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SHORT REVIEW

Management of Hyperglycaemic Emergencies in the Tropics

F. O. Anumah

Department of Medicine, Ahmadu Bello University Teaching Hospital, Zaria, Nigeria
Reprint requests to: Dr. F. O. Anumah, Department of Medicine, Ahmadu Bello University Teaching Hospital, Shika, Zaria, Nigeria

Abstract
Diabetic ketoacidosis (DKA) and hyperglycaemic hyperosmolar state are the two most serious acute metabolic complications of diabetes even if managed properly. These disorders can occur in both types 1and 2 diabetes, and remain an important cause of morbidity and mortality in diabetic populations especially, in the developing countries. Intravenous insulin and fluid replacement are the mainstays of therapy, with careful monitoring of potassium levels. Bicarbonate therapy is rarely needed. Infection, omission of insulin, and other precipitating factors should be treated. This review is intended to discuss some of the advances in the management of hyperglycaemic emergencies and also to highlight some of the peculiarities of the management of hyperglycaemic emergency in our setting if we are going to be able to improve outcome significantly.

Key words*:* Hyperglycaemic emergencies, diabetic ketoacidosis, hyperglycaemic hyperosmolar, fluid therapy, insulin therapy

Résumé
Ketoacidose diabétique (DKA) et l'état d'hyperglycémique hyperosmolaire sont les deux complications métaboliques aigues les plus sérieuses des diabètes même si on les avait correctement soignées. Ces troubles peuvent arriver dans le type 1 et type 2 les deux diabètes et demeure une cause importante de la morbidité et mortalité dans les populations diabétiques en particulier, dans les pays en voie de développement. Insuline intraveneuse et la remise en place du liquide sont les bases de la thérapie, avec une surveillance soigneuse du niveau du potassium. La thérapie bicarbonate est rarement exigée. L'infection l'omission de l'insuline, et des autres facteurs precipitants devraient être traités. L'objet de cette étude est d'étudier quelques uns de ces progrès dans la prise en charge des urgences hyperglycémique et aussi de souligner quelques singularités de la prise en charge d'hyperglycémique d'urgence dans notre milieu si nous aurions à mésure d'améliorer le résultat d'une manière remarquable.

Mots-cles: Urgences hyperglycémique, ketoacidose diabétique, l'état d'hyperglycémique hyperosmolaire, thérapie de liquide, thérapie de l'insuline

Introduction

Hyperglycaemic emergencies are the most common endocrinopathy requiring intensive care. Diabetic ketoacidosis (DKA) and hyperglycaemic hyperosmolar state (HHS) are two extremes in the spectrum of diabetic decompensation. They remain the most serious acute metabolic complications of diabetes mellitus and are still associated with excess mortality. The degree of metabolic derangement in this condition is severe enough to warrant emergency hospitalization, immediate correction with intravenous fluids and insulin therapy to improve the patient's chance of survival. [1-3]

DKA comprises of metabolic acidosis (pH <7.3), plasma bicarbonate <15mmol/l, plasma glucose >14mmol/l, and urine ketostix reaction ++ or plasma ketostix >+. [4, 5] HHS replaces the older term, "hyperglycaemic hyperosmolar non-ketotic state". There is severe hyperglycaemia >30mmol/l, hyperosomlality >340mOsm/kg, with minimal ketones in serum or urine. [6, 7] Studies have shown that mixed forms of DKA and HHS exist rather than either condition alone, suggesting the two are different parts of the same spectrum. [8, 9]

The annual incidence of DKA among subjects

with type 1 diabetes is 1-5% in the western countries and mortality rates are less than 5% in experienced centers. [6,10,11] However the mortality rate of patients with HHS still remains high at about 15%. [3, 7, 12]. The prognosis of both conditions is substantially worsened at the extremes of age. In the developing countries, mortality from hyperglycaemic emergencies is certainly higher 20-50% due to paucity of facilities, shortage of insulin supplies and qualified healthcare givers with specialist interest in diabetes and its complications. [13-15]

