, 1993; Gilfix et al., 1993; Whitehair et al., 1995; Constable, 2002; Wooten, 2004; Greenbaum and Nirmalan, 2005; Story and Kellum, 2005; de Morais and Constable, 2006; Morgan, 2009). The fundamental premise of the SIM is that the strong ion difference (SID) of plasma (difference between the sum of all strong cations and strong anions) is the most important determinant of the hydrogen ion activity in a system. In addition to pCO_2 and SID, the SIM considers a third variable, namely the sum of weak non-volatile organic acids, such as albumin and phosphate (denoted A_{tot}) (Fencl and Leith, 1993; Kellum, 2007). The SIM therefore provides rational explanations for acid–base disturbances that are not well understood in terms of the HH model, such as the effects of free water and plasma proteins (Kellum, 2008).

Notwithstanding the apparent advantage of the SIM, its application in medicine has met with some degree of opposition, as it violates the traditional dogma of the Arrhenius principle of acid–base chemistry (Kurtz et al., 2008). In spite of such criticism, the SIM has gained momentum in critical care medicine, mainly

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http://dx.doi.org/10.1016/j.tvjl.2014.01.017
1090-0233/

because it provides more information in terms of disturbances within the metabolic compartment (Constable, 2000; Sirker et al., 2002; Kellum, 2007).

Canine parvoviral (CPV) enteritis is characterised by severe vomiting and diarrhoea, often associated with a high mortality rate (Prittie, 2004; Goddard and Leisewitz, 2010; Schoeman et al., 2013). Medical therapy is implemented according to the severity of disease and includes fluid therapy, nutritional management and use of anti-emetic and/or antimicrobial drugs (Prittie, 2004). There is, however, a paucity of information available regarding the acid–base disturbances in CPV enteritis, on which to practise evidence-based medicine.

In one study, arterial blood gas and venous blood electrolyte data were collected for 17 puppies affected with CPV enteritis (Heald et al., 1986). Blood pH was within normal limits in 59% of cases and, of the remaining dogs, six were alkalaemic and one was acidaemic. In contrast, in the study by Rai and Nauriyal (1992) a significant acidaemia was demonstrated in 21 cases of CPV enteritis. Furthermore, a decrease in actual and standard HCO_3^- and base excess was observed. In a later study, plasma pH was consistently increased in dogs affected with CPV enteritis, compared to the healthy dogs, but HCO_3^- was consistently decreased and the pH increase was deemed to be due to compensation, in the presence of decreased HCO_3^- concentration (Nappert et al., 2002).

Of particular interest in the study by Nappert et al. (2002) is the fact that specific criteria were present that would allow a classification of metabolic acidosis (decreased HCO_3^- and increased L-lactate production), but the blood pH was in fact higher than normal (i.e. alkalaemia). Within this deviation of HCO_3^-, we predict that the SIM might unmask mixed acid–base disturbances, which would be obscured according to the HH model. Thus, the purpose of the present study was to utilize the SIM to dissect metabolic homeostasis in dogs affected with CPV enteritis, to provide further insights into the pathogenesis of the acid–base disturbances present.

Materials and methods

Sample population

Clinical and laboratory data, collected from 42 unvaccinated puppies affected with CPV enteritis and 10 age-matched control dogs were analysed using a modified strong ion approach, based on the base excess algorithm (Fencl and Leith, 1993; Hopper and Haskins, 2008). CPV had been confirmed in the clinical cases by electron microscopy, and confounding infection with rotavirus, coronavirus, *Ancylostoma* spp. and *Giardia* spp. had been excluded.

Affected dogs were recruited as part of a project to assess the utility of biomarkers in assessment of severity and survival in CPV enteritis (Schoeman et al., 2007, 2013; Schoeman and Herrtage, 2008). All data were collected on the day of admission, before any therapy had been initiated. Diagnostic testing was undertaken by the Department of Clinical Pathology, Faculty of Veterinary Science, University of Pretoria reference laboratory. The control population consisted of healthy vaccinated dogs under 6 months of age, which were presented for routine clinical examination. The study was approved by the Animal Care and Ethics committee (VO76/05, 20/12/2005).

A clinical score was assigned to each CPV-affected dog on admission, which stratified the population according to the severity of clinical signs (mild, moderate or severe). The clinical score was based on appetite, habitus, vomiting, diarrhoea and mucous membrane colour (see Appendix A: Supplementary Table 1). This clinical scoring system was designed for a PhD thesis (Schoeman, 2008) and, although not formally validated, has been used extensively in the Onderstepoort Veterinary Academic Hospital. All clinical scoring was performed by a single observer (JPS). Patients with scores <9 were classified as severely affected, scores between 9 and 16 were considered moderately affected and scores >16 were classified as mildly affected.

