*Q J Med* 2002; **95**:431–437

# Original papers

QJM

# Hyponatraemic states following 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') ingestion

T.K. HARTUNG[1], E. SCHOFIELD[2], A.I. SHORT[3], M.J.A. PARR[4] and J.A. HENRY[5]

*From the [1]Respiratory Unit, Ninewells Hospital, Dundee, [2]Medical Toxicology Unit, Guy's Hospital, London, [3]Broomfield Hospital, Chelmsford, UK, [4]The Cloisters, Cherrybrook, Sydney NSW 2126, Australia, and [5]Academic Department of Accident & Emergency Medicine, Imperial College, St Mary's Hospital, London, UK*

*Received 2 November 2002 and in revised form 21 February 2002*

## Summary

**Background:** Life-threatening and fatal hyponatraemic complications following ecstasy use have previously been documented.
**Aim:** To define clinical features of hyponatraemia following the ingestion of 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy').
**Design:** Retrospective case series.
**Methods:** All enquiries to the London centre of the National Poisons Information Service (NPIS) between December 1993 and March 1996 were screened for cases of MDMA use associated with hyponatraemia (serum sodium $<130$ mmol/l). History of fluid consumption, presenting features and subsequent clinical course were recorded.
**Results:** Seventeen patients, aged 15–26 years, were identified. Serum sodium levels ranged between 107 mmol/l and 128 mmol/l. In six patients, biochemical results were consistent with inappropriate secretion of antidiuretic hormone (SIADH). Analytical confirmation of MDMA ingestion was obtained in 10 patients. Ten patients were known to have ingested a large amount of non-alcoholic or alcoholic fluid. The clinical pattern was remarkably uniform, with initial vomiting and disturbed behaviour, followed in 11 patients by seizures. Drowsiness, a mute state and disorientation were observed for up to 3 days. Two patients died; 14 made a complete recovery.
**Discussion:** MDMA can cause life-threatening hyponatraemic encephalopathy when accompanied by excessive fluid ingestion. The mechanism involves inappropriate secretion of antidiuretic hormone.

## Introduction

During the 1990s, MDMA ('ecstasy') gained widespread popularity as a dance drug. Cases of hyperthermia began to be reported,[1–6] and, subsequently, hyponatraemia emerged as another acute complication.[7–14] Excessive fluid intake and inappropriate ADH secretion have been implicated in the emergence of this distinct clinical syndrome.[7] We carried out a study at the London centre of the

*Address correspondence to Professor J.A. Henry, Academic Department of Accident & Emergency Medicine, Imperial College, St Mary's Hospital, London W2 1NY. e-mail: j.a.henry@ic.ac.uk*