Pathogenesis

The basic underlying mechanism for DKA and HHS is a reduction in the net effective action of circulating insulin coupled with a concomitant elevation of counter regulatory hormones, such as glucagon, catecholamines, cortisol, and growth hormone. These hormonal alterations lead to hepatic and renal production and impaired glucose utilization in peripheral tissues, which result in hyperglycaemia and parallel changes in osmolality of the extracellular space. [16] The combination of insulin deficiency and increased counter regulatory hormones also lead to release of free fatty acids into the circulation from adipose tissue (lipolysis) and to unrestrained hepatic fatty acid oxidation to ketone bodies (β-hydroxybutyrate and acetoacetate), with resultant ketonaemia and metabolic acidosis. In HHS however, the plasma insulin concentration may be inadequate to facilitate glucose utilization but adequate to prevent lipolysis and subsequent ketogenesis. [17] Both DKA and HHS are associated with glycosuria, leading to osmotic diuresis with loss of water, sodium, potassium, and other electrolytes. [18]

Precipitating factors

A number of deaths due to hyperglycaemic emergencies (HE) arise from failure to recognize and treat the underlying precipitating factors, rather than the metabolic disturbances especially in the elderly. Infection remains the most important precipitating factor in the development of DKA and HHS. In 20-25% of cases, infections are the first manifestations of previously undiagnosed diabetes mellitus. [19] Infection, known or undiagnosed especially of the urinary tract, respiratory tract and skin is the most common precipitating factor causing more than 50% of identified causes. [4-7] Zouvanis et al in 1997 reported in Johannesburg Africans that infection was the leading precipitating factor for both DKA and HHS [20] while Umpierrez et al in the same year, in Atlanta also reported infections in 34% of patients presenting with diabetic emergencies. [21]

Omissions or inadequate doses of insulin are frequent precipitating factors, particularly for DKA. [18] Watchel et al found that omission of insulin was the most common cause identified with the onset of DKA in those with type 1 diabetes. [8] Other precipitating factors, especially for HHS, are silent myocardial infarction, cerebrovascular accident, mesenteric ischaemia, acute pancreatitis and use of medications such as steroids, thiazide diuretics, calcium-channel blockers, propranolol and phenytoin. [22] In 2-10% of cases of DKA, no obvious precipitating factor can be identified. [21]

The clinical implication of precipitating factors is that all of them trigger release of one or more of the catabolic hormones such as glucagon, cortisol, catecholamines and growth hormones. These worsen the relative insulin deficiency that exists. Often patients mistakenly take less insulin because of decreased food intakes, thus magnifying the effects of the catabolic hormones. [2, 3, 18-22]

Diagnosis of Hyperglycaemic Emergencies

The initial diagnosis of hyperglycaemic emergency can usually be made rapidly at the bedside by a combination of history, physical examination and simple diagnostic tests. However, a high index of suspicion is necessary in elderly patients and in non-ketotic cases that may present with nonspecific symptoms and signs.

DKA usually occurs in younger, lean patients with type I diabetes and develops within a day or so. When DKA occurs in individuals with type 2 diabetes, the precipitating illnesses are usually severe. Common symptoms that may be premonitory include dry mouth, polyuria, polydipsia, polyphagia, weight loss and weakness. These may blend rapidly into the symptoms related to ketoacidosis namely nausea and vomiting, laboured and increasingly deep rapid respiration (Kussmaul Kien respiration), prostration, drowsiness, abdominal pain, muscle cramps and altered state of consciousness. [2, 21-23] HHS occurs more commonly in older, obese patients with type 2 diabetes and can take days to weeks to fully develop.

Physical examination will usually reveal profound dehydration, which could be very severe in HHS, evidenced by tachycardia, hypotension (especially postural hypotension), dry skin and dry mucous membranes. In DKA, compensatory hyperventilation (Kussmaul breathing) is present. The breath may have the odour of nail vanish remover, the result of acetone produced by the decarboxylation of acetoacetate in the liver. Other findings are hypothermia and varying degrees of altered state of consciousness. Coma is reported to be present in <20%, and is associated with mortality rate of 15% to 20%. [4-11, 17] Mental obtundation and coma are more frequent in HHS because of hyperosmolarity, and focal neurological signs and seizures have been described. [16, 24]

Bedside biochemistry will confirm plasma glucose between 300 – 1000 mg/d1 and urine ketones ++ or more in DKA, patients with HHS have blood glucose concentration between 450 - 2000mg/d1. [4, 16,17] A more detailed biochemical investigation may show hypernatremia, elevated blood urea with calculated plasma osmolality, usually greater than 330mosm/1 in HHS patients. [7, 16] Glucose is the main osmole responsible for the hyperosmolar syndrome. The increased serum osmolality can be calculated as

follows: (2 serum Na) + serum glucose mosmol/l. [17, 24] In lactic acidosis, blood glucose concentration is usually normal or just slightly elevated, with markedly reduced bicarbonate level. [16]

