HHS – full or prophylactic anticoagulation?

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Abstract

Diabetes mellitus and, in particular, the hyperosmolarity associated with the hyperosmolar hyperglycaemic state (HHS) is associated with an increased risk of thrombotic events. This risk is acknowledged by the authors of the national HHS guideline who recommend prophylactic low molecular weight heparin (LMWH) for all patients with HHS for the full duration of their admission.

We present a case of fatal pulmonary embolism in a 39-year old man admitted with HHS who was treated according to local hospital trust and national guidance with prophylactic LMWH.

In the absence of evidence from randomised studies comparing prophylactic and treatment dose anti-coagulation in thrombosis prevention in HHS further research is needed to facilitate development of evidence-based guidelines.

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Introduction

It has been well documented that patients with diabetes mellitus have an increased risk of both arterial and venous thrombosis. The pathophysiological processes of hypercoagulability, venous stasis and platelet activation which underpin this increased risk[1] have been shown to be further magnified in those with both hyperosmolarity and DKA with uncomplicated diabetes.[2] Several case reports highlight the significant mortality and morbidity that can be associated with VTE and its complications in patients with hyperosmolarity including fatality from massive pulmonary embolism.[3]

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Abbreviations and acronyms

CPR	cardiopulmonary resuscitation
DKA	diabetic ketoacidosis
HHS	hyperosmolar hyperglycaemic state
HONK	hyperosmolar non-ketotic coma
LMWH	low molecular weight heparin
VTE	venous thromboembolism

Current national guidelines for the management of HHS acknowledge the increased thrombotic risk associated with HHS and recommend prophylactic LMWH for the full duration of admission.[4] As highlighted in the guideline, several regional UK hospital and previous HHS guidelines advocate the use of treatment dose LMWH, but the evidence for this is limited.

Case report

A 39-year old man had a background of Prader-Willi Syndrome (BMI 31.3kg/m^2) and type 2 diabetes mellitus diagnosed at age 17 for which he was taking no medication. He presented with a 4-day history of feeling generally unwell and lethargic. He reported no other specific symptoms although had mentioned a couple of episodes of diarrhoea on the day of admission. Of note, he had recently moved to alternative sheltered accommodation and his parents had expressed concerns about deterioration in his diet including increased snacking on junk food.

On admission he was haemodynamically stable, had a Glasgow Coma Score of 15/15 but was felt to be clinically dehydrated. He was pyrexial (temperature 40.3^{0}C) but there was nothing focal on clinical examination. A venous blood gas showed no acidosis (pH 7.37) but glucose was markedly raised (35.8 mmol/L) and confirmed by laboratory testing. Additional laboratory investigations indicated acute renal impairment and hypernatraemia (Na^+ 159mmol/L, K^+ 4.2mmol/L, urea 8.4mmol/L, creatinine 127µmol/L and eGFR 58ml/min). The calculated serum osmolality was 374 mosm/kg (278-305 mosm/kg); C-reactive protein was elevated (68mg/dL) with normal full blood count. Both urine dip and chest X-ray revealed no clear source of bacterial infection and there were no ketones present in the urine.

Diagnosis

The working admission diagnosis was HHS with infection (likely viral gastroenteritis) as a precipitant. He was commenced on the Trust's HHS protocol including cautious fluid resuscitation and appropriate potassium replacement. He was also commenced on prophylactic LMWH (Dalteparin) which was accurately dosed

according to weight (5000 units subcutaneously once daily). He improved on the above treatment regime and was started on a subcutaneous insulin regime 2 days into admission. His biochemical parameters, notably renal function, improved to baseline and all culture results including stool samples were negative for infection. He remained on prophylactic LMWH throughout admission and was deemed medically fit for discharge on day 8.

On day 10, whilst awaiting a change to his social care package, he suddenly became unwell whilst sitting out in the chair. A cardiac arrest call was made and on arrival of the resuscitation team he was unresponsive and in asystole. CPR was not successful. Post-mortem analysis revealed massive central and bilateral pulmonary emboli with evidence of residual thrombus in the deep calf veins of the left leg.