**Table 1** Clinical course of patients with hyponatraemia following MDMA ingestion

| Patient | Age and sex | History of MDMA and fluid ingestion | Hospital presentation | Day 1 | | | Day 2 | | | Analytical confirmation of MDMA | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | SNa | Sosmol | Uosmol | SNa | Sosmol | Uosmol | | |
| 1 | 20 M | 1 tablet 5 h previously; 3–4 pints of beer | Collapse; grand mal convulsion; GCS 4/15 T 34.8; HR 110; BP normal | 117<br>5 grand mal seizures; CT head normal | 249[c] | 355 | 129<br>140<br>Alert, not communicating | 262<br>296[c](day 3) | 146 | Yes | Pneumonia<br>Complete recovery |
| 2 | 18 F | Unknown amount 12 h previously | Collapsed on dance floor with grand mal seizure; T, HR, BP normal | 128<br>Talking coherently | 255[c] | | Clinical deterioration; CT head: extradural haematoma, skull fracture | | | | At 2 months: difficulty in concentration; poor short-term memory |
| 3 | 19 M | 2 tablets; excessive amount beer (7 pints) | Grand mal seizure; GCS 9/15; pupils dilated; T, HR, BP normal | 110<br>Urine $Na^+$ 77 mmol/l; CT head: normal | 238 | 543 | 137<br>Urine $Na^+$ 18 mmol/l; rousable, disorientated | 283 | 161 | Yes | Complete recovery |
| 4 | 22 F | 1.25 tablets 5 h previously; unknown amount soft drinks | Grand mal seizure; drowsy, agitated, not orientated; T, HR, BP normal | 118 | 252[c] | | 120<br>Not communicating; CT head normal | 257[c] | 486 | | Na 137 mmol/l on day 4<br>Complete recovery |
| 5 | 23 F | 2 ecstasy 5–8 h previously; excessive amount soft drinks | Tonic seizure; unresponsive; HR 120; T, BP normal | 125<br>Agitated, disorientated | 248 | 418 | 139<br>Orientated, anterograde amnesia | 278[c] | | Yes | Complete recovery |
| 6 | 26 M | 1.5 tablets 7 h previously; excessive amount soft drinks | Bizarre behaviour; tonic seizure; drowsy, rousable; HR 100; T, BP normal | 122<br>Given intravenous frusemide and mannitol | 263[c] | | 138<br>Orientated | 286 | 557 | Yes | Complete recovery |
| 7 | 23 M | 1 tablet; 3 bottles of beer; excessive amount soft drinks | Grand mal seizure; disorientated, uncooperative; HR 105; T, BP normal | 107<br>Suspected respiratory arrest; given intravenous frusemide | 237[c] | | 138<br>Drowsy, orientated amnesia; polyuric; pneumonia | 293[c] | | Yes | Complete recovery |
| 8 | 23 F | 1 tablet 6 h before onset of symptoms; excessive amount water | Vomiting, behaving incoherently; grand mal seizure; drowsy, amnestic; T 37.5; HR 110; BP normal | 123 | 253 | 624 | 135<br>Alert, orientated | 290[c] | | | Complete recovery |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 9 | 19 F | 1.5 tablets 8 h previously; 3 pints of beer | Disorientated, confused, agitated; GCS 8/15; pupils dilated; HR, T, BP normal | 121<br>Uncooperative | | 138 (day 3)<br>Alert, not responding to verbal commands | | Complete recovery |
| 10 | 22 M | 3 tablets | Found collapsed; obtunded; GCS 8/15; CK1220 HR 94; T 37.5; BP normal | 124 733<br>CT head: contusion in left temporal lobe | | 136 (day 3) | Yes | Head injury<br>Complete recovery |
| 11 | 22 F | 1/2 tablet 7 h previously; 1/2 bottle of wine; 1 pint of lager | Vomiting; confused uncooperative; GCS 7/15; HR, T, BP normal | 123 263[c] | | 133 282[c] | | Complete recovery |
| 12 | 15 M | 1/2 tablet 12 h previously; unknown amount alcohol | Grand mal seizure; semi-conscious; HR, T, BP normal | 112 | | 126<br>134 (day 3) | Yes | Complete recovery |
| 13 | 26 M | Unknown amount of ecstasy | Confused, agitated; HR, T, BP normal | 118 | | 141 (day 3) | Yes | Complete recovery |
| 14 | 21 F | 1 tablet 8 h previously; 1 glass of gin | Staggering, confused; vomiting; GCS 7/15; HR, T, BP normal | 128 267 | | | | Complete recovery |
| 15 | 19 F | 1 tablet 4 h previously; excessive amount water (13 bottles?) | Agitated, anxious, grand mal seizure; HR, T, BP normal | 116 230<br>Two further seizures; aspirated; intubated and transferred to ITU; given frusemide and mannitol | | 123 248<br>135 270 (day 3)<br>Extubated on day 3 | | Aspiration pneumonia; tracheitis with subglottic obstruction requiring tracheostomy |

SNa, serum sodium (mmol/l); Sosmol, serum osmolality (mmol/kg); Uosmol, urine osmolality (mmol/kg); BP, blood pressure (mmHg); HR, heart rate (beats per minute); T, core temperature (°C); CT, computed tomography; GCS, Glasgow Coma Scale; [c], calculated serum osmolality = $2\times(Na^{+}+K^{+})$ + urea mmol/l + glucose mmol/l.

NPIS, screening all telephone enquiries for cases of MDMA-associated hyponatraemia, and report 17 patients who presented with hyponatraemia, two of whom died.

## Methods

All documented telephone enquiries to the London centre of NPIS between December 1993 and November 1995 were screened by a professional information officer for cases where MDMA use was complicated by hyponatraemia (serum sodium concentration $<130$ mmol/l). Clinical details and blood and urine biochemistry results were requested from the hospital concerned. Furthermore, between December 1995 and March 1996, management advice was given for acute cases by NPIS medical staff and, where possible, serial measurements of plasma and urine osmolality and serum sodium levels were requested. Blood and urine samples were obtained for toxicological analysis at our laboratory. A further fatal case is included where our advice was sought. This case has since been reported.[12]