Recent studies have found that it is not uncommon to find mixed cases of diabetic acidosis and hyperosmolality. These are patients with a bicarbonate level <15mmo1/1, pH of 7.3 or less, and increased serum osmolality. [8, 25] The second group of patients identified are those with hyperglycaemia, normo-osmolality with no significant acidosis. [7]

Management of Hyperglycaaemic Emergencies

Principles of treatment

The best form of treatment prevention. Adequate education of patient, the general practitioner and hospital physical could prevent cases or at least ensure that they were referred while still mild. [2, 4-7] Once the diagnosis is established, the aim is the smooth restoration to normal, of the disordered clinical and biochemical states. In addition, treatment of the precipitating factor is very necessary to reduce morbidity and mortality. The therapeutic goals are to improve circulatory volume and tissue perfusion, decrease serum glucose level, clear the serum and urine of ketoacids at a steady rate and correct the electrolyte imbalance.

Fluid therapy

Disturbances in hydration and electrolyte balance are of great importance in hyperglycaemic emergencies and required prompt and aggressive therapy. The first priority therefore is fluid replacement. Fluid replacement alone will lower blood glucose. Tracer studies have found that during the first four hours of therapy for DKA, up to 80% of the decline in glucose concentration may be caused by rehydration. [23, 26] There is increase in renal blood flow with resultant glycosuria and osmotic diuresis, along with decrease in the levels of the counter regulatory hormones and blood ketones bodies concentration. These make the response to physiologic does of insulin more predictable. [2, 4, 26, 27]

An average adult patient in DKA will have a deficient of 5-7 litres of water, 500-700 mmol of sodium, 200-350mmol of potassium, 350-500mmol of phosphate, and 200-350mmol of chloride. [6,28]Intravenous fluid should aim to correct these water and electrolyte deficits over the first 24-48hpurs. In most adults with moderate or severe DKA there is a deficit of approximately 5 litres, plasma osmolality > 330mosm/kg are associated with large fluid deficits and plasma osmolality can be correlated with mental status.

Isotonic saline is generally accepted as the most appropriate initial replacement fluid. [23, 26, 27] This is because the rise in plasma sodium is gradual, thus balancing the fall in blood glucose osmoles and therefore plasma osmolality falls only gradually. Infusion of 1-1.5 litres (5-20ml/kg/hour) of 0.9% saline in the first hour is appropriate in most cases, subsequently 250-1000ml/hour for the next four hours (4-14ml/kg/hour). If corrected sodium concentrations are high (> 155mml/l) after the initial 1-2 litres of normal saline, 0.45% saline should be considered. However it is recommended that no more than one litre should be given over eight hours. [6,16,29] Once plasma glucose falls to <14mmol/l then 5% dextrose (10% dextrose if less fluid/more insulin required) should be started at 100-125ml/hour and 0.9% saline continued at a slower rate to complete rehydration and electrolyte replacement.

In HHS, there is an average deficit of 10.5 litres of water, 350-900mmol of sodium, 350-1050mmol of potassium, 210-490mmol of chloride, 70-150mmol of phosphate and 70-140mmol of magnesium. [17, 28] Presently, fluid replacement in HHS is guided by the plasma sodium concentration. Initially 0.9% saline is given at the rate of 5-20ml kg/hour in the first hour, subsequently 500-1000ml/hour for 4 – 6 hours depending on the degree of dehydration then it is slowed as necessary. [3, 27] However, it is recommended that effective serum osmolality should not change by > 3mosm/kg/hour. [4]

Insulin therapy

Hyperglycaemic emergency is a life threatening complication of diabetes resulting from severe insulin deficiency. The aim of insulin administration is to restore normal homeostasis. Insulin inhibits lipolysis, ketogenesis, and gluconeogenesis. In addition, improves extrahepatic utilization of glucose and ketone bodies, and restores normal transmembrane electrolyte balance. [2, 4,17,18,21]

