Acid-Base Balance of Cerebrospinal Fluid in Acute Uncompensated Metabolic Acidosis of Infancy

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SUMMARY

The acid-base of cerebrospinal fluid was studied in infants with an uncompensated metabolic acidosis due to gastro-enteritis. No clinical prognostic value could be obtained from these analyses. Cerebrospinal fluid bicarbonate behaved differently in infants who were alert as opposed to those in stupor. Cerebrospinal fluid bicarbonate rose relative to arterial bicarbonate in the alert patients, but with the advent of stupor, returned to the levels seen in the control patients. The possible significance of this finding is discussed.

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Gastro-enteritis is endemic among the paediatric population which our hospital serves; many of the patients are stuporous on admission to hospital. The aim of this investigation was to assess the prognostic value of cerebrospinal fluid (CSF) acid-base balance in the presence of a severe uncompensated arterial metabolic acidosis. This was thought to be of importance, as it had been observed in a pilot study that in 2 stuporous, as opposed to 8 alert, infants there was a marked decrease in the CSF bicarbonate concentration relative to that of arterial blood.

The acid-base composition of CSF has been previously investigated under physiological and pathological circumstances; the subject is reviewed by Davson[1] and Leusen.[2] Albert *et al.*[3] carried out the only study in this field in the paediatric age group. Moreover, this was the only study in which all the patients had an uncompensated metabolic acidosis.

PATIENTS AND METHODS

Clinical Material

Twenty-three infants with gastro-enteritis were investigated. Ten infants, aged 2 - 9 months, were moderately dehydrated and alert, but were irritable or had meningeal signs warranting lumbar puncture. The remaining 13 infants, aged 21 days - 16 months, were severely dehydrated and stuporous. For ethical reasons it was not possible to obtain control specimens of CSF from our paediatric patients for acid-base, lactate or pyruvate studies. A concomitant study of CSF acid-base in adults has been carried out at this hospital, situated at an altitude of 1 763 metres above sea level, by Professor R. Lipshitz (Department of Neurosurgery). We were able to use data from 40 adult patients for our control figures on CSF acid-base balance. All these patients were without pulmonary disease and had an inactive CSF.

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Clinical Procedures

Cerebrospinal fluid was obtained by lumbar puncture, with the patient as quiet as possible. Direct arterial sampling of the radial artery was carried out and this was followed by the collection of a venous sample. The patients were investigated only on admission to hospital before therapy was commenced, except in the case of a hypoglycaemic, dehydrated child who was given intravenous dextrose water as an emergency procedure.

Laboratory Techniques

Acid-base studies of arterial blood and CSF were performed on anaerobic samples using a Radiometer Astrup fitted with a blood microsystem BMS2, pH meter PHM71 and a pCO_2 electrode E5036. Actual bicarbonate and base deficit were derived from the Siggaard Andersen alignment nomogram and CSF bicarbonate was calculated using the constants described by Mitchell *et al.*[4] Other investigations included arterial and CSF lactate and pyruvate (Boehringer kits), urea, electrolytes, sugar and osmolality. CSF was also obtained for a cell count; no blood-stained samples or specimens with a pleocytosis greater than 5 white blood cells/mm^3 were included in the series.

Standard statistical methods were employed in this report.

RESULTS

Control Patients

The findings in these patients are summarised in Table I. Compared with arterial blood, the CSF was more acid, and pCO_2 was uniformly greater in the CSF. Bicarbonate concentration was slightly lower than in arterial blood. $^RHCO_3$ (where R is the CSF concentration of a substance divided by the simultaneous concentration in blood)[1]

TABLE I. THE RESULTS OF CSF ACID-BASE STUDIES ON 40 ADULT CONTROL PATIENTS AT AN ALTITUDE OF 1 763 m

	Mean	SD
pH	7,311	0,08
pCO_2 mmHg	43,4	2,4
Bicarbonate mEq/L	20,6	1,6
CSF—arterial pH diff.	−0,1	0,02
CSF—arterial pCO_2 diff.	+8,89	2,33
CSF—arterial HCO_3 diff.	−0,78	1,72
$^RHCO_3$*	0,96	0,07
Lactate mEq/L	1,75	0,49

* $^RHCO_3$ = CSF concentration ÷ arterial concentration (Davson 1967).[1]

represents another way of reflecting the CSF/blood bicarbonate relationship; the mean $^RHCO_3$ was 0,96. In this group of patients, CSF pH was more dependent on the bicarbonate content of CSF (r = +0,67) than the pCO_2 (r = +0,14). Arterial bicarbonate was not directly related to CSF bicarbonate (r = +0,27).

Alert Patients

Studies in these patients were limited to the acid-base balance of arterial blood and CSF. All survived and the findings are summarised in Table II.

