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ORIGINAL ARTICLE

Use of the osmolal gap to guide the start and duration of dialysis in methanol poisoning

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Abstract

Objective. Rapid diagnosis and treatment of methanol poisoning is mandatory. Dependence on serum methanol analysis in this situation may delay diagnosis and treatment. The anion and osmolal gaps have been recommended for use as diagnostic tools, but the use of these gaps to evaluate the length of hemodialysis treatment has only been emphasized in a few reports. We evaluated the usefulness of the osmolal gap in estimating the need for dialysis and the duration of this treatment in 17 methanol-poisoned subjects. *Material and methods*. Patients were part of a recent outbreak of methanol poisoning, in which the diagnosis upon admission was mainly based on use of the anion and osmolal gaps. The duration of dialysis generally followed the standard recommendation of 8 h. During dialysis, blood samples were frequently collected and analyzed to determine acid–base status and serum methanol and to calculate the osmolal gap. In nine patients, the duration of dialysis was compared with the duration necessary to normalize serum methanol and the osmolal gap. *Results*. There was a good correlation between serum methanol and the osmolal gap during hemodialysis ($y = 1.09x + 3.82$; $R^2 = 0.92$). The osmolal gap therefore gives a good estimate of the serum methanol level during hemodialysis, and could have saved a total of 23 h of dialysis treatment (34%) in nine patients had it been applied. *Conclusions*. In the absence of serum methanol analyses, the osmolal gap is useful to assess the indication for and duration of hemodialysis in methanol-poisoned patients. In mass poisoning situations, use of the osmolal gap makes it possible to reduce the duration of dialysis in a safe manner.

Key Words: *Hemodialysis, methanol, osmolal gap, osmolality, poisoning*

Introduction

Methanol poisoning is a medical emergency characterized by metabolic acidosis, visual disturbances and cardio-respiratory failure [1,2]. Rapid treatment is mandatory, and the cornerstones of such treatment are infusion of bicarbonate to correct metabolic acidosis, use of an antidote (ethanol or fomepizole) to block metabolism of methanol to formic acid and hemodialysis to remove methanol and formate [2]. Because of the variable intrinsic clearance of formate, the contribution of dialysis to total body clearance of formate has been discussed [3,4], but many authors still recommend dialysis in the severely acidotic patient in order to remove this toxic metabolite [2]. Hemodialysis also helps to correct metabolic acidosis.

Metabolism of methanol to formic acid results in profound metabolic acidosis with a high anion gap [5]. Ingestion of methanol also increases serum osmolality because of its high molar concentration [5]. Methanol (and ethylene glycol) poisoning is therefore one of the few conditions in medicine in which both the anion and osmolal gaps are elevated, and this may be diagnostically helpful [6]. This may be of crucial importance, because few hospitals are able to analyse for methanol on a 24-h basis, thus potentially delaying both diagnosis and treatment.

In most situations, the duration of dialysis depends on the residual serum methanol concentration. There have been no investigations regarding whether the osmolal gap reflects the serum methanol concentration during hemodialysis [2,7]. A recently proposed kinetic approach to this problem is inter-

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esting [8], but still requires serum methanol analyses to be performed.

In this study, we wanted to evaluate the usefulness of the osmolal gap as a guide to when to start, and when to end, hemodialysis in methanol-poisoned patients.

Material and methods

Patients

During an epidemic in 2002–03, 46 patients were hospitalized in 17 different hospitals in Norway because of methanol poisoning. They had all ingested illegally smuggled spirits, consisting of 20% methanol and 80% ethanol. Diagnosis was based on anamnesis, clinical and laboratory findings, and use of the osmolal and anion gaps [6]. Only three of the hospitals were able to analyze methanol. Initial treatment consisted of infusion of alkali, antidote administration and respiratory support in four patients. Three patients (Nos. 1–3) received ethanol and the rest received fomepizole as antidote. Hemodialysis was performed in 33 patients; in many of these, treatment was initiated before methanol levels were known. Some patients had to be transferred to the nearest hospital with dialysis facilities. Because of lack of data, 16 patients were excluded from further analysis, leaving 17 patients in this study. Nine of these were followed especially closely, with blood tests being performed hourly for determination of the methanol and osmolal gaps. The mean dialysis time was 8 h, based mainly on the present recommendations, when serum methanol analyses were not available [1,2].

