Clinical Toxicology

Cerebral depression due to propylene glycol in a patient with chronic epilepsy – the value of the plasma osmolal gap in diagnosis

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Summary: A case of propylene glycol poisoning is described in a 39 year old woman which resulted in her admission to hospital in status epilepticus. She had had a long-standing history of uncontrollable epilepsy. The diagnosis of propylene glycol poisoning resulted directly from the finding of a high plasma osmolal gap on admission. This finding would have been missed if later samples only had been analysed. Plasma osmolality and the osmolal gap should be considered first line investigations in patients presenting with metabolic acidosis and cerebral signs and symptoms. Since her discharge from hospital a year ago the patient has had no further seizures.

Introduction

Propylene glycol (1,2-propanediol) is an organic solvent widely used in the pharmaceutical and food industries, and in agriculture.^{1,2} Few cases of poisoning have been described, and serious toxic effects include raised plasma osmolality, lactic acidosis, intravascular haemolysis, cerebral depression, seizures and cardiorespiratory arrest.²⁻⁷ In all but one case,⁵ the source of propylene glycol was directly related to its use as a solvent in medication. We describe a case of propylene glycol poisoning in a patient with long-standing epilepsy.

Methods

The plasma and urine ethanol and propylene glycol were measured by gas-liquid chromatography (limit of detection 0.1 g/l for both)⁸ and the identification of propylene glycol was confirmed by GC-MS (LKB 9000). A general drug screen was performed by colour tests, thin layer and gas chromatography.

The plasma osmolality (mmol/l) was calculated using the formula: Plasma osmolality = $1.86 \times \text{Na (mmol/l)} + \text{plasma urea (mmol/l)} + \text{plasma glucose (mmol/l)}$.^{3,9} The plasma osmolality was measured by freezing point depression (Roebbling Osmometer, W. Germany).

The osmolal gap (mmol/kg H₂O) was calculated using the formula: Osmolal gap = plasma osmolality – (plasma osmolality/0.93).³

Case report

A 39 year old unmarried woman had been well up to the age of 16 years, when frequent generalized seizures developed. These episodes were preceded by a feeling of fear or auditory hallucinations and lasted up to one hour with loss of consciousness. They persisted throughout early adult life, despite treatment with phenobarbitone, phenytoin and sulthiame. In January 1986, her medication was changed to phenytoin 500 mg daily, sodium valproate 1 g twice daily, and clobazam 20 mg daily. She had fewer fits, but was admitted several times to hospital in status epilepticus, for which no apparent precipitating event was found. During these admis-

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Table I The biochemical data obtained from the 10.00 h, 13.00 h and the 16.00 h blood samples on the day of admission

Analyte	Time of sample			Reference range
	10.00 h	13.00 h	16.00 h	
<i>Plasma</i>				
Na ⁺ (mmol/l)	140		138	132–144
K ⁺ (mmol/l)	3.4		3.6	3.5–5.0
Urea (mmol/l)	3.5		4.1	2.5–6.7
Glucose (mmol/l)	5.4		5.8	3.3–9.0
Propylene glycol (g/l)	4.0		<0.1	
Ethanol (g/l)	0.9		not measured	
Osmolality (mmol/kg)	340		296	280–300
Osmolarity (mmol/l)	269		267	
Osmolal gap (mmol/kg)	51		9	<10
<i>Serum</i>				
Lactate (mmol/l)			0.43	<1.8
Pyruvate (mmol/l)			0.043	0.45–0.080
<i>Arterial blood</i>				
pH	7.39	7.29		7.37– 7.42
PO ₂ (kPa)	10.7	30.8		11.3–12.6
Pco ₂ (kPa)	4.4	5.5		4.86– 5.94
HCO ₃ (mmol/l)	19.6	18.0		21.3–24.8
	(on air)	(on O ₂)		

sions she had several episodes of apnoea and respiratory arrest, and required ventilation. The electroencephalogram (EEG) during the seizures showed a widespread post-central delta rhythm of 2–6 Hz, but no focal spike or complex waveforms.

Six months later she was again admitted in status epilepticus. On admission at 10.00 h she was stuporose with repetitive generalized convulsions. The results of routine haematological and biochemical investigations were within normal limits and the serum anticonvulsant drug levels were within the therapeutic ranges. The EEG showed no evidence of epilepsy. An hour after her admission she was having episodes of hypoventilation with periods of apnoea lasting 10–20 seconds and required assisted ventilation. Despite intravenous diazepam, fitting continued, and a chlormethiazole infusion was started. At 13.00 h she was noted to have a metabolic acidosis (Table I). Subsequently the fits became much less frequent, and by 16.00 h she was responsive to verbal commands. The relatively rapid recovery from status epilepticus and the unexplained metabolic acidosis raised the suspicion of a drug overdose. The serum lactate, pyruvate, electrolytes and plasma osmolalities were measured and the osmolal gap calculated on the 10.00 h and 16.00 h samples (Table I). Both plasma samples and the 10.00 h urine sample were screened for drugs and poisons, especially alcohols. Large amounts of propylene glycol (4.0 g/l) and ethanol (0.9 g/l) were

found in the 10.00 h plasma. Propylene glycol (0.1 g/l) was also found in the 10.00 h urine sample, but was less than 0.1 g/l in the 16.00 h plasma.

