*Short communication***Exaggerated vasopressin secretion and attenuated osmoregulated thirst in human survivors of hyperosmolar coma****K. McKenna¹, A.D. Morris², H. Azam², R.W. Newton², P.H. Baylis³, C.J. Thompson¹**¹ Department of Diabetes, Beaumont Hospital, Dublin 9, Republic of Ireland² Department of Medicine, Ninewells Hospital and Medical School, Dundee DD1 9SY, Scotland³ Endocrine Unit, Royal Victoria Infirmary, Newcastle-upon-Tyne NE1 4LP, England**Abstract**

Aims/hypothesis. To test the hypothesis that subnormal thirst sensation could contribute to the development of the hypernatraemia characteristic of hyperosmolar coma, we studied osmoregulation in survivors of hyperosmolar coma.

Methods. Eight survivors of hyperosmolar coma, eight control subjects with Type II (non-insulin-dependent) diabetes mellitus and eight healthy control subjects underwent water deprivation during which measurements of thirst, plasma osmolality and vasopressin were taken.

Results. Water deprivation caused greater peak plasma osmolality in the hyperosmolar coma group (301.7 ± 2.7 mmol/kg) than in Type II diabetic (294.3 ± 3.2 mmol/kg, $p < 0.01$) or control group (296.9 ± 3.0 mmol/kg, $p < 0.01$) and a greater increase in plasma vasopressin concentration (hyperosmolar

coma, 5.8 ± 1.3 pmol/l, Type II diabetes, 1.8 ± 1.3 pmol/l, $p < 0.001$, control subjects, 2.2 ± 1.8 pmol/l, $p < 0.001$). Thirst ratings were lower following water deprivation in the hyperosmolar coma group (3.5 ± 0.8 cm) than in Type II diabetes (7.7 ± 1.6 cm, $p < 0.001$) or control subjects (7.4 ± 1.3 cm, $p < 0.001$), and the hyperosmolar group patients drank less in 30 min following water deprivation (401 ± 105 ml) than Type II diabetic (856 ± 218 ml, $p < 0.001$) or control subjects (789 ± 213 ml, $p < 0.001$).

Conclusion/interpretation. Survivors of hyperosmolar coma have subnormal osmoregulated thirst and fluid intake, which might contribute to the hypernatraemic dehydration typical of the condition. [Diabetologia (1999) 42: 534–538]

Keywords Type II (non-insulin-dependent) diabetes, hyperosmolar coma, vasopressin, thirst.

Hyperosmolar non-ketotic coma (HONK) is characterised by marked hypernatraemic dehydration, which is the major cause of the associated mortality-rate of 50 % [1]. It is associated with thiazide diuretics and corticosteroid therapy [1], underlying infection [2] and residence in long-term institutions, but there is no unifying hypothesis to explain why some pa-

tients with Type II (non-insulin-dependent) diabetes mellitus develop HONK.

The key homeostatic mechanisms which prevent dehydration are the antidiuretic action of arginine vasopressin (AVP) and the sensation of thirst, which stimulates water intake [3]. Increased plasma AVP concentrations have been reported in HONK [4] but poorly controlled diabetes causes renal resistance to AVP [5], and marked glycosuria causes nephrogenic diabetes insipidus [3]. Thus, high plasma AVP concentrations fail to promote antidiuresis in HONK, and patients depend on adequate fluid intake to prevent hypertonic dehydration.

Thirst responses to dehydration are diminished in the elderly, particularly those in long-term institutions [6]. Most patients who develop HONK are el-

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Abbreviations: HONK, Hyperosmolar non-ketotic coma; AVP, arginine vasopressin.

Table 1. Patient characteristics in the three groups. Results expressed as mean (range). Local non-diabetic laboratory reference range for HbA_{1c} 3.5–5.2 %

	HONK	Type II diabetic	Control subjects
Sex (male : female)	6 : 2	7 : 1	7 : 1
Age (years)	70.6 (61–86)	70.5 (61–82)	69.8 (62–78)
HbA _{1c} (%)	7.6 ^a (5.2–10)	7.0 ^a (5.3–9.4)	4.5 (4.2–4.9)
Duration of DM (years)	4.9 (1–13)	5.8 (1–18)	N/A
Smokers	2	3	4
Other drugs	Insulin (1), Met (1), Gliclazide (2), T4 (1), ACEI (3)	Gliclazide (1), ACEI (3)	T4 (2), FeSO ₄ (1)
Mental test score	28.3/31 (26–30)	28.9/31 (28–30)	28.5/31 (27–30)

^a = $p < 0.01$ vs control subjects. DM = diabetes mellitus, Met = metformin, T4 = thyroxine, ACEI = angiotensin-converting enzyme inhibitor, FeSO₄ = ferrous sulphate

derly, with 28% admitted to hospital from nursing homes [7]. Reduced thirst sensation might therefore contribute to the marked hypernatraemia characteristic of HONK [8]. We tested this hypothesis by examining the thirst and AYP responses to water deprivation in patients with diabetes who had survived HONK.

