Pathophysiology and Treatment of Metabolic Acidosis in the Diarrhoeic Calf

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Abstract

Metabolic acidosis is a well recognised feature of calf diarrhoea irrespective of causal agent(s). The Harleco apparatus measures the total carbon dioxide concentration (TCO2) of whole blood and offers a means of diagnosing and quantifying metabolic acidosis. Metabolic acidosis in the diarrhoeic calf results from either bicarbonate loss or from titration of bicarbonate by organic acids. Measurement of the anion gap ($=Na^+ + K^+ - Cl^- - HCO3^-$) and Apparent volume of distribution of bicarbonate (AVD) afford insight into the pathophysiology and therapy of metabolic acidosis.

53 hospitalised diarrhoeic suckler calves under 21 d old receiving intravenous fluids were bled pre and post treatment. Acid base status was assessed using the Harleco whilst PCV, blood electrolytes, lactate, urea, creatinine and glucose were also measured. Therapy was based on the use of an isotonic solution containing 35 mmol/l bicarbonate. Very severely acidotic (TCO2 < 8 mmol/l) calves received an additional 400 mmol of bicarbonate in the first 5 l of infusion. Total volume of fluid administered was between 10 - 15 litres depending on clinical response and serial TCO2 measurements.

Calves > 6 days old were significantly more acidotic and less severely dehydrated than their younger counterparts. Anion gap was significantly increased in 45% of the calves and associated with increased severity of acidosis. The fall in TCO2 was greater than the increase in anion gap i.e. a mixed high anion gap metabolic acidosis was present due to both bicarbonate loss and acid production. Inclusion of lactate in the anion gap calculations had little effect on the distribution suggesting that endogenous acid production was relatively unimportant in these calves.

The AVD in these calves was 1.3 and 1.7 ml / kg Bwt respectively for calves receiving the isotonic fluid only and those receiving additional bicarbonate. These figures are considerably greater than those obtained by other workers.

It may be speculated that colonic production of acid by fermentation of partially digested foodstuffs may be of importance in the development of metabolic acidosis in these calves and may account in part at least for the magnitude of AVDs in this study. Such is their magnitude that exact amount of bicarbonate required for a calf cannot be calculated and administration must be empirical involving large amounts of bicarbonate using serial TCO2 measurements if available.

Keywords: calf diarrhoea, metabolic acidosis, anion gap, bicarbonate.

Introduction

Metabolic acidosis is a constant feature of calf diarrhoea and is often severe in nature (Naylor 1987, Groutides 1988, Michell *et al* 1992, Grove-White & White 1993). Whilst dehydration is also widespread in diarrhoeic calves, there is no relationship between severity of dehydration and acidosis (Grove-White & White 1993), with severe acidosis occuring in the absence of dehydration (Kasari & Naylor 1986). Clinical signs associated with metabolic acidosis are vague and non-specific and its existence may only be diagnosed and quantified by measuring plasma bicarbonate concentration and/or pH. The Harleco apparatus (Groutides & Michell 1990a) measures the total carbon dioxide (TCO2) liberated from a sample of venous blood on addition of an acid. Since this CO2 is derived almost entirely from plasma bicarbonate, it allows rapid estimation of plasma bicarbonate concentrations. The Harleco apparatus has been validated both experimentally (Groutides 1988) and in the field (Grove-White & White 1993). Fluid therapy, oral or parenteral, with bicarbonate containing (or yielding) solutions has been shown to be highly efficacious in correcting metabolic acidosis (Kasari & Naylor 1986, Michell *et al* 1992, Grove-White & White 1993). Parenteral solutions used in acidotic diarrhoeic calves include isotonic (1.3%) sodium bicarbonate (Kasari & Naylor 1986), a balanced solution containing 50 mmol/l bicarbonate (Groutides 1988), a balanced fluid