The patient recovered fully over the next 24 hours and consistently denied ingestion of ethanol or of any other unusual substances. She consented to a search of her home for a possible source of propylene glycol. Fifteen substances including her anti-epileptic medication were analysed for alcohols. Propylene glycol (0.6 g/l) was found in a carton of fruit juice and ethanol (30%) in a mouth wash. The patient denied ingestion of either of these two liquids prior to admission. It is notable however that since this episode, she has had no further seizures despite stopping all medication.

Discussion

The features observed in our patient of intractable epilepsy, respiratory depression, plasma hyperosmolality, a metabolic acidosis and rapid recovery, are consistent with propylene glycol poisoning.^{2–7} However, in most cases reported, the diagnosis was made retrospectively, after weeks to months of symptoms later attributed to propylene glycol.^{2–4,6,7}

When admitted our patient was in status epilepticus and developed respiratory depression soon after. Although the arterial pH was initially normal,

when tested several hours later, the pH had dropped to 7.29 and a metabolic acidosis had developed. The combination of the above raised the possibility of poisoning with an alcohol and the serum osmolality was measured and the osmolal gap calculated retrospectively in the plasma sample taken on admission.

The osmolal gap does not usually exceed 10 mmol/kg H₂O except in three clinical situations: (1) reduced plasma water because of hyperlipidaemia or hyperproteinaemia;¹⁰ (2) the presence of endogenous solutes such as amino acids in multiple organ failure;⁹ and (3) exogenous solutes such as mannitol and alcohols.¹⁰ The usefulness of the osmolal gap in screening for drug overdose is limited to toxins with low molecular weight such as ethanol¹¹ and furthermore the normal osmolal gap does not exclude their presence since small amounts will not cause a significant rise.¹² In general, this investigation can provide vital information when excess of an alcohol in blood is suspected, but it is not often considered as a first line investigation. However, because of the rapid metabolism of most alcohols, unless measured at an early opportunity, the transiently raised osmolal gap may be missed. Although there are few pharmacokinetic data for propylene glycol,³ the plasma half-life may be as short as five hours.² In our patient, the plasma concentration fell from 4 g/l to less than 0.1 g/l within 6 hours. This indicates an even shorter half-life possibly caused by enzyme induction secondary to chronic anticonvulsant treatment.

Propylene glycol is partly excreted unchanged by the kidneys, and partly metabolized to lactate, pyruvate and acetone.¹ Although no suitable samples were available for lactate and pyruvate analysis in our patient at the time when the metabolic acidosis was observed, in the absence of other causes for the acidosis it is likely that the concentration of these two acids would have been raised. It is not surprising that when admitted the patient was not acidotic, since acidosis is not an early biochemical abnormality following ingestion of an alcohol. Consequently the anion gap would be normal in the presence of a high osmolal gap. On subtracting the osmotic effect due to 0.9 g/l ethanol, the osmotic activity of propylene glycol in our patient appeared to be 81%, thus nearer the 100%

observed by some workers³ than the 16% observed by others.¹³ This suggests that the rise in osmolal gap due to propylene glycol is nearly equivalent to the molar concentration, and that the magnitude of the osmolal gap may be of predictive value. Even if at that stage there had been an acidosis the excess of unmeasured anion would not have significantly contributed to the hyperosmolality.⁹

Endogenous propylene glycol, thought to be derived from ethanol metabolism, has been found in blood from alcoholics and volunteers following ingestion of spirits, but at a concentration a thousandfold lower than the corresponding ethanol level in the same sample.¹⁴ As this was not the case in our patient, we believe propylene glycol was self-administered as she has had no seizures for a year following cessation of all anticonvulsant medication. Propylene glycol was present in fruit juice found at her flat, but at a concentration not thought to have been sufficiently high to account for the observed blood level, unless consumed in great excess. However, only 100–200 ml of neat propylene glycol would have to be taken or given for a plasma concentration of 4 g/l to be reached. According to the World Health Organization,¹⁵ a daily intake of up to 25 mg/kg body weight of propylene glycol is permitted, and the alcohol is used widely in consumer products.¹ Our patient, as well as a previous case,⁵ illustrate the possibility that unidentified products may contain sufficient amounts of propylene glycol to enable toxic plasma levels to be achieved following self-administration. We recommend that plasma osmolality and osmolal gap be considered first line investigations in patients presenting with an unexplained metabolic acidosis, and with cerebral signs and symptoms.

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