## Results

Of a mean 13 762 enquiries per month to the NPIS, 135 telephone calls per month concerned 'ecstasy' (1.0%). Over the 28-month study period, 17 cases of MDMA-associated hyponatraemia were identified (0.4% of all enquiries about 'ecstasy'): seven male and 10 female, aged 15–26 years. History of MDMA ingestion and concomitant fluid consumption, presenting features and subsequent clinical course of the 15 patients who recovered are summarized in Table 1. Analytical confirmation of MDMA ingestion was obtained in eight cases. Eight patients were known to have ingested a large amount of non-alcoholic or alcoholic fluid; in five patients, the history of fluid ingestion was not available. The clinical pattern was remarkably uniform, with initial vomiting and disturbed behaviour, followed by drowsiness, agitation and in 10 patients, seizures. Clinical findings did not necessarily reflect the magnitude of the hyponatraemia. Drowsiness, a mute state and disorientation were observed for up to 3 days. In six patients the blood and urine biochemistry were consistent with a diagnosis of SIADH, as evidenced by the presence of hyponatraemia, low serum osmolality and inappropriately concentrated urine.

Table 2 shows the sequence of events in the two fatal cases. Symptoms of hyponatraemic cerebral oedema occurred within 5 h of ingestion of one 'ecstasy' tablet. In both cases an excessive amount of fluid had been drunk.

## Discussion

Acute complications following MDMA use may be under-reported, but are relatively uncommon.[15] A pattern of fatal and near-fatal hyperthermic collapse with disseminated intravascular coagulation, rhabdomyolysis and acute renal failure[1–6] is now well-documented. Hyponatraemia has more recently been added to the list of complications. It appears to be a result of water consumption in excess of the body's requirements, compounded by failure of the renal response to water loading. Although unusual, it is important to recognize this distinct clinical entity as early as possible. Further fluid consumption to counteract evolving symptoms, or intravenous fluid administration could have fatal consequences. The clinical differentiation from hyperthermic collapse is important and should be straightforward; however, the management is very different in each case.

All of the patients developed symptoms within 12 h of drug ingestion. The observed neurological dysfunction was probably caused by a rapid fall in serum osmolar pressure, leading to intracellular movement of water, and subsequently to cerebral oedema. Early clinical features of hyponatraemic encephalopathy are well described and include headache, nausea, vomiting and weakness, progressing to confusion, hallucinations, reduced conscious level and seizures. Previously published cases of 'ecstasy'-associated hyponatraemia[8–10] reported clinical features of stupor, mutism and seizures occurring within 8–21 h of drug ingestion, followed by spontaneous recovery. In severe cases, cerebral oedema, tentorial herniation, respiratory arrest and cerebral hypoxia can ensue[16] as post-mortem findings confirmed in two patients of our series, and in four previously reported fatal hyponatraemic cases.[13,14,17,18]

The hyponatraemia appears to involve inappropriate secretion of antidiuretic hormone. In one case of severe MDMA-associated hyponatraemic encephalopathy, plasma arginine vasopressin was found to be inappropriately raised at 9 h post ingestion.[1] A recent report demonstrated that a rapid rise in arginine vasopressin concentrations followed administration of MDMA in eight normally hydrated healthy male volunteers.[19] The syndrome of inappropriate secretion of antidiuretic hormone (SIADH), first described by Bartter and Schwartz,[20] may occur post-operatively,[14] as a feature of a concurrent medical condition or following the administration of psychotropic drugs.[21]

**Table 2** Two fatal cases of MDMA toxicity

| History | Patient 1 | Patient 2 |
|---|---|---|
| Age and sex | 15 F | 18 F |
| Previous MDMA abuse | Yes | Yes |
| Amount MDMA taken | 1 'ecstasy'* | 1 'ecstasy'* |
| Time of ingestion | Midnight | 19.45 |
| Behavioural pattern | Dancing, talking and drinking water (at least 3 litres) in rotation | Talking, smoking cannabis, drinking (some alcohol); water from 22.00 onwards |
| Onset of toxicity | 05.00: began to feel ill, vomited; was given considerable amount of water; taken home, where she periodically convulsed; 08.00: semi-conscious, incontinent of urine; 10.00: confused; collapse; inadequate airway for estimated 12 min | 00.15: began to feel ill; numb legs; drank 6–7 cups of water; symptoms progressing over 30 minutes to vomiting, severe headache, loss of vision and rigidity; respiratory arrest, artificial ventilation by parents |
| Hospital transport | 10.30: apnoeic; pupils unreactive; GCS 3/15; pulse 120 bpm; BP 80 systolic; intubated and ventilated, given naloxone and 1.5 litres of intravenous fluid | 00.55: unconscious; given, oxygen, ventilation by ambulance crew en route |
| Hospital presentation | 11.30: GCS 3/15; pupils fixed and dilated; absent brain stem reflexes; pulse 110 bpm; BP 80/50; temp 32.6 °C; given 1 litre of 0.9% saline | 01.30: GCS 3/15; pupils fixed and dilated; papilloedema; well oxygenated; temp 33 °C; pulse 123 bpm; BP 108/60; intubated and ventilated |
| Investigations | 12.00: serum $Na^+$ 125 mmol/l; WCC 13.5; calculated serum osmolality 269 mmol/kg; CXR: pulmonary oedema; CT head: diffuse cerebral oedema and cerebellar herniation; given mannitol, diuretic; 18.00: serum $Na^+$ 135 mmol/l | 02.00: serum $Na^+$ 126 mmol/l; CXR: pulmonary oedema; CT head: marked cerebral oedema, given diuretic an 0.9% saline; 09.00: serum $Na^+$ 145 mmol/l; 2 l negative fluid balance |
| Hospital course | Remained unresponsive requiring ventilatory support; NMR head: general cerebral oedema, poor cerebral blood flow; developed diabetes insipidus; declared brain dead on day 2 | Remained unresponsive requiring ventilatory support; CT head: no change; declared brain dead on day 3 |
| Post-mortem findings | Brain swollen with evidence of herniation through the foramen magnum; haemorrhage in the vicinity of the pituitary | Brain diffusely softened and swollen, vessels distended in keeping with severe hypoxic brain damage |
| Ante-mortem blood toxicology | MDMA 0.05 mg/l | MDMA 0.209 mg/l<br>MDA 0.029 mg/l<br>Ethanol 0.8 g/l |