Subjects and methods

Patients. We studied eight patients who had recovered from HONK, altered consciousness, plasma osmolality > 330 mmol/kg, blood glucose > 30 mmol/l, arterial pH > 7.30 and absent or 1+ ketonuria), eight patients with Type II diabetes and eight matched non-diabetic control subjects (Table 1). All HONK patients had made a full recovery to independent daily life and had normal cognitive function. Six patients presented with HONK at the time of diagnosis of diabetes. Patients with cardiac failure, hypertension treated with two antihypertensive drugs, renal impairment, cerebrovascular disease, or who had localising neurological signs or abnormal computerised brain tomography at the time of hyperosmolar coma, were excluded from study. Studies were done at least 3 months after discharge from the hospital following recovery from HONK.

Protocol. Antihypertensive drugs were discontinued for 1 week before the study. After an overnight fast for 12 h, during which time alcohol, caffeine and nicotine were prohibited, patients were admitted on the morning of the study at 0800 hours. Oral hypoglycaemic drugs were withheld on the day of the study. Volunteers were allowed one cup (200 ml) of water at 0800 hours. If the blood glucose was > 7 mmol/l on admission, an intravenous infusion of insulin (50 U Human Actrapid in 50 ml of 0.9% sodium chloride solution) was used to maintain blood glucose between 4 and 7 mmol/l for the duration of the study. Three subjects of the HONK group and two of the Type II diabetic group required an insulin infusion.

Once stable euglycaemia had been achieved, which took less than 1 h in all patients, volunteers underwent water deprivation for 8 h. Blood for measurement of plasma osmolality and AVP were collected at baseline and at hourly intervals and a final blood sample was taken 15 min after water deprivation. Urine was collected at 2-hourly intervals for measurement of volume and osmolality. Patients were then allowed free access to water, and the volume drunk in 30 min was recorded.

Blood samples were collected into chilled lithium heparin (10 ml) and EDTA (10 ml) tubes for subsequent measurement of plasma vasopressin and plasma renin activity, respectively. Blood pressure was measured at the times of blood sampling using an automated sphygmomanometer. Thirst was measured at 2-hourly intervals during water deprivation using a 10 cm long visual analogue scale, which we have previously shown to be an accurate [9] and reproducible [10] method. The study was approved by the local ethics committees.

Analyses. Blood glucose was measured using a glucose oxidase technique. Plasma and urine osmolality were measured by the depression of freezing point method. Plasma vasopressin was measured using a sensitive and specific radioimmunoassay [11], after magnesium silicate (Florisil) extraction from plasma (limit of detection 0.3 pmol/l, intra- and inter-assay CVs 9.7% and 15.3% respectively). Plasma renin activity was measured by a commercial antibody (Soten, Milan, Italy).

Statistical analysis. All results are expressed as means $\pm$ SD. Differences between baseline variables were calculated using unpaired Student's *t* tests. Changes in variables with time and between patient groups were analysed by ANOVA. Linear regression analysis was calculated by the method of least squares.

Results

Water deprivation was tolerated well by all patients. There were no differences in baseline blood variables, blood pressure, or thirst ratings between the groups, with the exception of plasma osmolality, which was higher in the HONK group (293.5 ± 2.8 mmol/kg) than either Type II diabetic (286.8 ± 2.0 mmol/kg, $p < 0.001$) or control subjects (287.3 ± 2.5 mmol/kg, $p < 0.001$, Table 2). Mean arterial pressure and blood glucose remained unchanged in the euglycaemic range throughout water deprivation in each group. Water deprivation caused a greater peak plasma osmolality in the HONK group (301.7 ± 2.7 mmol/kg, $p < 0.01$) than in Type II diabetic (294.3 ± 3.2 mmol/kg) or control subjects (296.9 ± 3.0 mmol/kg, Fig. 1). There was a greater rise in plasma AVP concentrations in HONK (0.9 ± 0.5 to 5.8 ± 1.3 pmol/l,

Fig. 1. Changes in plasma osmolality, thirst and plasma AVP during water deprivation in HONK ($\square$), Type II diabetes ($\circ$) and control subjects ($\bullet$). Results expressed as means, with SD bars. LD = lower limit of detection for plasma AVP (< 0.3 pmol/l)

$p < 0.001$) than in Type II diabetic (0.6 ± 0.3 to 1.8 ± 1.3 pmol/l, $p < 0.001$) or control subjects (0.5 ± 0.3 to 2.2 ± 1.8 pmol/l, $p < 0.001$). There was a similar peak urine osmolality in the three groups (HONK, 766 ± 118 mmol/kg; Type II diabetic patients, 776 ± 92 mmol/kg; control subjects, 710 mmol/kg). Water deprivation caused a lower rise in thirst ratings in HONK (0.8 ± 0.3 to 3.5 ± 0.8 cm, $p < 0.001$) than in Type II diabetic (1.0 ± 0.9 to 7.7 ± 1.6 cm, $p < 0.001$) or control subjects (1.1 ± 0.5 to 7.4 ± 1.3 cm, $p < 0.001$). HONK drank less water in 30 min at the end of water deprivation (401 ± 105 ml) than Type II diabetic (856 ± 218 ml, $p < 0.001$) or control subjects (789 ± 213 ml, $p < 0.001$). Baseline plasma renin activities were similar in the diabetic and control groups but rose significantly in the HONK group (0.9 ± 0.8 to 1.9 ± 1.2 ng $\cdot$ ml $^{-1} \cdot$ h $^{-1}$, $p = 0.009$).