In the past, many different regimens of insulin administration were advocated in the management of HE. Phear in 1963 was reported to have stated that the more severe the acidosis, the more insulin is needed, while some other authors were guided by the blood glucose levels. [30] Until mid 1970s, insulin was generally given intravenously, intramuscularly and/or subcutaneously as bolus injections. [31] But the technique of intravenous infusion of insulin is said to have been first described by Rossier et al in 1960, with an initial dos of 100 units per hour. Infusion of low dose insulin in the management of HE was reported to have been described later by Sonksen et al in 1972 who used amounts between 1.5 to 12 units per hour. [30]

Low dose insulin regimen is now widely accepted in preference of large dose of insulin. [32, 33] Alberti et al [34] found no advantages for large doses of insulin, which carry the risks of hypoglycaemia, hypokalaemia and hyperlactaemia. He used small hourly doses of insulin, which were given intramuscularly to achieve adequate blood concentrations and found this regimen effective in the management of patients with HE.

Presently, the continuous insulin infusion and the bolus intramuscular or intravenous injections of low dose insulin are used in the management of HE. [16,29,32-34] The constant intravenous infusion of insulin is the gold standard and has advantages over the intermittent regimen; these include immediate onset

of action, maintenance of a steady blood concentration in the effective range and avoidance of the vagaries of absorption from tissue depots. In addition, it overcomes the problem of the short half – life of intravenous insulin given in boluses and can be altered or ended almost instantaneously. [30, 32, 34] It is usually started as a continuous infusion of six units per hour of fast acting insulin. The aim is to bring plasma glucose concentration down by 3-5mmol/l/hour. If plasma glucose does not fall by 3mmol/l in the first hour, and hydration status appropriately treated, then the dose of insulin may be doubled. When plasma glucose levels are <14mmol/l the rate of infusion may be decreased to 3units/hour and intravenous dextrose started. Insulin and glucose infusions should be adjusted to maintain plasma glucose between 8-12mmol/l until the acidosis has resolved when regular insulin therapy may start if the patient is able to eat and drink. [18, 22, 28, 29]

The full effect to intramuscular injection of insulin is not apparent until the insulin is completely absorbed. The time required for absorption following intramuscular injection is variable, particularly when the volume status of the patient is rapidly changing, and thus the risk for hypoglycaemia is not easily predictable in any given patient. [30, 32, 34]

Although the intermittent intramuscular route of insulin administration has the disadvantages mentioned above, it is better suited for developing countries like ours, where medical and biochemical services are grossly inadequate. The American Diabetes Association position statement suggests that 0.4 units of fast acting insulin/kg body weight are given, half as an intravenous bolus, half subcutaneously or intramuscularly as a statim dose, and then 0.1 units/kg are given intramuscularly each hour until plasma glucose is less than 14mmol/l. At this stage 5-10 units of fast acting insulin are administered every two hours, with concomitant dextrose infusion, until normal insulin can be started. [29] The advantages are in the fact that it does not require any special instruments and it is simple to follow. Also complex apparatus and complicated calculations of insulin doses are not necessary, timing of insulin injections are straight forward, the rate of fall in plasma glucose is predictable and blind injections may be given for 2-3 hours before blood sugars are obtained.

Potassium therapy

The treatment of DKA and HHS with rehydration and insulin is typically associated with a rapid decline in the plasma potassium concentration, particularly during the first few hours of therapy. [21, 28] This rapid decrease is due to several factors, the most important being the insulin mediated re-entry of potassium into the intracellular compartment. Other factors are correction of acidosis, increased urinary loss, extracellular fluid volume expansion, and secondary hyperaldosteronism. It is recommended that potassium replacement should commence as soon as hyperkalaemia is excluded. If potassium levels are between 3.3-3.5mmol/l then give 20-30mmol of potassium added to each litre of infused fluid in early stages of treatment. Aim is to keep potassium > 4mmol/l. if the serum potassium level is less than 3.3 mmol/L, then the patient is at risk of cardiac arrhythmia and muscle weakness with institution of insulin therapy. This should be withheld until plasma potassium has been corrected by infusion of potassium at 40mmol/hour. [6, 16, 17] Our practice is to start potassium replacement between the second and third hour after commencement of fluid therapy when usually satisfactory urine output would have been achieved in the patients.

