Diabetic Ketoacidosis

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Introduction

The diabetic-related comas listed in order of their probable frequency are;

1) Hypoglycaemic coma.
2) Diabetic Ketoacidosis
3) Hyperglycaemic Hyperosmolar non-ketotic coma.
4) Lactic acidosis.

Whilst in general, diabetic ketoacidosis occurs in patients with the insulin-dependent form of the disease, and the syndrome of hyperosmolar non-ketotic coma is commoner in the elderly diabetic, it is not uncommon to meet a combination of these disorders in a variable degree of severity in the same patient.

This discussion, taken from studies and accounts by leading investigators including Foster and McGarry in the U.S.A. and Alberti, Johnston and Owens in England (see chart) wll concentrate on diabetic ketoacidosis. Although as stated above a combination of diabetic comas can occur, in general, Insulin Dependent Diabetes Mellitus (I.D.D.M) patients ordinarily do not progress to marked hyperosmolar coma, but hyperosmolar non-ketotic coma can develop in a patient with a Type I diabetes.

Diabetic Ketoacidosis is a common illness among diabetics, especially Type I patients, in whom it still has a mortality rate as seriously high as 6-10%. Death may be due to:

(a) Derangements that are directly attributable to ketoacidosis.
(b) Complications associated with the illness itself.
(c) Abnormalities induced by the treatment.

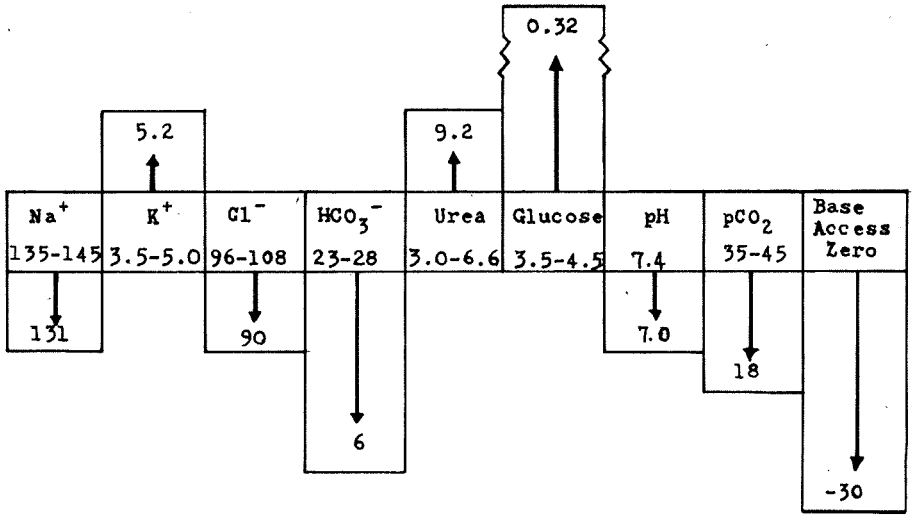
Since a substantial amount of deaths is probably preventable if appropriate treatment is applied, sound education on this disorder is crucial.

Metabolic Derangements

Among the many effects of uncontrolled diabetes, two interdependent processes are of primary importance:

(i) Alterations in glucose production and disposal, which cause osmotic diuresis, volume depletion and dehydration;

(ii) Accellerated ketogenesis which causes metabolic acidosis.



Plasma (Serum) osmolality averages 320 (normal range 280 - 300).

Potassium

Total body stores of potassium are depleted in D.K.A. patients on admission. Potassium concentrations in plasma however tend to be high initially, decreasing once therapy is started because of extended losses and potassium returns to cells as acidosis is reversed and normal glucose metabolism is restored. The degree and rate of replacement should be guided by direct measurements of the cation in plasma and E.C.G. monitoring.

Bicarbonate

Administration of bicarbonate is the controversial practice. It seems wise to reserve bicarbonate only for very severe acidosis i.e. when the pH is less than 7- and stop administration when the pH reaches 7.2, in order to avoid rebound metabolic alkalosis as ketone bodies are metabolised.

