Decreased anion gap associated with monoclonal and pseudomonoclonal gammopathy

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Nine patients with monoclonal and one with pseudomonoclonal gammopathy were found to have a decreased anion gap. Eight of the patients had multiple myeloma, one had plasma cell leukemia and one had chronic active hepatitis. In all of them the decreased anion gap was associated with an increased concentration of IgG greater than 5 g/dl.

Chef neuf malades avec une gamma-globulinopathie monoclonale et chez un autre avec une gamma-globulinopathie pseudomonoclonale on a noté une diminution de la lacune anionique. Huit de ces malades souffraient d'un myélome multiple, un d'une leucémie des cellules plasmatiques et le dernier d'une hépatite chronique active. Chez tous, la réduction de la lacune anionique était associée à une augmentation de la concentration de l'IgG supérieur à 5 g/dl.

The potential usefulness of the "undetermined acids" or anion gap in diagnosis has been known for almost 30 years.[1] The anion gap is calculated from the serum electrolyte values as either the difference between the sum of the sodium and potassium values and the sum of the chloride and bicarbonate values, as in formula I, or, more conveniently, the difference between the sodium value and the sum of the chloride and bicarbonate values, as in formula II.

Formula I:

$$[Na^+] + [K^+] - ([Cl^-] + [HCO_3^-]$$

Formula II:

$$[Na^+] - ([Cl^-] + [HCO_3^-])$$

Although the second calculation is less accurate, variation in potassium values usually contributes little to the anion gap. The bicarbonate is measured as total CO_2 but, practically, this does not affect the calculations.

The anion gap is known to be increased in acidosis when concentrations of unmeasured anions such as lactate or ketoacids are increased.[2-4] Little attention, however, has been paid to the clinically important situations in which the anion gap is decreased. In this paper we describe a group of patients with monoclonal or pseudomonoclonal gammopathy and a greatly decreased anion gap.

Patients and methods

Over a period of 18 months we investigated 10 inpatients with a decreased anion gap at The Vancouver General Hospital (Table I). Monoclonal gammopathy was confirmed by immunoelectrophoresis in agarose gel in all but patient 8, whose apparent monoclonal peak on cellulose acetate electrophoresis (the ratio of height to width, at half height, of the gamma peak was 3.5) proved to be polyclonal.

We calculated the "normal" anion gap from the electrolyte values in blood samples from 100 apparently healthy hospital employees (50 women and 50 men) and also calculated the mean anion gap of 295 inpatients whose individual electrolyte values were within normal limits.

To assess the relation between the albumin/globulin (A/G) ratio and the anion gap, we surveyed protein electrophoreses of hospital inpatients, then measured electrolyte concentrations in 40 consecutive inpatients with normal values for both albumin and globulins and a normal A/G ratio (1 to 1.8), and in 34 inpatients with an abnormal A/G ratio (1.0 or less) due to either a decrease in albumin alone (5 patients) or a decrease in albumin and a polyclonal increase in globulins (29 patients).

Serum electrolyte concentrations were determined on either a four-channel Technicon AutoAnalyzer II or on a Technicon SMA 6/60. Several sodium and potassium determinations were repeated on the Beckman KLINA flame photometer. When more than one method was used, the correlation between the results was excellent.

Total serum protein concentration was determined by the biuret method on the Abbott ABA-100; albumin and globulin concentrations, by protein electrophoresis on the Beckman Microzone system and scanning with a Beckman or Clifford scanner after staining with Ponceau S; calcium, by a modification of the cresolphthalein complexone method;[5] phosphorus, by the Technicon AutoAnalyzer modification of the method of Fiske and Subbarow;[6] and serum viscosity, by the method of Harkness.[7]

Results and discussion

The pertinent clinical and biochemical findings in the 10 patients are summarized in Table I. The mean value of 11.0 mmol/*l* (formula II) for the anion gap in the apparently healthy individuals and in the 295 inpatients is the same as that reported in similar series from Europe[3] and Australia.[4]

In the 10 patients with monoclonal or pseudomonoclonal gammopathy the anion gap was less than 10 mmol/*l* by formula I and less than 6 mmol/*l* by formula II; the patients had either monoclonal or polyclonal IgG values of more than 5 g/dl. (This group of 10 patients includes all the patients with myeloma-protein values of more than 5 g/dl seen in the hospital during the 18-month period.) There was slight hyponatremia in two thirds of the patients. In one patient (no. 6) hypercalcemia definitely contributed to the decrease in the anion gap.

Complete or partial blocking of the AutoAnalyzer lines is frequently caused by serum paraproteins, but this did not seem to apply in our investigation. It is possible that a large amount of myeloma protein may affect the sampling or the dialysis characteristics, or both, over the small dialyzer area in the AutoAnalyzer II or SMA 6/60.