Discussion

This case highlights the increased and potentially fatal thrombosis risk associated with hyperosmolarity and HHS, thereby highlighting the difficulties in producing guidelines for prophylactic versus treatment dose anti-coagulation in the absence of a strong evidence base.

Development of guidelines for the prevention of thrombosis in patients with HHS is complicated by a number of clinical obstacles. The typical patient presenting with HHS is elderly and often has multiple medical co-morbidities. When completing VTE risk assessments, clinicians must balance the risk of thrombosis against the risk of major bleeding (notably gastrointestinal or intracranial) in these patients. Ageing is one of the strongest risk factors for venous thrombotic disease, resulting in a high incidence of VTE in the elderly population.[5] Furthermore, the incidence of VTE in those with HHS - when adjusted for age, race, gender and recent hospitalisation - was found to be higher than that of patients with uncomplicated diabetes and DKA, suggesting that the increased risk in patients with HHS can be attributed to the more profound hyperosmolarity and hyperglycaemia associated with HHS.[2] Indeed three months after a venous thromboembolic event, 3.7% of patients ≥80 years died of a pulmonary embolism compared to 1.1% of patients <80 years.[6]

Given this higher mortality burden of venous thrombosis in the elderly, one could argue that full dose anti-coagulation is more appropriate in the face of the combined effects of ageing and hyperosmolarity. In demonstrating that the VTE risk in those with HHS persists beyond discharge from hospital, Keenan and colleagues suggest it may also be necessary to consider extended VTE prophylaxis (e.g. 3 months' duration) for higher risk patients.[7]

In contrast, consideration must be given to the risk of major bleeding in elderly patients prescribed full dose anti-coagulation and whether this risk outweighs the benefit of full dose LMWH in patients with HHS. For LMWH, the rates of major bleeding in the adult population range from 0–3% and from 0–0.8% for fatal bleeding. There is a paucity of trial data directly comparing the effects of different doses of heparin on bleeding risk in patients with established VTE, but *in vitro* studies suggest that bleeding is more likely to occur when coagulation is excessively prolonged.[8] In addition to LMWH dosing, there is good evidence that patient factors can considerably impact on the risk of heparin-induced bleeding. Several studies have reported a higher risk of bleeding in the elderly (>75 years)[9] and, when combined with other co-morbid factors such as renal impairment and concomitant anti-platelet therapy, this risk is likely to be magnified further. One study in uncomplicated diabetes, but not HHS, suggested that the risk of VTE is higher in younger than older patients;[5] it may not be unreasonable to consider full dose LMWH in patients less than 75 years of age for whom the bleeding risk is lower.

Key messages

- HHS increases risk of VTE
- Risk remains beyond resolution of HHS
- Post-HHS, consider prophylactic anticoagulants
- Consider therapeutic anticoagulation in HHS unless contraindications

Evidence to support action

A second major issue for researchers in this field is the paucity of evidence to support either prophylactic or treatment dose anti-coagulation in patients with HHS. The majority of evidence suggesting an increased risk of arterial and venous thrombosis in those with HHS dates back to case studies from the 1970s.[10] No randomised prospective studies comparing the risk-benefit profile of prophylactic versus treatment dose LMWH exist. Additionally, any new studies would in all likelihood be significantly underpowered in guiding best practice. Whilst limited by causal inference, evidence from more feasible case control studies in patients suffering a major in-hospital thrombotic event may nevertheless be useful.

This case supports the evidence of an increased risk of thromboembolic events in patients with hyperosmolarity and HHS. In view of fatal pulmonary embolism in a patient on accurately dosed prophylactic LMWH, it also calls into question whether treatment dose anti-coagulation would be more appropriate in patients with HHS and no concurrent bleeding risk. It has been suggested that a pre-emptive venous doppler of the lower limbs in patients with HHS and a BMI >30kg/m^2 may be helpful, however there is no evidence in the literature at present to support this practice. We appreciate this is a simple case report and further research is needed but may be difficult to undertake. Evidence-based medicine has its limits and, in the absence of such evidence, should we be assessing our patients on an individual basis and making full anti-coagulation the default unless there are high risks of bleeding?

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