In all these patients, except cases 4 and 10 who were indistinguishable from the remainder of the group on clinical grounds, CSF pH was more alkaline than arterial pH—a reversal of the normal situation. This was achieved by a lowering of the CSF pCO_2 and by a relative increase in the bicarbonate concentration. The latter is shown both by the CSF-arterial bicarbonate difference and $^RHCO_3$ In this group of patients, CSF pH was again more dependent on the bicarbonate content (r = +0,7) than on pCO_2 (r = +0,34). Arterial bicarbonate was closely related to CSF bicarbonate (r = +0,92). $^RHCO_3$ differed significantly in these patients compared with the controls (P = 0,005).

Stuporous Patients

These children were fully investigated as described earlier. The only infant who died, case 12, was severely malnourished and showed considerable electrolyte disturbance (serum Na^+ 112 mEq/litre, serum K^+ 2,6 mEq/litre and serum albumin 1,3 g/100 ml). Case 5 was hypoglycaemic on admission to hospital.

The results of the acid-base studies are shown in Table III. Nine of the patients had an alkaline CSF relative to arterial blood. CSF pCO_2 was diminished in most of these infants.

$^RHCO_3$ in this group showed a mean level (0,91), similar to that of the control group (0,96), but lower than that of the alert patients (1,38). CSF bicarbonate was related to arterial bicarbonate (r = +0,78), but not as closely as in the alert patients. There was no dependence of CSF pH on bicarbonate (r = 0,36) while that for pCO_2 remained poor (r = +0,45).

Table IV shows the results of urea, sodium, potassium, sugar and osmolality determinations in blood and CSF. Three infants exhibited hypernatraemia (serum Na^+ of 150 mEq/litre or more), while 2 infants were hyponatraemic. Two infants had serum potassium levels of less than 2,5 mEq/litre. The majority of the patients were hyperglycaemic; no statistical correlation could be found between the blood sugar concentration and serum sodium, potassium, arterial pH, pCO_2, bicarbonate or base deficit. Osmolality, as expected, correlated with sodium concentration in both blood (r = +0,76) and CSF (r = +0,92).

Table V shows the results of the lactate and pyruvate studies in arterial blood and CSF. Both arterial lactate and pyruvate concentrations differed significantly from those of control patients (lactate P = 0,05 - 0,02; pyruvate P = 0,05 - 0,02). However, CSF lactate did not differ significantly from the control values (P = 0,5). A marginal correlation existed between arterial and CSF lactate (r = +0,65), none existed for pyruvate (r = −0,04), while that for the lactate/pyruvate ratio was significant (r = +0,82). There was no correlation between CSF lactate and bicarbonate (r = −0,24).

TABLE II. RESULTS OF STUDIES ON 10 ALERT INFANTS WITH METABOLIC ACIDOSIS

	Arterial blood				CSF			
Case No.	pH	pCO_2 mmHg	HCO_3 mEq/L	Base deficit	pH	pCO_2 mmHg	HCO_3 mEq/L	$^RHCO_3$
1	7,26	21	9,2	16	7,3	23,5	10	1,08
2	7,25	25,5	8,5	19	7,26	30	12,5	1,47
3	7,23	22	8,6	17	7,39	20	11,5	1,34
4	7,38	23,5	13,4	10	7,25	27,5	15,8	1,18
5	7,31	24	8,1	18	7,35	23,5	12,1	1,49
6	7,32	24	12	12	7,37	23	12,6	1,05
7	7,13	19	6	21	7,18	24	8,4	1,39
8	6,97	13	1,5	30	7,09	12	2,7	1,87
9	6,91	12	2,6	30	7,08	19	5,2	2,0
10	7,34	16,5	8,7	15	7,33	17,5	8,2	0,94
Mean	7,21	20,1	7,9	18,8	7,26	22	9,9	1,38
SD	0,16	4,8	3,7	6,7	0,11	5,1	3,9	0,35

$^RHCO_3$ is statistically different from that of the controls. C-A diff. = CSF—arterial concentration.

TABLE III. RESULTS OF STUDIES ON 13 STUPOROUS INFANTS WITH A METABOLIC ACIDOSIS

	Arterial				CSF			
Case No.	pH	pCO_2 mmHg	HCO_3 mEq/L	Base deficit	pH	pCO_2 mmHg	HCO_3 mEq/L	$^RHCO_3$
1	7,16	13,5	3,8	2,6	7,27	16,5	1,9	0,5
2	7,23	22,5	8,2	19	7,12	25	7,6	0,93
3	7,19	18,5	6,9	20	7,27	16	6,6	0,95
4	7,08	14	4,2	27	7,21	15	5,8	1,38
5	7,0	21	5,4	24	7,14	16,5	5,1	0,93
6	7,3	26	12,5	12	7,3	22	9,9	0,79
7	7,15	15	6,4	23	7,10	19	5,4	0,84
8	7,23	24,4	11,0	16	7,26	20,5	7,5	0,68
9	7,23	21,5	8,8	17,5	7,28	17,5	7,9	0,89
10	7,21	18,5	7,2	19	7,3	26	10,3	1,43
11	7,11	13,8	4,3	24,5	7,15	15,5	4,9	1,13
12	7,13	16,5	5,2	23	7,09	18,5	3,8	0,73
13	7,21	13	5	23	7,23	14,5	3,8	0,77
Mean	7,17	18,3	6,84	21,1	7,21	18,7	6,2	0,91
SD	0,08	4,4	2,7	4,28	0,08	3,7	2,4	0,26