Methods

Blood samples for methanol determination were spun, serum-separated and frozen until analysis. Methanol in serum was measured by gas chromatography using a headspace injector (Fisons GC 8000; Carlos Erba Instruments, Rodano, Italy) with a sensitivity of 1.3 mmol/l and a day-to-day coefficient of variation of 5%. Calibrators and controls were made by dilution of 100% methanol (Merck, Darmstadt, Germany). The levels of the methanol and osmolal gaps were compared retrospectively.

Anion and osmolal gaps

The anion gap (AG) in serum was calculated from the standard equation

$$AG = ([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-])$$

The reference range is 13 ± 8 mmol/l (mean ± 2 SD) [9].

The osmolal gap (OG) is the difference between the measured (MO) and calculated osmolalities. The following equation was used:

$$OG = MO - \frac{(1.86[Na] + [glucose] + [urea])}{0.93}$$

The reference range is 5 ± 14 mOsm/kgH_2O (mean ± 2 SD) [9]. Serum osmolality was measured using the freezing point depression method. The osmolal contribution from ethanol found in four patients was subtracted from the measured osmolality: 100 mg/dl ($=22$ mmol/l) of ethanol contributes 24 (22/0.93) mOsm/kgH_2O to the osmolal gap; 32 mmol/l ($=100$ mg/dl) of methanol contributes 34 (32/0.93) mOsm/kgH_2O to the osmolal gap. To convert methanol concentration from millimoles per liter to milligrams per deciliter multiply by 3.2.

Results

As can be seen from Table I, the 17 patients studied were severely poisoned, with pronounced metabolic acidosis. The median serum methanol concentration was 34.0 mmol/l (range 6.3–146.9 mmol/l) and the median osmolal gap was 61 mOsm/kgH_2O (range 16–159 mOsm/kgH_2O). In all patients, normalization of the acid–base status and anion gap was accomplished within 4 h of dialysis treatment. After termination of hemodialysis, there was no relapse in acidosis or increase in methanol concentration.

Two of the 17 patients died (Nos. 11 and 17 in Table I). Patient No. 8 suffered from impaired vision and four patients (Nos. 8, 9, 11 and 17) needed mechanical ventilation.

Figure 1 presents the relation between serum methanol concentration and osmolal gap during hemodialysis treatment, including start values, in the 17 patients. The regression line was described by the equation $y = 1.09x + 3.82$ ($R^2 = 0.92$). From the above equation, the mean reference value for the osmolal gap when serum methanol was zero ($x = 0$) was approximately four in these patients, which is in accordance with the reference range determined in the prospective study [9] (see *Methods*). When the values from the start of dialysis were omitted, the regression line was almost identical: $y = 1.09x + 2.55$ ($R^2 = 0.91$).

Retrospectively, we analyzed data from the nine patients who were followed by means of hourly blood sampling during dialysis. Compared to the standard recommendation for duration of hemodialysis of 8 h [2], dialysis could have been terminated 2–6 h before it actually was, which would have saved a total of 23 h of dialysis (34%) (Table II). Comparing the values of methanol concentration and duration

Table I. Essential parameters on admission in 17 methanol-poisoned patients.

Patient No.	Sex/age (years)	metOH (mmol/l)	pH	pCO_2 (kPa)	BD (mmol/l)	AG (mmol/l)	OG (mOsm/kgH_2O)	HD (h)
1	F/53	6.3	7.21	2.3	20	38	29	8
2	M/59	9.4	7.17	2.0	23	32	30	8
3	M/44	12.5	7.22	2.8	21	32	20	8
4	M/38	12.5	7.19	1.3	24	35	34	7
5	M/45	12.5	7.25	2.7	17	26	23	13
6	F/69	15.6	7.12	1.6	25	34	21	4
7	F/54	15.6	6.92	1.9	30	40	16	5
8	M/41	32.5	6.87	2.9	29	40	61	8
9	F/65	34.4	6.85	1.9	28	50	36	6
10	F/58	75.0	7.06	2.1	24	35	82	7
11	F/46	76.3	6.62	4.3	ND	30	94	5
12	M/52	84.4	6.86	2.1	28	33	124	8
13	F/42	96.9	7.40	5.3	0	16	134	8
14	M/69	102.8	7.33	3.9	9	24	101	8
15	M/63	103.1	7.35	2.1	11	26	106	9
16	M/53	140.6	7.5	4.8	5	23	138	8
17	M/53	146.9	6.9	7.9	28	47	159	9
Median	53	34.0	7.17	2.3	24	33	61	8

metOH = serum methanol concentration; BD = base deficit; AG = anion gap; OG = osmolal gap; HD = duration of hemodialysis; ND = not determined.