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containing 35 mmol/l bicarbonate to which up to 400 mmol sodium bicarbonate would be added as a spike if required (Grove-White & White 1993). Metabolic acidosis in the diarrhoeic calf may arise by virtue of loss of bicarbonate into the gut lumen, dilution of plasma and ECF bicarbonate during inappropriate fluid therapy, or by consumption of plasma bicarbonate by hydrogen ions which may be endogenous or exogenous in origin (Michell *et al* 1989). Anion gap is calculated by adding up the conveniently measured anions and subtracting them from the sum of measured cations thus:

$$\text{Anion Gap} = (Na^+ + K^+) - (Cl^- + HCO3^-)$$

Since the levels of measured cations usually exceed those of measured anions and the body is electrically neutral, anion gap represents the levels of unmeasured anions in the plasma (Michell *et al* 1989). If a metabolic acidosis is due to loss of bicarbonate the anion gap will remain unchanged since chloride will rise reciprocally. If the cause is added acid ($H^+ A^-$) the anion gap will increase due to the presence of the anion A^- accompanying the hydrogen ions, unless the added anion is chloride. Thus anion gap calculations afford insight into the origins and nature of metabolic acidosis.

Bicarbonate is primarily resident in the extra-cellular fluid compartment of the body, thus true bicarbonate space (TBS) is roughly equivalent to ECF volume. The apparent volume of distribution of bicarbonate (AVD) is substantially greater than the TBS since it takes into account non-bicarbonate buffering systems such as phosphates and intra-cellular buffering. As a rule AVD is taken as 30 - 50% of bodyweight although it may be substantially increased in severe acidoses (Narins 1994).

Materials and Methods

Fifty three diarrhoeic spring borne single suckled beef calves less than 21 days old were hospitalised and received intravenous fluids (Grove-White & White 1993). Heparinised jugular venous blood samples were collected enophth anaerobically at start and finish of therapy. Packed cell volume (PCV) was measured using a Hawkesley micro-haematocrit and TCO2 was measured using a Harleco apparatus on whole blood. Presence of enophthalmus on clinical examination was taken as an indicator of dehydration. Severity of acidosis was classified as follows (modified after Groutides & Michell 1990a):

Acid-Base Status	TCO2 mmol/l
Normal	21.1 - 28
Mild	16.6 - 21.0
Moderate	12.1 - 16.5
Severe	8.1 - 12.0
Very Severe	< 8.0

Plasma sodium and potassium concentrations were determined simultaneously using an integrating flame photometer (Radiometer FLM3) utilising standard quality controls (Groutides & Michell 1990b). Plasma chloride, calcium, magnesium, total protein, albumin, urea, creatinine, glucose and lactate concentrations were measured using a Gilford selective batch analyser (SBA 300) as described by Michell *et al* (1992). Thirteen apparently healthy spring borne single suckled calves were also sampled and analysed as above.

Anion gap measurements (Michell *et al.*, 1989) were calculated as follows:

$$\text{Anion gap} = [Na^+] + [K^+] - [Cl^-] - [HCO3^-].$$

Calves with an initial TCO2 reading > 8 mmol/l received a balanced isotonic fluid (Electrolyte ED: Univet Ltd.) containing 144 mmol/l Na^+, 35 mmol/l $HCO3^-$, 4 mmol/l K^+ and 113 mmol/l Cl^-. Calves with an initial TCO2 < 8 mmol/l received an additional 400 mmol of sodium bicarbonate (as a molar solution) added to the first 5 litres of infusion. Rate of administration of fluid and total quantity given was governed by clinical response but as a rule calves received between 10 - 20 litres over a period of 36 - 72 hours.

Results

Mean biochemical and physiological data for the 13 apparently normal calves sampled is given in Table 1.

Table 1. Apparently healthy non-diarrhoeic calves. Mean (+ S.D.) haematological data.

