



The Treatment of Diabetic Acidosis

THADDEUS S. DANOWSKI

Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

The patient with diabetes mellitus who becomes unconscious presents a problem in differential diagnosis. We now recognize six possible causes of coma in the diabetic patient. These include the usual diabetic keto-acidosis, and five possible non-ketotic causes:

I. Keto-acidosis

II. Non-ketotic causes of coma

- A. Unconsciousness unrelated to diabetes, e.g. barbiturate intoxication, "stroke," uremia
- B. Hypoglycemia
- C. Lactic acidosis
- D. Hyponatremia
- E. Hyperglycemia

Of the non-ketotic types, the first may be considered to be a coincidence of unrelated events in a diabetic patient, i.e., diabetes plays no direct and immediate causal role in the coma.

Hypoglycemic coma most commonly follows excessive dosage of insulin, but may also be caused by the oral hypoglycemic agents, especially in patients with impaired renal function who do not excrete the sulfonylureas well. Hypoglycemia four to five hours after eating also may be a manifestation of early, untreated diabetes, with delayed secretion of insulin by the pancreas.

Lactic acidosis results from tissue hypoxia, with inability to convert lactate to pyruvate, the accumulation of lactic acid resulting in acidosis. This is most often seen in patients who have been in prolonged shock, as from slow bleeding or from myocardial infarction. Often they have an alcoholic history. The prolonged shock with tis-

sue hypoxia causes excessive production of lactic acid, which is not adequately removed by the liver. The serum bicarbonate and pH are down, but no acetone is present in the urine or in the plasma.

Hypernatremic coma and hyperglycemic coma are both produced by cellular dehydration resulting from excessive hyperosmolarity of the extracellular fluid. Generally in hypernatremic coma serum sodium levels are as high as 156 to 188 mEq/liter. Hyperglycemic coma is characterized by blood sugar levels of 600 to 1000 mg% or higher. Hyperosmolar coma occurs chiefly in older individuals. Their diabetes is often of recent onset, with no treatment or inadequate treatment, and a slow development of stupor and unconsciousness. Treatment consists of the administration of hypotonic fluids and insulin as needed. These patients do not have the extreme resistance to insulin seen in keto-acidosis, and the amount of insulin required is usually much less than in keto-acidotic coma.

In the patient who develops keto-acidosis, a shortage of insulin is the key defect. This shortage can arise from a variety of circumstances, such as undiagnosed, untreated diabetes, omission of insulin in the known diabetic, or failure to meet the increasing requirement for insulin caused by infection, inactivity, or emotional disturbances. We recognize that the key ingredient in therapy is insulin. However, as the acidosis develops, there occur a number of changes in extracellular and intracellular fluid and electro-

lytes. I would like to spend a little time discussing these because they represent important facets of this disturbance.

FLUID AND ELECTROLYTE DISTURBANCES

Depletion of Cell Potassium

Patients who develop keto-acidosis usually have anorexia and vomiting. Obviously, anything that interferes with the intake of food and fluids will interfere with the intake of potassium, so that the ordinary supply of potassium is cut off. At the same time, the interruption of glycolysis, a source of energy for maintenance of the intracellular distribution of potassium, results in a leaking out of potassium from the cells. Also, because patients with keto-acidosis are not eating, they will have a negative nitrogen balance. Cell protein is ordinarily laid down in a proportion of 1g of nitrogen to 3 mEq of potassium. When a negative nitrogen balance occurs, potassium is lost from the cells. Also, the patient in diabetic keto-acidosis is not storing carbohydrate in the liver as glycogen. This process ordinarily removes from the extracellular fluid a certain amount of potassium. As the liver becomes deglycogenated in the keto-acidotic patient, this potassium is released. So we now have three processes transferring potassium from the cells into the extracellular fluid; loss of the pump effect, negative nitrogen balance, and deglycogenation of the liver.