of dialysis shown in Table I, other patients who were not studied so intensively were also probably dialyzed for too long.

Discussion

The efficacy of hemodialysis in removing methanol is well established [2,10]. If methanol metabolism is blocked by antidotal treatment (ethanol or fomepizole), the intrinsic half-life of methanol is then prolonged to ≈40–70 h [2,10,11]. If hemodialysis is initiated in this situation, dialysis represents close to 100% of the total body clearance of methanol [10]. There is no clear indication regarding when to start dialysis on the basis of serum methanol levels alone, but levels of 16–32 mmol/l (50–100 mg/dl) are generally proposed in the absence of acidosis and/or visual disturbances [1,2].

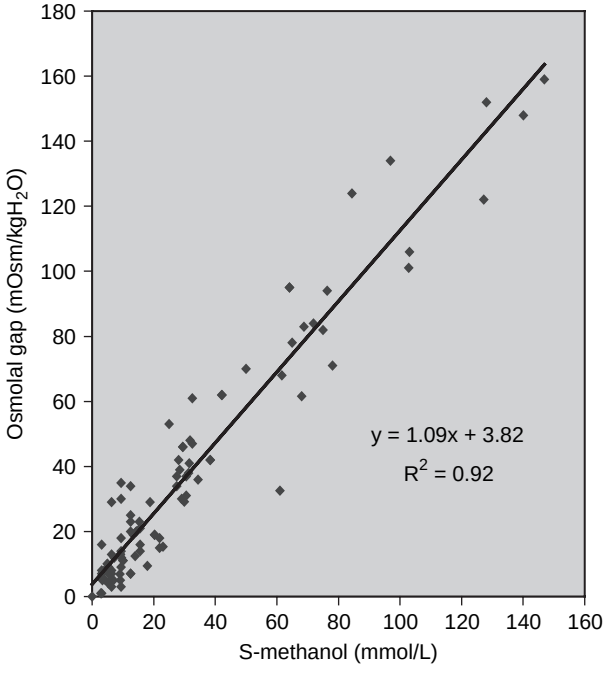

Figure 1. Serum methanol concentration versus OG ($n = 80$) during hemodialysis (including values at start of dialysis).

Some authors have suggested estimating the duration of dialysis based on the initial serum methanol concentration, the dialyzer manufacturer's urea clearance and patient demographics [8]. The required dialysis time (RDT) to reach a methanol concentration of 5 mmol/l was estimated by applying the formula

$$\text{RDT (h)} = [-V \ln (5/A)]/0.06k$$

where V (l) represents the Watson estimation of total body water, A (mmol/l) the initial methanol concentration and k (ml/min) 80% of the dialyzer urea clearance given by the manufacturer. Although this formula gives a good prediction of the duration of hemodialysis, the method is still limited by the need for serum methanol analyses before estimation can be done, and this reduces its applicability.

Regardless of methanol level, Figure 1 clearly demonstrates the close correlation ($R^2 = 0.92$) between the serum methanol concentration and osmolal gap measured simultaneously. This means that the recently demonstrated good correlation between serum methanol concentration and the osmolal gap on admission [6] continues after treatment with hypertonic sodium bicarbonate and the start of hemodialysis. In the absence of methanol

Table II. Survey of spared dialysis time in nine patients using the OG for guidance[a].