Phosphate

Phosphate depletion in D.K.A. is often severe. As is the case with potassium, initial plasma values may be low or high because of trans-membrane shifts in distribution of the ion, and hypophosphataemia can easily occur once treatment has begun. Although some studies seem to indicate that phosphate infusion has no effect on the course of diabetic ketoacidosis, nevertheless if pretreatment phosphate levels are low, it may appear reasonable to consider administering potassium phosphate (when potassium is also needed) to avoid extreme hypophosphataemia.

Insulin

Insulin is required for the treatment of D.K.A.. It lowers the plasma glucagon level, counteracts the effect of glucagon on the liver, inhibits the flow of fatty and amino acids from the periphery, and enhances glucose use in target tissues. In recent years, investigators have been concerned primarily about the amount of insulin that should be given, with a general trend moving from the high dose to the low dose regimens.

Although most patients are found to respond adequately to low-dose regimens, some patients with D.K.A. require large amounts of insulin to reverse the illness-this being thought to be due to insulin resistance operating in D.K.A.

-i- The rarer type, which could be called "prereceptor-receptor resistance" this being caused by antibodies to insulin, high concentrations of stress hormones, intrinsic abnormalities of the insulin receptor, or a combination of these factors. It can only be overcome by achieving high concentrations of insulin in plasma (and interstitial fluid).

-ii- The commoner type of insulin resistance in D.K.A. is probably caused by defects in intracellular metabolism that are beyond the receptor level-"post-receptor-binding resistance" - a deficiency in glucose transport units being suggested as the cause. Low doses usually suffice in these cases, where the resistance is not generally overcome by increasing the concentration of insulin in plasma.

Regarding insulin therapy some salient points should be made:

(I) Volume depletion and vascular collapse may impair the absorption of insulin injected intramuscularly, and therby delay the response in some patients-in such cases i.v. insulin is recommended.

(2) If the low-dose schedule is to be followed, at least 6-10 units per hour (for adults) should be given; and if there is no fall in the level of ketones or increase in pH within 3-4 hours after start of therapy, large doses of insulin should be given without delay.

(3) Because plasma glucose levels often fall before the reversal of ketogenesis, glucose should be infused as necessary during treatment to avoid hypoglycaemia, but insulin should **not** be slowed or stopped when the acidosis or ketosis are still present simply because the glucose level is falling.

Complications

Shock

Vascular collapse in D.K.A. is ordinarily due to a combination of profound volume depletion and acidosis. It usually responds to treatment with fluids and bicarbonate. If the response is not satisfactory, gram-negative sepsis or silent myocardial infarction may be present. If shock persists, blood should be given.

Infection

Infection is a common accompaniment of decompensated diabetes hence a careful search for this should be made in every patient particularly if fever is present. Pneumonia, pyelonephritis and septicaemia are the commonest problems. A rare infection, peculiarly associated with D.K.A. is mucormycosis, and death my follow in 10 days if treatment with amphotericin B is delayed.l.

Vascular Thrombosis

Many features of D.K.A. (including dehydration, contracted intravascular volume, low cardiac output, increased blood viscosity, underlying atherosclerosis and other haemostatic changes) favour thrombosis. Although this may occur in any muscular artery, cerebral vessels seem particularly susceptible especially when plasma osmolality is high.

Cerebral Oedema.

This is a rare but generally fatal complication of D.K.A. occuring usually in children, and developing several hours after the start of therapy. The cause is unknown, and various factors including osmotic disequilibrium, insulin, hypoxia and a rapid decrease in plasma oncotic pressure have been incriminated. Mannitol appears to be the only effective treatment, although dexamethasone is usually administered simultaneously. Passive hyperventilation seems a reasonable adjunct to therapy. Even in the uncommon cases where the patient survives, permanent brain damage may result.

Diabetic ketoacidosis is generally initiated by decreased insulin therapy or by 'stress' that renders the normal insulin inadequate. In either situation glucagon concentrations rise, and the ratio of glucagon to insulin increases, usually with concomitant increases in the levels of adrenalin, noradrenaline, cortisol, and growth hormone. In the periphery a catabolic state is produced, with mobilization of substrates that are used by the liver for synthesis of glucose and ketone bodies.