Parameter	Mean	S.D.	Range
PCV	33.6	4.3	27 - 41
TCO2 mmol/l	22.4	1.7	19.5 - 25
Na mmol/l	141.7	1.7	139 - 145
K mmol/l	4.89	0.38	4.2 - 5.5
Cl mmol/l	96	2.7	91 - 102
Ca mmol/l	2.44	0.19	2.03 - 2.69
Mg mmol/l	0.72	0.15	0.50 - 1.06
Lactate mmol/l	2.58	2.44	0.7 - 8.7
Anion Gap	28.5	2.2	24.6 - 32.8
Tot Protein g/l	62.4	10.1	41.3 - 74.8
Albumin g/l	28.8	2.9	22.2 - 33.2
Urea mmol/l	3.3	0.8	2.0 - 5.7
Creat mol/l	101	13.7	79 - 129
Glucose mmol/l	5.8	0.88	3.9 - 7.3

Acidosis was widespread and severe amongst the diarrhoeic calves at admission. There was a marked age difference with calves > 6 days old (n = 42) being significantly ($p < 0.05$) more acidotic but less dehydrated than their younger counterparts (n = 11) (Table 2, Figs 1, 2).

Table 2. Calves receiving intravenous fluid therapy. Mean (+ S.D.) values for pretreatment haematological data.

	Calves < 6 d old n=11		Calves > 6 d old n=42		Range
Parameter	Mean	S.D.	Mean	S.D.	
PCV	49.1	13.7	48.3	9.4	29 - 75
TCO2 mmol/l	11.8	5.7	7.1	2.3	3.0 - 22.0
Na mmol/l	135.4	9.2	137	8.9	113 - 150
K mmol/l	5.61	1.2	5.69	1.4	3.7 - 9.6
Cl mmol/l	95.5	8.2	103.5	8.6	83 - 123
Ca mmol/l	2.59	0.27	2.47	0.4	1.43 - 3.75
Mg mmol/l	1.25	0.44	1.08	0.34	0.52 - 2.26
Lactate mmol/l	3.66	2.57	2.23	2.24	0.1 - 12.8
Anion Gap	33.7	7.9	32.1	8.6	14.2 - 52
Tot Protein g/l	71.2	18.3	65.5	10.3	41 - 102
Albumin g/l	28.9	3.5	29.7	4.3	13.1 - 38.4
Creat mol/l	253.9	167.2	212.1	118.7	80 - 594
Glucose mmol/l	5.73	3.03	4.64	1.44	0.00 - 11.7

The mean (+ S.D.) anion gap for the apparently healthy calves was 28.5±2.4 mmol/l, thus normal values were taken as lying within two standard deviations either side of the mean value. Anion gaps for the diarrhoeic calves were classified as follows:

Anion gap (mmol/l).	Group.
< 23.7	Low
23.7 - 33.3	Normal
> 33.3	High

with the "High" values being sub-divided further to allow recognition of calves with a detectable organic acidosis, as follows (Polzin & Osborne 1986):

> 0.5 (TCO2) + 33.3	Very High

Anion gap was significantly increased in 24/53 of the calves receiving intravenous fluids (Fig 3), whilst in 14 calves it was classified as "Very high".

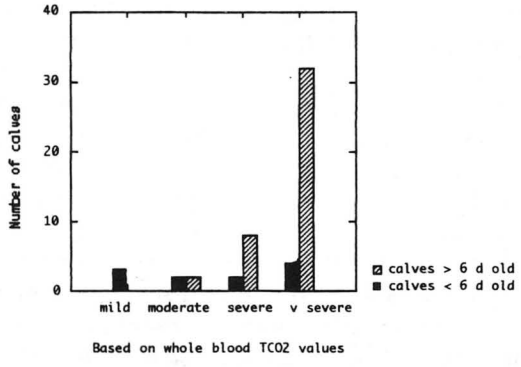

Figure 1. Distribution of severity of acidosis prior to treatment in calves receiving intravenous fluid therapy.