Patient No.	HD duration (h)	HD duration if OG was guide (h)	Spared dialysis time (h)	metOH at proposed termination of dialysis (mmol/l)[b]
3	8	2	6	<9
4	7	5	2	6
8	8	5	3	6
9	6	4	2	3
10	7	4	3	15
11	5	4	1	19
14	8	6	2	7
15	9	7	2	7
16	9	7	2	11
Mean	8	5	2.6	9

[a]For explanation of abbreviations, see Table I.
[b]Based on the OG.

analyses, the decision regarding when to start dialysis may therefore safely be based on the osmolal gap, which is based on laboratory parameters available in most hospitals on a 24-h basis, and which clearly reflects the concomitant methanol concentration. If ethanol is used as an antidote, the osmolal contribution from ethanol must be subtracted (see *Methods*). If ethanol analyses are not available, this is another argument in favor of fomepizole as an antidote to methanol poisoning [12]. Fomepizole is present in small molar concentrations and does therefore not affect serum osmolality [13].

If no serum methanol analysis is available, some authors recommend a dialysis duration of 8 h in methanol-poisoned patients [1,2]. In general, this recommendation was followed when the present patients were dialyzed. The use of the osmolal gap as a guide to estimate the duration of dialysis has been suggested but not documented by means of clinical data [2,7]. Interestingly, the long dialysis treatment in patients Nos. 1–2 and especially in patient No. 5 (Table I) could have been avoided if the duration of dialysis had been determined by the osmolal gap. For these three patients there were insufficient data available from later in the treatment course to include them in the calculation of spared dialysis time (Table II). However, the inclusion of these three clearly over-dialysed patients would have resulted in an even greater spared dialysis time. In situations in which many patients are poisoned with methanol at the same time, methods to avoid unnecessary dialysis may be especially valuable. For only 9/17 patients were there enough data for them to be included in the study of spared dialysis time. This may have introduced bias into the study sample. As discussed above, however, the same trend was also observed in patients without sufficient data to be included in the study (Table I).

According to international guidelines, hemodialysis can be discontinued when the serum methanol concentration is $\approx$10 mmol/l (32 mg/dl), provided that acidosis is corrected [2]. This methanol level corresponds to a mean osmolal gap of $\approx$15 (4+11) mOsm/kgH_2O in the present series of patients. However, in patients with an osmolal gap in the lowest part of the reference range (-9 to $+19$ mOsm/kgH_2O), hemodialysis may not be discontinued until the osmolal gap is $\approx$2 mOsm/kgH_2O ($-9+11$ mOsm/kgH_2O; see *Methods*), provided no acidosis and no ethanol (or other alcohols) are present. In those with a high normal osmolal gap, this cut-off level would be 30 mOsm/kgH_2O (19+11 mOsm/kgH_2O). Given this relatively wide reference range of the osmolal gap, a pragmatic guideline is indicated for safety reasons based on the present data. We therefore recommend dialysis until the osmolal gap is normalized ($\leq$19 mOsm/kgH_2O) in two samples taken 1 h apart, provided there is no acidosis.

As illustrated in Table II, the potential reduction of the duration of dialysis was 23 h (34%) in the nine patients studied. If for safety reasons we take into account the reference range of the osmolal gap, as discussed above, the actual effect on spared dialysis time may be less pronounced in some patients, i.e. those with an osmolal gap in the upper part of the reference range.

The frequency of measurement of the osmolal gap should be determined according to its initial value. If it is 159 mmol/l, as in patient No. 17, there is no need to make another determination of the osmolal gap for 6–7 h, given that the serum half-life for methanol during hemodialysis is 1.7–3.7 h, depending on blood flow and dialyzer characteristics [10]. After 6 h (about two serum half-lives), the serum methanol level in patients Nos. 16 and 17 would then have been $\approx$35 mmol/l (25% of the initial value), provided standard antidote therapy was given.

Conclusions

Treatment of methanol poisoning represents a difficult emergency, especially in the absence of methanol analyses. In this setting, the use of hemodialysis can be guided by the osmolal gap. Based on our results, we suggest that dialysis should be continued until the osmolal gap is ≤ 19 mOsm/kgH_2O in two samples taken 1 h apart. The frequency of blood sampling depends on the initial osmolal gap and the acid–base status. If ethanol is the antidote used, the osmolal contribution from ethanol must be subtracted in the calculation of the osmolal gap. This simple approach is safe and may be cost- and capacity-sparing, especially in larger outbreaks of methanol poisoning. Further development of this method should be an issue for future prospective studies.

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