Bicarbonate therapy

The use of bicarbonate in the treatment of DKA remains controversial. [21, 35] Bicarbonate replacements are recommended, only if the pH level is below 6.9 or serum bicarbonate level is lower than 10.mmol/L. [4, 9,18,21,35] This is because bicarbonate administration is associated with risks such as hypokalaemia, induction of paradoxical central nervous system acidosis, worsening of intracellular acidosis owing to increased carbon dioxide production and prolongation of ketoanion metabolism. If indicated, 100mmol of sodium bicarbonate infused with 20mmol potassium chloride over 30minutes is the recommended dose, with serial monitoring of calcium and potassium. In our practice, bicarbonate level usually normalizes with rehydration thus avoiding the need for replacement. Could it be that our patients are not presenting with very severe acidosis?

Phosphate

Although the phosphate level frequently is low in patients with DKA, studies have shown that routine phosphate replacement does not improve outcome in DKA, thus if the patient's serum phosphate level is below normal, one third of the potassium may be given in the form of potassium phosphate, provided the level of serum calcium is monitored closely. [22, 23]

Sodium

The whole body sodium deficits typically are 7-10mmol/l. serum sodium is falsely lowered by 1.6mmol for every 100mg/l increase in blood glucose. Hyponatraemia needs to be corrected only when the sodium is still low after adjusting for this effect. [23]

Complications of Treatment of Hyperglycaemic Emergencies

The most common complications of DKA and HHS include hypoglycaemia due to overzealous treatment with insulin, hypokaelemia due to insulin administration and treatment of acidosis with bicarbonate, and hyperglycaemia due to interruption/discontinuation of intravenous insulin therapy after recovery without subsequent coverage with subcutaneous insulin.

Commonly, patients recovering from DKA develop hyperchloraemia caused by the use of excessive saline for fluid and electrolyte

replacement and metabolic acidosis as chloride from the fluids replaces ketoanions lost as sodium and potassium salts during osmotic diuresis. These biochemical abnormalities are transient except in cases of acute renal failure. [4, 6,9,29]

Cerebral oedema

This is rare but frequently fatal complication of DKA, occurring in 0.7-1% of children with DKA, can also occur in young people in their twenties. [36] Fatal cases have been reported with HHS. Clinically cerebral oedema is characterized by deterioration in the level of consciousness, with lethargy, decrease in arousal and headache. Neurological deterioration may be rapid, with seizures, incontinence, papillary changes, bradycardia and respiratory arrest. Once the clinical symptoms other than lethargy and behavioral changes occur, mortality is high (>70%) with only 7-14% of patients recovering without permanent morbidity.

Although the mechanism of cerebral oedema is not known, it likely results from osmotically driven movement of water into the central nervous system when plasma osmolality declines too rapidly with the treatment of DKA and HHS. Prevention in high risk patients are gradual replacement of sodium and water deficits in patients who are hyperosmolar (maximal reduction in osmolality 3mOsm/kg, and the addition of dextrose to the hydration solution once blood glucose reaches <14mmol. [4, 36]

Adult respiratory distress syndrome

Hypoxaemia and rarely noncardiogenic pulmonary oedema may occur at presentation of DKA or few hours after the onset of treatment. Hypoxaemia is attributable to a reduction in colloid osmotic pressure that results in increased lung water content and decreased lung compliance. Patients who have a widened alveolo- arteriolar oxygen gradient on initial blood gas measurement or with pulmonary rales on physical examination appear to be at higher risk. [2, 37, 38]

Vascular thrombosis

Many features of DKA and HHS predispose the patient to thrombosis: dehydration and contracted vascular volume, low cardiac output, increased blood viscosity and the frequent presence of underlying atherosclerosis. In addition a number of haemostatic changes favour thrombosis and this complication more likely when osmolality is very high. Low molecular- weight heparin should be considered for prophylaxis in patients at high risk of thrombosis. [39]

Conclusion

Many cases of hyperglycaemic emergencies are preventable. A major part of the challenge is to ensure proper management of the African diabetic to prevent complications. This will include: Improved education and effective communication with those with diabetes in order to prevent admissions with DKA and HHS. Educating the healthcare givers including nurses, general practitioners and physicians with adequate diagnostic and therapeutic knowledge of the management of diabetes and hyperglycaemic emergencies.

The observation that stopping insulin for economic reasons is a common precipitant in the tropics is disturbing and underscores the need for the health care delivery systems to address this problem. These measures should reduce morbidity and the unacceptably high mortality significantly in the developing countries.

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