The so-called "dehydration reaction" is a fourth cause of potas-

sium loss from cells. These patients become dehydrated, first of all because they are not taking fluids. At the same time, they usually have an osmotic diuresis and continue to lose fluids from the skin and through the lungs. As dehydration progresses, the body tries to maintain the integrity of the extracellular and intracellular fluid as close to normal as possible. Most of the losses are from the extracellular fluid in the initial phase, but ultimately transfers from cells to extracellular fluid occur. A variety of mechanisms bring these transfers about. First, as the toxicity of the extracellular fluid rises because of hyperglycemia, water is drawn out of the cells. Secondly, there is a dehydration reaction which permits the release of potassium from cells and with it a modicum of water. In other words, the transfer of potassium out of the cells reduces the osmolarity of the cells and raises the osmolarity of the extracellular fluid, and therefore water is transferred with the potassium. These mechanisms serve to prevent excessive depletion of extracellular fluid, but at the same time they deprive the cells further of potassium.

That a deficit of cell potassium of sufficient degree produces histologic evidence of cell destruction is clearly demonstrable in heart and skeletal muscle. Interference with normal cell function by potassium depletion is recognized in electrocardiographic changes, and in altered function of the nervous system, the gastrointestinal tract, and the kidneys. But more important than any of these is that potassium deficits within the cell are associated with increased mortality. This is amply demonstrated in animal studies and has its counterpart in the clinical situation.

Serum Potassium Levels

Although the patient with diabetic keto-acidosis is markedly depleted of potassium, the initial level of serum potassium is often high. This is because, during the

development of keto-acidosis, potassium has been transferred from cells into the extracellular fluid, and as dehydration and decreased renal blood flow diminish the urine output, potassium may not be well excreted. With fluid replacement and insulin treatment, potassium will quickly re-enter the cells and the serum potassium may drop sharply during the first few hours of treatment. In children, the initial serum potassium levels are not so often elevated, but may be normal or occasionally low. The reason may be that in children there is possibly a greater osmotic diuresis and a more rapid excretion of the potassium that has passed from the cells into extracellular fluid. In either case a low initial serum potassium level should alert one to the presence of very severe potassium depletion and the danger of severe hypokalemia developing in the course of treatment.

Sodium Loss, Dehydration, and Shock

With respect to sodium, some of the comments already made concerning potassium apply. The intake of this electrolyte is cut off, and further losses occur through vomiting and from renal loss as part of the osmotic diuresis. All these losses of sodium result in sodium depletion. When extracellular sodium is reduced by 25% a prompt decrease in circulatory efficiency occurs. If sodium is lost from extracellular fluid in excess of water, hypo-osmolarity of the extracellular fluid results. This causes water to move into the cells. This by itself has no particular significance, but the loss of circulating volume from the extracellular fluid, either by loss to the exterior or by transfer into cells, results in circulatory inefficiency. With the reduction in plasma volume the hematocrit rises. There is slowing of the circulation, with diminished venous return, decreased cardiac output and increased peripheral resistance. The end result is circulatory collapse,

just as real as that which can follow hemorrhage, extensive trauma, or any other cause.

It is very important to recognize the occurrence of sodium deficits. Such deficits are invariably present but the signs of circulatory collapse may not be. I think surely all of us now realize that we can have circulatory inefficiency with a normal blood pressure. As the blood volume falls, the blood pressure can be maintained for a while by arteriolar constriction, but this will lessen the delivery of blood to the tissues, which in turn interferes with cell function.

THERAPY

Insulin

The treatment of diabetic keto-acidosis begins with insulin. Generally this can be given in the home before the patient is referred to the hospital. Time is of the essence and one has to make sure that valuable time is not lost transporting the patient to the hospital, getting him admitted, finding out about hospital insurance, etc., and moving him to his bed. How much insulin, what route of administration, frequency of dosage etc., you and I could discuss for a long time. I think it is interesting to recall that some 20 years ago, Rabinowitz, in Montreal, routinely administered 200 units of insulin on admission and gave no further insulin, and in that particular series of patients all of them recovered. You and I are more apt to approach this problem in a gradual fashion, so to speak. We back into a final decision. Of course we can be a little bit more scientific if we call it "the method of successive approximations toward the need," but fundamentally "chicken" is a better term. I think it is better to remember that you can quite safely give too much insulin because you can counteract this subsequently by administering carbohydrate. But if you do not give enough insulin, the one thing that you cannot recapture is time. So, if you are going to make a mis-

take, do so in a very bold fashion. Experience indicates that ordinarily 300 or 500 units of insulin in the first 24 hours have proved to be adequate. This does not mean that there are not going to be patients that require a good deal more. Also you will have patients who will do well on a smaller quantity. This is an average figure and ordinarily in this "chicken" fashion, you will first administer 100 units as soon as the patient comes into the emergency room. This gives you a chance to get a little information as to the level of blood sugar, the decrease in "CO₂," the presence of plasma acetone, and the status of the circulation.