$^RHCO_3$ differed statistically from the alert group, but not from the controls.

TABLE IV. MEANS OF RESULTS OF ELECTROLYTE AND OSMOLALITY STUDIES IN BLOOD AND CSF IN 11 STUPOROUS INFANTS*

	Serum					CSF				
	Urea mg/100 ml	Na mEq/L	K mEq/L	Gluc. mg/100 ml	Osm. mOsm/L	^RUrea	$^RNa^+$	$^RK^+$	$^RGluc.$	$^ROsm.$
Mean	92,8	136,2	4,1	297,3	294	0,97	0,97	0,8	0,58	1,03
SD	63,5	15,1	1,34	227,3	36,4	0,18	0,09	0,22	0,2	0,04

* 2 cases are excluded, as they were in the pilot study and were not fully investigated.

TABLE V. ARTERIAL AND CSF MEAN LACTATE AND PYRUVATE RESULTS IN 11 STUPOROUS INFANTS WITH A METABOLIC ACIDOSIS

	Arterial			CSF		
	Lactate mEq/L	Pyruvate mEq/L	L/P ratio	Lactate mEq/L	Pyruvate mEq/L	L/P ratio
Mean	1,96	0,11	21,6	1,8	0,13	15,6
SD	1,08	0,095	12,1	0,82	0,06	8,9

Normals for this laboratory:	Mean	SD
Arterial lactate mEq/L	1,08	0,39
Arterial pyruvate mEq/L	0,10	0,03
Arterial pyruvate mEq/L	0,10	0,03

CSF pyruvate (Lasch 1953) = 0,1 mEq/L

DISCUSSION

Previous investigations in the field have proceeded predominantly along two lines. Firstly, those in which the immediate responses in both blood and CSF have been studied after acid loading;[5] secondly, studies have been performed in patients with chronic metabolic acidosis secondary to renal disease.[6,7] In the first group, plasma bicarbonate and pCO_2 fall rapidly; CSF pCO_2 falls, but bicarbonate remains static, and thus pH rises. In patients with chronic metabolic acidosis, the general finding is that the bicarbonate concentration is reduced, but owing to the lowered pCO_2, pH returns to normal.

Neither of these situations necessarily reflects the problem in a patient with an acute metabolic acidosis. It was for this reason that Albert *et al.*[3] performed their study. Their findings were that CSF pH remained within normal limits, the pCO_2 falling and the bicarbonate adjusting to a new low level. These findings are similar to those in the chronic situation. The authors thus concluded that CSF bicarbonate adjusted rapidly to acute changes in arterial acid-base balance, since their patients who had gastroenteritis had been ill for only 1 - 4 days. We cannot concur with this, since, in our patients who were ill for similar periods, CSF pH departed from normality (that is, fell beyound 2 standard deviations from the normal mean value) in 2 out of the 10 alert infants and 4 out of the 13 stuporous patients. All these patients recovered, except case 12, despite the fact that 3 of the stuporous infants had a more acid CSF than arterial blood. It would thus appear that an uncompensated CSF metabolic acidosis has no particular prognostic significance in this clinical context. CSF pCO_2 fell in all cases, both in absolute terms and when seen as the CSF-arterial pCO_2 difference.

The most interesting change in these infants occurred in the bicarbonate concentration. There was a statistically

significant rise in $^{R}HCO_3$ in the alert patients when compared with the controls; however, in association with a stuporous state, this could no longer be discerned (Fig. 1). To consider firstly the alert infants with an acute uncompensated metabolic acidosis, a retrospective review of the literature reveals that previous authors have observed the same phenomenon—that is, a rise in $^{R}HCO_3$ in the presence of metabolic acidosis (Table VI). Posner *et al.*[7]

TABLE VI. $^{R}HCO_3$ COMPARISONS BETWEEN PATIENTS IN THE PRESENT STUDY AND THE FINDINGS OF PREVIOUS INVESTIGATORS

Investigator	Controls (mean)	Acidosis (mean)
Albert *et al.*[3]	**0,99**	**1,75**
Pauli *et al.*[5]	**0,99**	**1,49**
Posner *et al.*[7]	**0,98**	**1,35**
Mitchell *et al.*[8]	**0,87**	**1,12**
Present study: Alert group	**0,96**	**1,38**
Stuporous group	**0,96**	**0,91**