*Tablets of 'ecstasy' usually contain 50–150 mg MDMA. CT, computed tomography scan; NMR, nuclear magnetic resonance scan; GCS, Glasgow Coma Scale; MDA, 3,4-methylenedioxyamphetamine; MDMA, as in text; temp, core temperature (°C); BP, blood pressure (mmHg); calculated serum osmolality as in Table 1.

However, in these cases it tends to develop gradually as a result of normal fluid intake with inhibition of the urinary response by excessive ADH production. The mechanism by which MDMA causes SIADH remains to be established. Animal experiments have shown that vasopressin secretion is regulated by serotoninergic pathways.[22,23] It seems possible that MDMA, an indirect serotonin agonist, augments ADH release from the neurohypophysis. Acute stress and excessive visual and auditory stimuli might also contribute to exaggerated ADH secretion.[24] Nicotine, a

known ADH-releasing agent, could add to the deleterious water-conserving effects.[21] We do not know whether the cases in this series had been smoking.

The acute onset of symptoms in 'ecstasy'-associated cases can be explained by excessive intake of fluid over a short space of time rapidly leading to symptomatic hyponatraemia. In contrast, if hyponatraemia develops slowly, patients often remain asymptomatic.[21] Recovery appears to be uneventful if fluid intake is discontinued in time; the recovery is consistent with the elimination of MDMA and its metabolite MDA over 24–48 h.

MDMA users were initially advised in underground magazines and in the lay press to 'drink plenty of fluids'. This harm limitation message was aimed at preventing hyperthermic collapse, since adequate hydration is essential for thermoregulation in situations of prolonged heavy exertion. However, the advice did not specify that a high fluid intake could be detrimental in the absence of prolonged exertion. This was subsequently rectified, particularly after the publicity attaching to the fatal cases.

The management of acute hyponatraemia remains controversial.[25] Fluid restriction to $<1$ l/day is usually sufficient. The use of intravenous mannitol or loop diuretics may be considered if there is evidence of cerebral oedema. While Arieff[16] favoured rapid correction of post-operative hyponatraemia with hypertonic saline, this did not appear necessary in most of the 15 non-fatal cases of this series, who were managed conservatively with fluid restriction only. Three patients received frusemide, and mannitol was used in two. Whether early, pre-hospital administration of hypertonic saline could have altered the outcome in the two fatal cases is speculative. In a retrospective study, Sarnaik *et al*. found the treatment of hyponatraemic seizures in children with a 3% saline solution to be safe and effective.[26] However, once respiratory arrest due to cerebral oedema has occurred, the likelihood of recovery is extremely remote.

The hyperthermic and hyponatraemic complications of MDMA use appear to be largely avoidable. Although the safest counsel is not to take the drug, the advice regarding fluid ingestion given to intending MDMA users should be carefully worded and take into account the circumstances under which 'ecstasy' is taken, i.e. level of physical exertion (dance) and environmental temperature (indoor club vs. outdoor event). 'Ecstasy' users who experience marked or unusual symptoms should seek urgent medical assessment.