Fluids

After withdrawing blood from one vein, you start an infusion of 0.9% sodium chloride solution. There are many choices of solutions. We still prefer sodium chloride. First it is generally available. Secondly, all of the solutions that are offered represent confusion in a sense. If you use Ringer's lactate solution, it has a little bit of bicarbonate in it and it has a little bit of potassium and you may think you are doing something, but you are only deluding yourself. So we recommend beginning fluid replacement with sodium chloride. It is a useful rule of thumb to keep in mind that an adult diabetic coma patient comes in with a water deficit equal to 10% of the body weight, a sodium deficit of 10 mEq/kg, a chloride deficit of 10 mEq/kg, and a potassium deficit of 5mEq/kg. This means that in an adult weighing 70 kg, on admission there is a deficit of 7 liters of water, 700 mEq of sodium, 700 mEq of chloride, and 350 mEq of potassium. Our goal is not to replace these deficits at once. Our goal is one of turning the patient around and starting him toward recovery and away from death. The administration of sodium chloride following the initial dose of insulin provides an adequate beginning in most in-

stances. Ordinarily it will be sufficient to give two liters of sodium chloride, which contains approximately 18 g, or 308 mEq of sodium and of chloride. Please note that we are not trying to replace the total deficit of 700 mEq at once. We are giving part of it over the course of several hours. We recognize that during these several hours some of what we have administered will continue to be lost in the urine or by other routes. But it is enough just to turn the patient around. At the end of the 2 liters of saline, which will probably take some 3 hours to administer, one will have further laboratory data. At that point it may very well be that the laboratory indicates that the serum potassium is now down to normal or below normal, and at this point one can start therapy with potassium. Also laboratory reports will often indicate that the blood sugar is decreasing. At this point the potassium can be administered in 5% glucose. Generally it is desirable to use potassium phosphate rather than chloride. The reason for this is that we are using sodium chloride which has 154 mEq of chloride which is higher than the concentration normally present in extracellular fluid. We do not want to give KCl because we will be further adding to the chloride load and in some patients a hyperchloremic acidosis may result. The second reason is that patients with diabetic keto-acidosis develop deficits of phosphate from lack of intake and from loss of this solute in the urine. This phosphate does not come from the extracellular fluid; it comes from the cells. Some of it comes from protein breakdown, but the majority of it represents the breakdown of high-energy phosphate compounds such as ATP and creatine phosphate which are not being rebuilt because carbohydrate metabolism is reduced. No one has ever succeeded in demonstrating that these huge deficits of phosphate do any harm. Nonetheless, it does seem logical to give the potassium replacement as buffered phos-

phate, both to help somewhat in replacement of phosphate, and to avoid adding to the chloride load. How much potassium would you give? If the total deficit is estimated to be 350 mEq, it would probably be enough to set as a goal the administration of approximately one third of that over 3 or 4 hours, at the rate of approximately 40 mEq per hour.

Glucose

There has been great controversy in the past as to whether glucose should be given in the initial phase of treatment. Glucose solutions given even at the start of treatment do no harm except possibly to contribute further to the osmotic diuresis. Glucose does help to replete liver glycogen and diminish the ketosis, but many prefer not to begin glucose administration until there is definite evidence that the blood sugar has begun to fall with treatment. We should remember that even an initial blood sugar of 500 mg% may not represent more than 50 or 60 g of total glucose in the extracellular fluid, and this amount can be put back into cells fairly quickly once enough insulin is given. It is imperative that glucose be provided as the blood sugar falls, in amounts adequate to cover the large doses of insulin that have been given, and at a rate rapid enough to prevent hypoglycemia.

