Case report

Hyponatraemia and cerebral oedema due to a modafinil overdose

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SUMMARY

Modafinil is a non-amphetamine stimulant that is prescribed for narcolepsy-associated sleepiness as well as reported off-licence uses among university students looking to improve wakefulness and focus. There is limited information in the medical literature about supratherapeutic modafinil dosage, symptomatology and management of overdose. We report a case of a healthy 32-year-old man who was found unconscious, having vomited, with an empty modafinil blister strip. At the emergency department, he presented with reduced Glasgow Coma Scale and prolonged episodes of vomiting. This acute presentation was conservatively managed in the intensive care unit. Antibiotics were also given for a suspected aspiration pneumonia. CT of the head showed cerebral oedema and biochemistry investigations revealed hyponatraemia. Result aetiology was unclear, however, it has been theorised to be secondary to a sizeable modafinil overdose.

BACKGROUND

Modafinil (2-[(Diphenylmethyl)sulfinyl]acetamide), Provigil, is a wakefulness-promoting agent whose complex pharmacological mechanism of action is not yet fully understood, however, it is known to increase dopamine concentrations extracellularly, while decreasing the levels of gamma-aminobutyric acid in the neocortex.[1 2] In the UK, it is currently licensed for narcolepsy-associated somnolence.[3] Reported off-licence use include fatigue in multiple sclerosis,[4] sleepiness in Parkinson's disease[5] as well as potentially improving academic performance in university students.[6]

There is limited literature on symptomatology as well as management associated with modafinil overdose. In addition to 49% of adverse effects happening during off-licence use[7] as well as increasing reports of drug abuse,[8] it is pertinent and imperative to investigate the effects of supratherapeutic levels of modafinil.

CASE PRESENTATION

A 32-year-old man was found on the bathroom floor face down in his vomitus without apparent cause. An empty blister strip of modafinil and paraphernalia for insufflation was found nearby. The patient came back from Australia a few weeks before admission having undergone a faecal microbiota transplantation procedure to aid irritable bowel symptoms. Afterwards he attended a religious retreat. Normally, he leads an active lifestyle, drinks very little alcohol and does not smoke. He is not a known drug user.

Medical history included:

Irritable bowel syndrome.
Lyme serology positive in 2013.
Previous urinary infections (for which he was on D-mannose over the counter).
Wolff-Parkinson-White syndrome.
Bicuspid aortic valve.
Splenomegaly.

He was admitted to the emergency department with a Glasgow Coma Scale (GCS) of 4–6, consequently intubated while sedated (200 µg of fentanyl, 80 µg of rocuronium and 200 µg of propofol) and moved to the intensive treatment unit (ITU). During this, the patient suffered from intractable vomiting. He had ecchymosis which, on review by ophthalmology and radiology, was not complicated. He was apparently hypertonic and vocalising with incoherent moans. Biochemistry analysis revealed sodium of 116 mmol/L, C-reactive protein of 36 mg/L and elevated white cell count (table 1). He was clinically hypovolaemic. CT of the head showed evidence of raised intracranial pressure (ICP), without coincident structural abnormalities that might have explained this.

The presentation was treated as a head injury and central nervous system infection with aspiration. Empirical antibiotics were given: amoxicillin, metronidazole and tazobactam piperacillin. Multiple tests—porphyria screen, vasculitic screen, voltage-gated potassium channels, repeat creatine kinase (tables 1 and 2) and MRI of the brain—were conducted. Chest X-ray (CXR) was performed. Due to upper lung lobe consolidation a bronchoscopy with alveolar lavage was performed.

Serum sodium did not initially respond to fluid restriction. Sodium level was restored with hypertonic saline at guideline rate with successful normalisation. GCS was 14/15 after extubation on the second day. No significant respiratory support was required post extubation and the patient's previous neurological issues improved.

INVESTIGATIONS

Biochemistry investigations

See table 1.

Additional tests

Drug screen performed on day 2 was negative for methadone, cocaine, opiates and amphetamines,

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Table 1 Successive biochemistry results

	Day										
Biochemistry test (units)	**0**	**1**	**1**	**1**	**1**	**2**	**2**	**3**	**4**	**5**	**6**
Na (mmol/L)	116	119	120	128	136	137	139	137	140	139	136
Creatinine (mmol/L)	69	74	86	79	76	75	70	67	79	83	76
K (mmol/L)	4.6	4.7	4.5	4.3	4.8	4.2	4.1	4.3	4.4	4.5	4.6
C-reactive protein (mg/L)	35	83	165	151	108	77	50	39	28	16	11
Amylase (U/L)		146	91	49	49	53	85				
Creatine kinase (U/L)		31 616			28 593		47 066				
Magnesium (mmol/L)	0.51	0.64	0.96	0.89	0.86	0.78	0.78				
White cell count (10^9/L)	16.6	11.5	9.5	5.6	4.6	3.3	3.9	3.3	4.3	4.3	3.9
Phosphate (mmol/L)		0.93	0.88			0.7	1.34				

but was positive for benzodiazepines. Haemoglobin, Liver panel, urea, calcium, chloride were normal throughout.