## References


1. Chadwick IS, Curry PD, Linsley A, *et al*. Ecstasy, 3,4-methylenedioxymethamphetamine (MDMA), a fatality associated with coagulopathy and hyperthermia. *J Roy Soc Med* 1991; **84**:371.
2. Campkin NT, Davies UM. Another death from ecstasy. *Ann Intern Med* 1992; **111**:1039–40.
3. Henry JA, Jeffreys KJ, Dawling S. Toxicity and deaths from 3,4-methylenedioxymethamphetamine ('ecstasy'). *Lancet* 1992; **340**:384–7.
4. Screaton GR, Singer M, Cairns HS, *et al*. Hyperpyrexia and rhabdomyolysis after MDMA ('ecstasy') abuse. *Lancet* 1992; **339**:677–8.
5. Watson LD, Ferguson C, Hinds CJ, *et al*. Exertional heat stroke induced by amphetamine analogues. *Anaesthesia* 1993; **48**:542–3.
6. Mueller PD, Korey WS. Death by 'ecstasy': the serotonin syndrome? *Ann Emerg Med* 1998; **32**:377–80.
7. Holden R, Jackson MA. Near-fatal hyponatraemic coma due to vasopressin over-secretion after 'ecstasy' (3,4-MDMA). *Lancet* 1996; **347**:1052.
8. Kessel B. Hyponatraemia after ingestion of 'ecstasy'. *Br Med J* 1994; **308**:414.
9. Matthai SM, Davidson DC, Sills James, *et al*. Cerebral oedema after ingestion of MDMA ('ecstasy') and unrestricted intake of water. *Br Med J* 1996; **312**:1359.
10. Maxwell DL, Polkey MI, Henry JA. Hyponatraemia and catatonic stupor after taking 'ecstasy'. *Br Med J* 1993; **307**:1399.
11. Satchell SC, Connaughton M. Inappropriate antidiuretic hormone secretion and extreme rises in serum creatine kinase following MDMA ingestion. *Br J Hosp Med* 1994; **51**:495.
12. Parr MJA, Low HM, Botterill P. Hyponatraemia and death after 'ecstasy' ingestion. *Med J Aust* 1997; **166**:136–7.
13. Balmelli C, Kupferschmied H, Rentsch K, *et al*. Toedliches hirnoedem nach einahme von ecstasy und benzylpiperazine. *Dtsch Med Wschr* 2001; **126**:809–11.
14. O'Connor A, Cluroe A, Couch R, *et al*. Death from hyponatraemia-induced cerebral oedema associated with MDMA ('ecstasy') use. *N Z Med J* 1999; **112**:255–6.
15. Solowij N, Hall W, Lee N. Recreational MDMA use in Sydney: a profile of 'ecstasy' users and their experiences with the drug. *Br J Addict* 1992; **87**:1161–72.
16. Arieff AI. Management of hyponatraemia. *Br Med J* 1993; **307**:305–8.
17. Milroy CM, Clark JC, Forrest ARW. Pathology of deaths associated with 'ecstasy' and 'eve' misuse. *J Clin Pathol* 1996; **49**:149–53.
18. Braback L, Humble M. Young woman dies of water intoxication after taking one tablet of ecstasy. *Lakartidningen* 2001; **98**:871–9.
19. Henry JA, Fallon JK, Kicman AT, *et al*. Low dose MDMA induces vasopressin secretion. *Lancet* 1998; **351**:1784.
20. Bartter FC, Schwartz WB. The syndrome of inappropriate secretion of antidiuretic hormone. *Am J Med* 1967; **42**:790–806.
21. Spigset O, Hedenmalm K. Hyponatraemia and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) induced by psychotropic drugs. *Drug Safety* 1995; **12**:209–25.

22. Brownfield MS, Greathouse J, Lorens SA, *et al*. Neuropharmacological characterization of serotonergic stimulation of vasopressin secretion in conscious rats. *Neuroendocrinology* 1988; **47**:277–83.
23. Iovino M, Steardo L. Effects of substances influencing brain serotonergic transmission on plasma vasopressin levels in the rat. *Eur J Pharmacol* 1985; **113**:99–103.
24. Neumann F, Schenck B. *Endokrinpharmakologie*. In: Forth W, Henschler D, Rummel W, eds. *Allgemeine und spezielle Pharmakologie und Toxikologie*, 4th edn. Mannheim, Wien, Zuerich, Wissenschaftsverlag, 1987:398–447.
25. Ellis SJ. Severe hyponatraemia: complications and treatment. *Q J Med* 1995; **88**:905–9.
26. Sarnaik AP, Meert K, Hackbarth R, *et al*. Management of hyponatraemic seizures in children with hypertonic saline: a safe and effective strategy. C*rit Care Med* 1991; **19**:758–72.