Linear regression analysis was used to calculate the relation between plasma AVP and plasma osmolality for each group. The linear regressions lines were similar in Type II diabetic [$pAVP = 0.18$ (pOsm -285.0), $r = 0.79$, $p < 0.001$] and control subjects [$pAVP = 0.18$ (pOsm -284.7), $r = 0.81$, $p < 0.001$]. The slope of the regression line was steeper in the HONK group [$pAVP = 0.64$ (pOsm -292), $r = 0.84$, $p < 0.001$] than in Type II diabetic ($p < 0.001$) or control subjects ($p < 0.001$), indicating enhanced AVP release [3]. The abscissal intercept, or osmotic threshold for AVP secretion [3], was higher in the HONK group than either Type II diabetic ($p < 0.05$) or control subjects ($p < 0.05$, Fig. 2).

The characteristics of osmoregulated thirst were similar in the Type II diabetic [Thirst = 0.67 (pOsm -283.9), $r = 0.86$, $p < 0.001$] and control groups [Thirst = 0.50 (pOsm -285.5), $r = 0.83$, $p < 0.001$]. The slope of the regression line was less steep in the HONK group [Thirst = 0.25 (pOsm -289.7), $r = 0.71$, $p < 0.001$] than in Type II diabetic ($p < 0.01$) or control subjects ($p < 0.001$), confirming hypodipsia in HONK. The osmotic threshold for thirst onset was also higher in the HONK group than in Type II diabetic ($p < 0.01$) or control subjects ($p < 0.05$).

Discussion

Our data show clearly that survivors of HONK respond to water deprivation with exaggerated secretion of AVP, blunted thirst sensation and attenuated drinking during rehydration. Although increased plasma AVP concentrations have been reported during the acute phase of HONK, these abnormalities of osmoregulation have never been described previously in survivors of hyperosmolar coma.

Although patients with Type II diabetes have been reported to have elevated plasma vasopressin concentrations when hyperglycaemic [12], our data show that osmoregulation of thirst and AVP release are normal in Type II diabetes, as they are in Type I diabetes [13, 14]. Renal sensitivity to the antidiuretic effects of AVP, as shown by the urine osmolality at the end of water deprivation, was also normal in the Type II diabetic group. Thus, as osmoregulation in Type II diabetes is normal, the osmoregulatory abnormalities in survivors of HONK were not due to diabetes per se.

Only the HONK group responded to water deprivation with a rise in plasma renin activity, which implies that the HONK group was more volume depleted following water deprivation than the control groups. Hypovolaemia enhances osmotically-stimulated AVP release, thirst and drinking [15]. This may explain the exaggerated rise in plasma AVP in HONK, but the attenuated thirst and drinking responses emphasize the abnormal osmoregulatory

Fig. 2. Linear regression lines relating plasma AVP and plasma osmolality (A) and thirst and plasma osmolality (B) in HONK, Control and Type II diabetic patients

function in the HONK survivors despite relative hypovolaemia.

One explanation for the hypodipsic responses in the HONK group is that these patients have subtle cognitive impairment secondary to hyperosmolar coma. The normal mean mental test scores which were similar in all three groups, however, exclude any gross abnormalities of cognitive function. We

were additionally careful to exclude patients from the study who developed localising neurological signs during hyperosmolar coma or who had abnormal computerised tomography of the brain. Hyperosmolar coma could have induced ischaemic or metabolic damage to the osmoreceptor cells which govern thirst appreciation, but the osmoreceptors governing thirst and AVP release are in close anatomical proximity [16], such that ischaemic insults tend to cause a combination of hypodipsia and cranial diabetes insipidus [17]. As the HONK group responded to dehydration with a very different pattern of hypodipsia and exaggerated AVP release, it seems unlikely that these abnormalities are second-

ary to a cerebral insult at the time of hyperosmolar coma.

The only other context where reduced thirst and drinking responses have been reported in association with exaggerated AVP release is in elderly humans [6]. This has led to the proposed concept of an aging osmoreceptor. Although our three patient groups were well matched for age, it may be that a form of "premature ageing" of the osmoreceptor in the HONK group has produced the pattern of hypodipsia and exaggerated AVP responses similar to that described in elderly humans. This hypodipsia caused slightly higher baseline plasma osmolality in the HONK group but in addition we hypothesize that it renders them unable to correct water losses caused by insults such as glycosuric diuresis [1], thiazide diuretics [1], infection [2] or diabetes insipidus [18], and predisposes them to severe dehydration. Most cases of HONK occur in patients with restricted access to water [2]; our data suggests that even where access to water is good, the reduced drive to drink may prevent adequate hydration and cause the development of the hypernatraemia typical of the condition. We therefore hypothesize that hypodipsia is the common pathophysiological mechanism that predisposes to the development of hyperosmolar coma.

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