Dextran and Alkalis

It is a good rule in seriously ill patients to consider two additional elements in the early therapy. The first of these is the use of dextran, or less desirably, the use of whole blood or plasma. Whole blood or plasma is less desirable because of the problem of hepatitis. In patients on the verge of circulatory collapse or in actual circulatory collapse, a unit of dextran is a kind of insurance and I would rather give it needlessly to 99 patients than fail to give it to the one who needs it. The second item is the use of alkali

solutions shortly after admission. I like to reserve these for patients who have a reduction of the pH down to seven or so. The routine administration of alkali interferes with the use of "CO₂" (bicarbonate) as a precise index of improvement. It is very reassuring to find that a bicarbonate of 5 mEq/liter has risen after several hours of treatment to 8 or 9 mEq/liter. I know that the patient is clearing ketone bodies and is responding to insulin. I cannot tell this quite as precisely when one uses the plasma acetone or the urine acetone as the sole index. This index is lost when 6 molar lactate or sodium bicarbonate is administered. On the other hand if the pH is reduced sufficiently, we know that this by itself threatens survival, and under these circumstances one should give alkali.

Use of Fructose

Another point that deserves mention is the use of fructose instead of glucose. Theoretically there are several advantages to fructose. First of all, it can enter the glycolytic cycle without the intervention of insulin. Secondly, it is an excellent glycogen former and, as we have indicated, hepatic glycogen is depleted. Thirdly, the Tm for glucose and the Tm for fructose are independent and non-additive. The kidneys reabsorb glucose and fructose independently, and therefore one can carry higher blood sugar levels with less glycosuria. All of these are cogent arguments, but from the practical point of view, they are not significant. Fructose further complicates therapy and there may be some hazard because in children fructose causes massive deposition of glycogen in the liver which itself might be harmful. The liver becomes greatly distended and you have the feeling that only the capsule is preventing it from bursting.

I have said nothing about lavage of the stomach or passage of a stomach tube. Life is already complex when you have a keto-acidotic patient to look after, and passing a

tube into an unconscious patient is not the easiest thing to do. The stomach tube should be put down only in those patients who continue to vomit. Most patients will not continue vomiting if you do not give anything by mouth. Whatever is in the stomach and gastrointestinal tract will be absorbed as therapy continues, so generally it is reasonable to avoid this additional complication.

MANAGEMENT AFTER THE FIRST FEW HOURS

We have come now to the sixth, seventh or eighth hour and the patient is responding to treatment in a satisfactory fashion. We have seen some decrease in the blood sugar, some rise in the "CO₂," some decrease in the acetonemia. The urine continues to contain sugar; it still contains ketone bodies but perhaps in reduced quantities. By this time the patient is partially restored to consciousness, perhaps asking for food and fluids by mouth. We can begin to relax a little, but we should not take the needle out of the vein. The patient can be started at this point on some intake by mouth. If vomiting ensues, this should be discontinued. One can alternate tea fortified with glucose and sucrose and lactose with 0.5% sodium chloride broth. The real problem is encountered between the 12th and 24th hour. The difficulties stem from the fact that the house staff has been working all night long on the coma patient; morning arrives, and it is time to have the report and to make rounds. So everyone relaxes as far as attention to the patient goes. Or, if the house staff has worked all day, it is midnight and time to go to bed. The nurses are very considerate, so they do not report promptly when the glucose infusion is not working properly. There are two problems that develop. One is hypoglycemia and the other is hypokalemia. Twenty percent of the patients who are in the 12th to 24th hour of therapy develop blood sugars which are in the

hypoglycemic range. Approximately 20% develop hypokalemia with potassium levels below 3.5 or 3.0 mEq/liter. These are the two sequelae which undoubtedly account for unexplained deaths in comas that have been otherwise treated very successfully. When the patient reaches the 24th hour of treatment, usually we put him back on his usual dosage of insulin or on regular insulin. With resumption of a normal dietary intake, the remaining deficits are made up.

MORTALITY

There is no question that some centers have a better record than others. Certainly the Joslin Clinic record is most impressive with mortalities of 1%, 2%, or 3%. It is recognized that these low mortality rates represent a very selected type of experience, under unusually favorable circumstances. The Joslin Clinic has a laboratory that is set up to look after keto-acidosis seven days a week. Unfortunately, in many other centers the mortality is still high. It ranges between 15% and 25% in adults. The mortality in pediatric diabetic coma is much less. Indeed, you hardly ever see a death in childhood provided the diabetes had been recognized previously, the patient is under therapy, and the coma is treated in a qualified institution. But there are still deaths in children which result from previously undiagnosed diabetes terminating in coma, or that result from the assumption that all hospitals are equivalent in terms of their ability to treat diabetic keto-acidotic coma. Properly treated, keto-acidosis in children and adults should be nothing but an event, certainly an avoidable event in many cases, in the life of the diabetic.