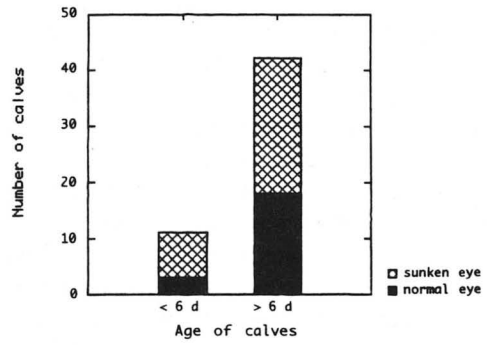

Figure 2. Age distribution of enopthalmus at admission in calves receiving intravenous fluids.

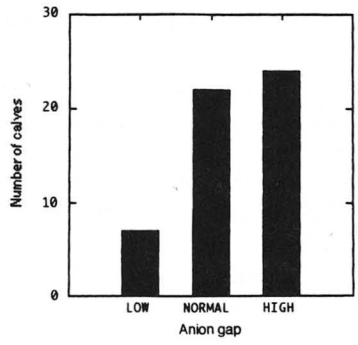

Figure 3. Distribution of anion gap values amongst the diarrhoeic calves.

Only in three calves, all of which had anion gap values classified as "Very high" were pre-treatment plasma lactate concentrations increased such as to lie outside the range of normal plasma lactate concentrations (defined as mean plasma lactate ± 2 SD's for the apparently normal calves). In order to further assess the contribution of lactate to the anion gap, a modified anion gap was calculated as follows: Modified anion gap = (Na + K) - (Cl + HCO3 + Change in Lactate during therapy) and classified as before according to magnitude (Fig 4). This could only be calculated for successfully treated calves for whom a post-treatment lactate value was available.

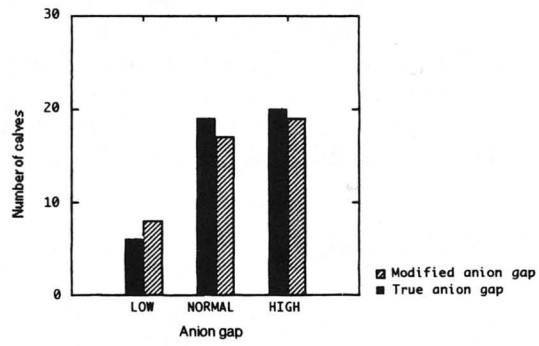

Figure 4. Comparison of the magnitude of anion gap and modified anion gap amongst the successfully treated diarrhoeic calves.

Inclusion of lactate in the calculation of anion gap had no significant effect on the distribution of anion gaps amongst the successfully treated calves, with similar frequencies of distribution for both true and modified anion gaps (Fig 4), suggesting that lactate is not a major contributor to the increased anion gap in these calves.

Plasma chloride concentrations were significantly higher, ($p<0.05$) in calves with anion gaps classified as "low" or "normal" compared to calves with high anion gap values (Table 3).

Table 3. Mean (+ S.D.) plasma chloride concentrations within the anion gap groups for diarrhoeic calves.

Anion gap	Mean	S. D.	Range
High	99	7.5	87 - 110
Normal	102.6	8.4	83 - 116
Low	109.5	12	91 - 123

Treatment was successful in 85% of calves. Treatment resulted in a significant improvement in acid-base status in surviving calves although the correction was often incomplete, compared to the apparently healthy calves sampled, at the time of discharge form the hospital (Table 4).

Table 4. Post-treatment acid-base status and AVD values of successfully treated diarrhoeic calves.

	Calves receiving no additional BIC n = 12		Calves receiving additional BIC n= 33	
Parameter	Mean	S. D.	Mean	S. D.
TCO2 mmol/l	20.6	2.4	17.9	2.8
AVD l/kg	1.35	0.59	1.66	0.34

The "apparent bicarbonate space" or "apparent volume of distribution" of bicarbonate (AVD) may be defined as the amount of bicarbonate (mmol) administered per Kg bodyweight to produce 1 mmol rise in whole blood bicarbonate concentration and is calculated as follows: AVD = [total bicarbonate received] / [change in TCO2 during therapy X BWt].

In Table 4 bodyweight is assumed to be 45 kg, a reasonable assumption for beef suckler calves. The AVD was greater than body volume in both groups of calves being significantly greater in the spiked calves compared to their non-spiked counterparts.