In the liver the enzymes that carry out these processes are simultaneously activated. Cyclic AMP activates glycogen phosporylase, which stimulates the breakdown of glycogen; at the same time glycogen synthesis is inhibited. Most other hepatic events are related to the glycogen-induced fall in the level of fructose 2,6-diphosphate which increases the liver capacity for gluconeogenesis through disinhibition of fructose biphosphate and which blocks glycolysis with the subsequent impairment in the formation of Malonyl-CoA. The fall in the level of Malonyl-CoA in turn activates the oxidation of fatty acids which leads to increased production of acetoacetic and beta-hydroxybutyric acids. The end result is hyperglycaemia and ketoacidosis.

Clinical Manifestations

Presentation

Classically, patients in Diabetic Ketoacidosis (D.K.A.) present with vomiting, thirst, polyuria, weakness, altered sensorium and air hunger. Abdominal pain and other symptoms are less frequent.

The commoner precipitating factors are cessation of insulin intake, infection and/or emotional distress, but in many cases no evident cause can be detected.

On physical examination, patients tend to have tachycardia, but blood pressure is usually normal. Although an elevated temperature strongly suggests infection, the latter may still be present even if the temperature is normal. Kussmaul's respiration is frequently present, however the ventilatory rate may fall with seven acidosis, and thus respiration may paradoxically increase after treatment is initiated.

Regarding the term 'Diabetic coma' only about 10% of the cases are actually unconscious and as many as 20% have no discernable clouding of consciousness beteen these extremes, the spectrum ranges from drowsiness to precoma.

Although there are no specific findings in D.K.A., concurrent illnesses may leave their characteristic signs.

Laboratory Findings.

Although the average concentration of plasma glucose in D.K.A. is about 500 mg/dl., levels range from near normal to the extreme concentrations that are characteristic of hyperosmolar coma.

Volume depletion (the severity of which probably determines the degree of hyperglycaemia) is usually moderate, with plasma levels of urea nitrogen in the range of 25 to 30 mg/dl.

Metabolic acidosis is due primarily to the accumulation of acetoacetic and beta-hydroxybutyric acids in the plasma, and plasma acetone (derived from non-enzymatic deoxycarboxylation of acetoacetate). Levels are very frequently high on admission-in the range of 5mMol.

The plasma level of sodium tends to be low despite a modest increase in osmolar concentration, because glucose, in the absence of insulin, is osmotically active across the cell membrane. Avery low sodium level (Less than 120 mMol./L) is usually due to severe hypertriglyceridaemia, which can be recognized from visual inspection of the plasma (presence of fat) and for ophthalmoscopic examination (lipaemia Rentinalis).

The initial potassium concentration in plasma tends to get high because of metabolic anicdoisis, but may be normal or even low depending on the duration of illness and previous nutrition.

The only important abnormality in the rountine blood could and in the picture is leukocytosis.

Treatment

The management of this disorder consists basically of:

(a) Establishing the diagnosis.
(b) Assessing fluids and electrolytes.
(c) Administering Insulin.
(d) Keeping a fluid chart.

Fluids

Both depletion of extracellular fluid volume and dehydration occur because of the osmotic diruesis induced by glucose, and both electrolytes and free water are needed in the therapy. Most investigators favour 0.9% saline, reserving half-strength (0.45%) saline if hypernatraemia supervenes; some authorities consider lactated Ringer's solution in cases of hyperchloraemic acidosis. The rates of administration of replacement fluids depends on the degree of dehyration, body weight, urine output and clinical response.

The fluids are meant for the repair of the circulation and renal function; they also lower the plasma glucose level (even in the absence of insulin), by enchancing glucose excretion via increased urine flow and by decreasing levels of counter regulatory hormones that stimulate hyperglycaemia.

In contrast to glucose levels, concentrations of acetoacetate and beta-hydroxybutyrate do not fall when fluids are given without insulin.

The free water deficit needs to be reversed only after extracellular fluid volume is restored; solutions containing glucose (e.g. 5% glucose) or 0.45% saline being appropriate vehicles.