Imaging

- CXR: bilateral consolidation consistent with clinical findings of pneumonia.
- CT head: slit like ventricles and evidence of raised ICP. No focal lesion or signs of trauma.
- MRI: by the time this was performed the raised ICP had apparently improved. Ventricles were normal size and cortical effacement had resolved.
- CT neck was unremarkable, other than confirming the finding of the CXR that he had bilateral pneumonia, which may have been due to aspiration.

DIFFERENTIAL DIAGNOSIS

Hypo-osmolar serum, with inappropriately hyper-osmolar urine, and a high urinary sodium (>40 mmol/L) points to sodium wasting pathologies. This includes renal and extrarenal causes. Renal causes for sodium loss (with a hypertonic urine) such as renal failure or acute tubular necrosis were excluded by an unchanged creatinine. Another renal cause, thiazide diuretic use, was excluded by a lack of exposure. Polydipsia was considered, however, this would have caused a low urinary sodium and low urine osmolality. The main non-renal causes for this picture are syndrome of inappropriate antidiuretic hormone and cerebral salt wasting. Of these the latter is more likely due to the patient's hypovolaemic status. The patient took D-mannose as a supplement. There have been cases of hyponatraemia-associated cerebral oedema in herbal remedies and non-prescription supplements,[9] but there is no evidence that D-mannose would cause this effect, and the patient was on no other known supplements or herbal remedies. Cerebral oedema, as well as other neurological sequelae of disordered osmolalities, is known to be caused by hyponatraemia.[10]

When the patient was lucid, it was established that he had insufflated a large amount of modafinil, though the exact quantity was uncertain. The patient also recalled that he had taken methylphenidate. This was at a much lower dose than the modafinil (he estimates less than 200 mg, while the modafinil was more than 600 mg). The clinicians concluded that the modafinil overdose led to severe hyponatraemia and subsequent hyponatraemic cerebral oedema.

TREATMENT

The patient was treated on admission ceftriaxone and acyclovir. He was intubated and supported on ITU. Initial fluid restriction failed to increase his serum sodium and saline, and mannitol were instead used. He eventually made a full recovery with gradual correction of sodium level.

OUTCOME AND FOLLOW-UP

The patient recovered well and was discharged from hospital soon after stepping down from ITU. He remained mildly cognitively impaired and amnestic for around a month after the event. Endocrine studies and follow-up did not show any long-term disorders of sodium or other biochemistry.

DISCUSSION

The most common findings related to modafinil overdose were tachycardia and central nervous system toxicity.[2 11 12] A deadly

Table 2 Other results, including osmolalities

Day 0		Day 1		Day 2	
Test	**Result (units)**	**Test**	**Result (units)**	**Test**	**Result (units)**
Serum osmolality	242 mosmol/kg	Lactate dehydrogenase	728 iu/L	R.A latex	15.2 (high)
		Urine osmolality	567 mosmol/kg	Antinuclear antibodies	Negative
		Random urine potassium	44.8 mmol/L	Cytoplasmic antineutrophil cytoplasmic antibodies	Negative
		Random urine sodium	57 mmol/L	Perinuclear antineutrophil cytoplasmic antibodies	Negative
		Serum osmolality	249 mosmol/kg	Cardiolipin IgG	Negative
		Random urine creatinine	15.3	Cardiolipin IgM	Negative
		Urate	132		
		Cortisol	1586 nmol/L		
		IgG	6.2		
		IgA	1.45		
		IgM	0.64		

dose has not been described before, with the highest in the literature describing a non-fatal suicide attempt with 5000 mg of modafinil taken at once.[12] Regular therapeutic doses range between 100 and 400 mg.[12 13]

While the dose in this case is uncertain, a presentation of hyponatraemia this extreme, with cerebral oedema as the presenting feature, has not previously been reported following modafinil overdose. While it is unlikely to be related, we must consider deranged fluid intake, D-mannose and/or the faecal transplant may have contributed to his presentation. Likewise, because of the patient's amnesia around the event there could have been other substances involved that were not recollected or detected on the screen.

Because the pharmacology of modafinil is not yet well understood, the processes underlying this presentation are unclear. The diagnosis of cerebral salt wasting can be reached through analysis of osmolalities and fluid status as discussed above.

This would represent an index case of cerebral oedema as a result of modafinil overdose. Along with other drug overdoses, modafinil should be considered a causative agent for patients presenting with hyponatraemic cerebral oedema. Further information on the pharmacology of modafinil at extremes of dose may inform as to both the mechanism of this presentation and also more targeted therapies to treat it.

Learning points

- Differential diagnosis of hyponatraemia should be considered through clinical findings and consideration of serum and urine osmolalities, and urine sodium.
- With increasing off-license or non-prescribed use of modafinil, clinicians should be aware of it as a potential agent of overdose.
- The most common neurological effects of modafinil overdose include headache and dizziness, heightened anxiety and agitation as well as tremors and dystonia.[11]
- The management of modafinil overdose is largely supportive, with a focus on sedation, and control of dyskinesias and blood pressure.
- The possibility that supratherapeutic doses can cause hyponatraemia or cerebral oedema should mean it is considered a differential in these cases, and that clinicians should be mindful of these sequelae following an overdose of modafinil.

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