Discussion

Acidosis was widespread and severe amongst the diarrhoeic calves with the younger calves tending to be less acidotic than their older counterparts. This is in agreement with previous studies (Naylor 1987, Grove White & White 1993). Naylor (1987) found collapsed diarrhoeic calves less than 8 days old to be suffering from severe dehydration and lactic acidosis, with older calves having significantly less lactate concentrations. He postulated that the age related difference in severity of acidosis may be explained by the age susceptibilities of calves to enteric pathogens whereby the younger calf is likely to be affected by enterotoxogenic *E. coli* which results in rapid dehydration, reduced tissue perfusion and production of lactic acid by the tissues, together with intestinal loss of bicarbonate whilst older calves are more likely to be affected by pathogens such as rotavirus which result in the development of a malabsorbtive diarrhoea with subsequent colonic overload and an increase in production and absorbtion of volatile fatty acids. In all cases reduced renal perfusion and excretion of hydrogen ions would exacerbate the acidosis (Michell *et al* 1989). In the present study there was no clear evidence of lactic acidosis in either age group.

A significantly increased anion gap was evident in 24 (45%) of the diarrhoeic calves suggesting that accumulation of hydrogen ions occurred in these calves (Michell *et al* 1989). In the 14 calves with anion gaps classified as "Very high", it was increased such as to allow diagnosis of an identifiable organic acidosis, based on data from human medicine (Polzin & Osborne 1986).

There was a tendency for reduced or normal anion gap to be associated with increased plasma chloride compared both to healthy calves and diarrhoeic calves with increased anion gaps, although there was considerable variation around mean chloride values. Thus in the calves with normal or reduced anion gap, the acidosis was largely caused by bicarbonate loss (i.e. hyperchloraemic). In the calves with increased anion gaps, the decrease in TCO2 was greater than the increase in anion gap suggesting that a mixed high anion gap and normal anion gap metabolic acidosis (Narins 1994) was present, due to both net bicarbonate loss and accumulation of acid.

The almost unchanged distribution of anion gap values when lactate is included in anion gap calculations (Fig. 4) demonstrates that lactic acidosis was of little importance in this study. Thus exogenous acid production, as can occur in the colon (Argenzio 1992), may be a major contributor to the profound acidosis seen in filed cases of diarrhoea, although bicarbonate loss also plays a role. The absence of any clear age difference in size of anion gap, even amongst the calves with profuse liquid diarrhoea, would suggest that similar mechanisms operate in the development of metabolic acidosis in diarrhoeic suckler calves irrespective of age of calf or severity of diarrhoea. It is likely however, that the rela-

tive contribution of these mechanisms, namely endogenous acid production, exogenous acid production and bicarbonate loss, varies between calves.

The "apparent bicarbonate space" or "apparent volume of bicarbonate distribution" (AVD) is usually taken to be equivalent to between 0.3-0.5 of body weight, but can be increased in severe acidoses (Narins 1994). In this study the mean AVD for the very severely acidotic calves was at least three times the assumed AVD (0.3-0.5) mentioned above whilst for their less acidotic counterparts it was double (Table 4). It is apparent that in this study the bicarbonate requirements were considerably greater than might be expected especially in the very severely acidotic calves, such that administration of bicarbonate assuming an AVD of 0.5 BWt would have resulted in gross under-dosing. Possible explanations for the increased AVD in this study include increased titration of non-bicarbonate intracellular buffers and ongoing production of exogenous acid. Anion gap data suggests the latter is an important mechanism in the development of acidosis in these calves. The mean AVD's in this study are of a much greater magnitude than those obtained by other workers (Kasari & Naylor 1985, 1986, Naylor & Forsyth 1985, Groutides 1988) who obtained values between 0.3-0.73 l/kg. Garella *et al* (1973) and Narins (1994) state that in very severe metabolic acidoses in man, the AVD can exceed total body volume, as in the calves in this study.

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