There appeared to be no correlation between anion gap and serum viscosity. Only 1 of the 10 patients (no. 5) had a clinical hyperviscosity syndrome; his relative serum viscosity at 37°C was 8.5 (normal range, 1.4 to 1.8). The patient with the highest concentration of myeloma protein (no. 3) had a relative serum viscosity of 2.6. Whereas the anion gap returned to normal in patient 5 after plasmapheresis (with a decrease

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Table I—Clinical and biochemical findings in patients with monoclonal gammopathy

Patient no.		Sex	Age (yr)	Na*	K*	Cl*	Total CO_2*	Ca*	P*	Total protein†	Albumin†	Globulin†	A/G ratio	Anion gap Formula I	Anion gap Formula II	Diagnosis
1		M	66	141	4.1	104	32	2.45	1.35	10.2	3.6	6.6	0.5	9	5	IgG multiple myeloma
2		M	77	138	3.6	106	28	2.43	1.13	12.0	2.9	9.1	0.3	8	4	IgG multiple
	After treatment			137	3.6	107	27			8.6	2.3	6.3	0.4	3	−1	myeloma
3	1970	M	80	126	4.3	99	23	2.05	1.35	14.2	3.2	11.0	0.3	8	4	IgG multiple
	January 1973			125	3.9	99	22	1.95	0.96	11.0	2.1	8.9	0.2	8	4	myeloma
	April 1973			133	3.5	109	19	1.90						8	5	
4		F	80	134	4.2	107	29	2.60	1.13	10.4	3.4	7.0	0.5	2	−2	IgG multiple myeloma
5		M	69	130	4.1	110	22	2.20	1.29	12.8	2.6	10.2	0.3	2	−2	IgG multiple myeloma
	After plasma-pheresis			137	2.9	97	27			8.4	3.0	5.4	0.6	16	13	with cryo-globulinemia Hyperviscosity syndrome
6		M	53	130	2.1	84	43	4.28	1.45	10.6	2.5	8.1	0.3	5	3	IgG multiple myeloma
7		M	63	129	4.0	102	23	2.30	0.87	10.2	2.4	7.8	0.3	8	4	Plasma cell leukemia
8		F	33	134	3.0	111	19			7.8	2.2	5.6	0.4	7	4	Chronic active hepatitis
9		M	67	138	4.2	105	33	2.33			1.8	6.4	0.3	4	0	IgG multiple myeloma
10		M	59	131	2.9	106	24	3.40	1.40	10.4	2.3	8.1	0.3	4	1	IgG multiple myeloma
Mean ± SD																
	100 apparently healthy individuals			144 ± 1.2	4.2 ± 0.15	105 ± 0.9	28 ± 1.2							15.2 ± 1.6	11.0 ± 2.5	
	295 inpatients													15.2 ± 1.6	11.0 ± 2.5	

*mmol/l
†g/dl

in relative plasma viscosity to 2.5), the gap in patient 3 has not changed for 3 years. Thus, it is possible that the absolute amount of the myeloma protein and its inability to function as an anion, rather than plasma viscosity, may be one of the underlying causes of the observed decrease in anion gap.

The cationic nature of myeloma proteins at a physiologic pH was recently proved by Murray, Long and Narins,[8] who found a decrease in the anion gap (by formula II) to less than 6 mmol/l in 28% of patients with multiple myeloma. We found a decrease in the anion gap only in patients with IgG values of more than 5 g/dl. Our eight patients with multiple myeloma represent approximately 10 to 15% of all patients with the disease seen over the 18 months.

There was no significant correlation ($P > 0.05$) between the A/G ratio and the anion gap in serum specimens of patients with either normal or abnormal A/G ratios (Fig. 1). The patients with multiple myeloma form a characteristic group with an anion gap of 5 or less and A/G ratios of 0.5 or less.

Conclusion

Although sometimes a low anion gap may be due to laboratory error, and other factors have to be taken into consideration (e.g., concentrations of serum calcium, magnesium, lithium and bromide), we consider the low anion gap to be of significance. In our laboratory the low gap, confirmed on repeat determination, is an indication for assay of serum total protein and protein electrophoresis. In fact, in one of our patient (no. 4) the diagnosis of multiple myeloma was made in this manner.

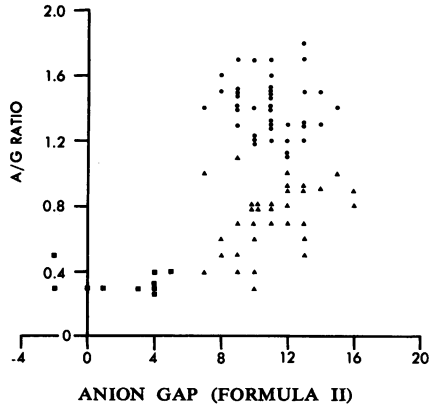

FIG. 1—Relation of anion gap and albumin/globulin ratio. Squares represent our patients with a decreased anion gap; circles, patients with normal serum protein electrophoresis; and triangles, patients with low albumin or high gamma globulin values or both.

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