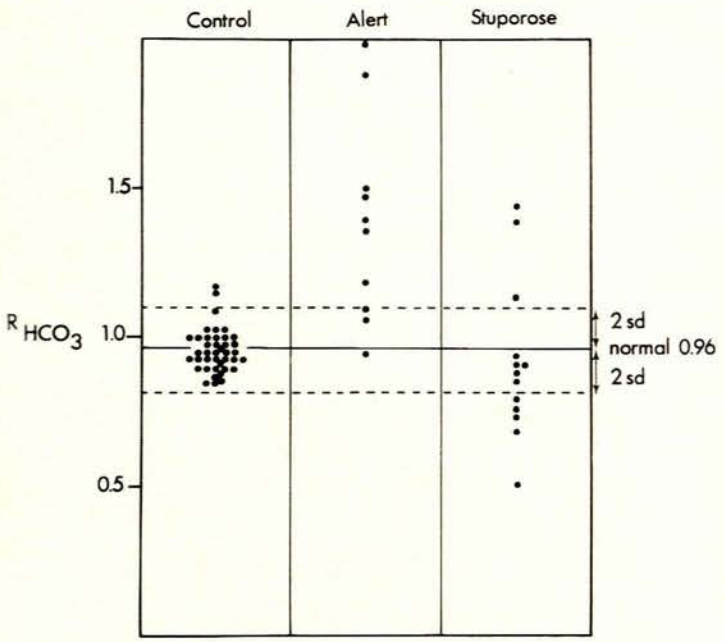

Fig. 1. $^{R}HCO_3$ in the groups of patients studied. The controls differ significantly from the alert patients (P = 0,005), as do the alert and stuporous group (P = 0,01). There is no statistically significant difference between the controls and the stuporous patients (P = 0,2).

and Mitchell and his colleagues[8] commented on this observation. The latter concluded that the regulation of CSF pH appeared to take precedence over other factors in the acid-base balance of both CSF and arterial blood. The bicarbonate 'shift' described above seems to form an integral part of this concept.

This leads to the question of whether or not bicarbonate transport to the CSF is an active or a passive process. This has been the subject of much debate and has been reviewed in detail elsewhere.[2] It is known that CSF is normally electropositive to plasma. If an ion can pass across a semipermeable membrane separating two compartments which show an electric potential difference, its distribution between the compartments can be predicted from the Nernst equation.[2] Held *et al.*[9] found that chloride and calcium showed a passive distribution, sodium and magnesium were actively transported, while potassium and bicarbonate showed some features compatible with active transport. Active transport of bicarbonate is further supported by the $^{R}HCO_3$ changes in metabolic acidosis. However, no direct estimations of bicarbonate flux between CSF and blood exist. Passive regulation remains a possibility.[10] In summary, to quote Leusen,[2] 'it can be concluded that the mechanisms of bicarbonate exchange between blood and CSF are still largely unknown'.

In our patients, a pattern was discernible. In the controls, CSF pH was linked to the bicarbonate concentration, although the latter was not directly correlated to arterial bicarbonate. In the alert group, CSF pH remained linked to the bicarbonate concentration and arterial and CSF bicarbonate showed a close correlation. However, in the stuporous patients CSF pH showed a poor correlation with the bicarbonate concentration and the relationship between CSF and arterial bicarbonate deteriorated. It could be argued from these findings that under normal circumstances an active transport mechanism for bicarbonate might be present and, in the presence of an acute metabolic acidosis, the activity of this mechanism is accelerated.

However, this activity appears to cease in the presence of stupor. Why $^{R}HCO_3$ should fall in the presence of stupor is not clear. It is known that lactic acid accumulation in the CSF can displace bicarbonate;[11] this does not appear to have been the case in our patients, since statistically the stuporous patients did not show an increase in CSF lactate, nor was there any correlation between CSF bicarbonate and lactate. Other possibilities exist. Ponten and Seisjo[12] have observed an increase in brain intracellular bicarbonate in metabolic acidosis at the expense of CSF bicarbonate. This possibility could not be assessed in the present study. The final consideration, which is conjecture, is that active transport ceases with the advent of stupor. Whether this is cause or effect cannot be stated on the evidence presented. It would be necessary to study patients in stupor from other causes before passing any further comment. Against this possibility it must be said that those ions thought to be actively secreted, such as sodium and potassium, showed normal R values[1] in these same patients, thus being of no prognostic value in the assessment. It would therefore be necessary to postulate a selective derangement of active transport of bicarbonate. At the present time the changes in $^{R}HCO_3$ associated with stupor reported in this communication remain unexplained.

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