Data analysis

Comprehensive records were obtained for each animal, containing a complete serum biochemistry profile, with the exception of chloride and serum inorganic phosphate. Serum stored at −70 °C was analysed for these latter electrolytes, using a Cobas Integra 400 Plus (Roche) analyser. Since no blood gas measurements had been taken, it was not possible to assess pH, base excess or bicarbonate. The calculation of the contribution of each of the components to the base excess (according to the SIM) is shown in Appendix A: Supplementary Table 2. The data for each category were compared to the control group using a commercial statistics package (Medcalc, version 12.7.2). D'Agostino–Pearson test for normality was performed for all data sets. The Mann–Whitney *U* test was used to compare medians, and Spearman's rank correlation was used to assess the relationship between different variables.

To assess the relative contribution of each component to the overall metabolic acid–base changes, each of the components was summated and the sum obtained compared to each individual component by means of a Spearman's rank correlation. Each of the variables used in the quantification of the metabolic acid–base compartment were compared, according to clinical disease severity. Using the principle of the base excess algorithm, the free water, chloride and L-lactate effect were summated and, if a negative value was obtained (within a −2.0 to 2.0 mEq/L tolerance range), a strong ion acidosis was diagnosed; whereas a strong ion alkalosis was diagnosed if the value was positive.

The albumin and phosphate effects were summated to yield the A_{tot} and the values interpreted as for the strong ion compartment. This calculation was performed for each CPV-affected dog and a diagnosis for the metabolic compartment was assigned as follows: strong ion acidosis, A_{tot} acidosis (designated A); strong ion acidosis, A_{tot} alkalosis (designated B); strong ion alkalosis, A_{tot} acidosis (designated C) and strong ion alkalosis, A_{tot} alkalosis (designated D). The sum of all the effects was taken to represent the base excess, and significantly negative values interpreted as a metabolic acidosis and positive values as a metabolic alkalosis. When the value of the sum was within the tolerance range, but significant changes were present in the constituents, a mixed neutralising disorder was diagnosed. A final classification for the metabolic compartment could then be assigned as follows: metabolic acidosis/alkalosis (or neutralising), characterised by strong ion acidosis/alkalosis, and A_{tot} acidosis/alkalosis. The metabolic acid–base status of the dogs was displayed visually, using Venn diagrams as previously described by Viu et al. (2010).

The base excess algorithm suggested by Hopper and Haskins (2008), based on the original work of Fencl and Leith (1993), has not been validated in dogs, and is based on the assumption that albumin is the most important contributor to A_{tot}. A simplified technique (referred to subsequently as the simplified model, SM), using experimentally-determined values, validated for dogs was used (Constable and Stampfli, 2005) and compared to the traditional base excess algorithm. Briefly, the SID_4[1] was calculated from four major strong ions (Na + K − Cl + L-lactate) for both the CPV-affected and control groups. The A_{tot} was estimated from albumin, based on the determination of a net protein charge of 0.42 mEq/g of albumin in dogs, yielding a value of 15.8 mEq/L for normal dogs (Constable and Stampfli, 2005). The net protein charge was also determined using total protein (0.25 mEq/g of total protein). This was determined for both groups and compared to the experimentally-determined normal value of 15.8 mEq/L (Constable and Stampfli, 2005). SID_4 and the A_{tot} derived from albumin and total protein (TP) in the CPV-affected and control groups were compared using the Student's *t* test.

Finally, using the simplified model, a metabolic acid–base classification was assigned to each case, by comparing the CPV-affected group values for SID_4 and A_{tot} (calculated from albumin and TP) to the experimentally-validated values for these variables (values taken from Constable and Stampfli, 2005). In addition, the SID_4 and A_{tot} obtained from the SM were compared to those obtained for the control dog samples. This enabled assessment of the validity of comparing samples from CPV-affected dogs to experimentally-determined values. Diagnoses were then assigned to the categories A–D as described previously, with the outcomes of this simplified method and the base excess algorithm compared using an inter-rater agreement plot.

Results

According to the SIM, 20 of 42 patients in the CPV-affected group were considered to have a metabolic acidosis, 10/42 had a metabolic alkalosis and in 12/42 patients the overall effect was neutralizing. Of the 20 patients affected with metabolic acidosis, all had a SID acidosis and within this group, 19 had a concurrent A_{tot} alkalosis and one had a mild A_{tot} acidosis, due to mild hyperphosphataemia (Fig. 1a). Of the individuals with metabolic alkalosis, 9/10 had a SID alkalosis and 1/10 had a SID acidosis. All 10 patients had a concurrent A_{tot} alkalosis (Fig. 1b). Within the neutralizing group, 8/12 had a SID acidosis, with all eight of these having an A_{tot} alkalosis. The remaining four dogs had a SID alkalosis and, within this group, two had an A_{tot} alkalosis, with the remaining two having an A_{tot} acidosis (Fig. 1c).

[1] SID_4 denotes the SID as estimated from the difference between four major strong ions.