A Disturbance in Calcium Metabolism Leading to Tetany Occurring Early in Acute Pancreatitis*

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INTRODUCTION

WHEN SERUM IS subjected to ultrafiltration, the concentration of calcium in the ultrafiltrate is about 5.5 mg. per cent. The remaining 4.5 mg. per cent is not ultrafiltrable, being in a nonionized combination with proteins as calcium proteinate. Less than 1 mg. per cent of the diffusible calcium is also nonionized. It is probably composed of calcium complexes, with citric acid and other organic acids containing hydroxyl groups. A trace perhaps exists in the form of colloidal calcium phosphate. Thus, from 4.5 to 5.0 mg. per cent is present as divalent calcium ions.

In the adult, the calcium of the circulating plasma and interstitial fluid is not primarily a nutritional substance. It is a functional constituent of the internal environment of the body cells, along with sodium, potassium and magnesium. The balanced concentrations of these four ions (plus hydrogen ions) determines the integrity of all cellular processes, including neuromuscular irritability. The important regulator of serum calcium levels in most situations is the hormone of the parathyroid glands; the normal daily secretion of which has been estimated at 50 to 75 units.

In acute pancreatitis the study of serum enzymes is of the greatest value. A significant rise in serum enzyme activity begins within several hours of onset of acute symptoms, and becomes maximal within 12 to 72 hours. Amylase values usually return to normal in three or four days, and lipase levels in seven to 14 days. Serum calcium levels are diminished in most or all adequately studied cases of acute pancreatitis, low levels being observed between the second and fifteenth day after onset. Levels are lowest, however, on about the sixth day. There is an apparent correlation between the clinical severity of the attack and the degree of depression of serum calcium concentration; values below 7 mg. per 100 cc. appear to have occurred only in fatal cases.

MATERIALS AND METHODS

Two patients have been studied on a detailed metabolic program because each displayed a moderately severe degree of neuromuscular irritability within 24 hours of onset of acute pancreatitis.

With the recognition of acute pancreatitis in these two male patients and the demonstration of the moderately severe degree of tetany evident by positive Chvostek's and Trousseau's signs, each was started on a metabolic balance based on four six-hour study periods in each day. During the early period of each study no calcium intake was given except for purposes of the study; when feeding was permitted, the patients were

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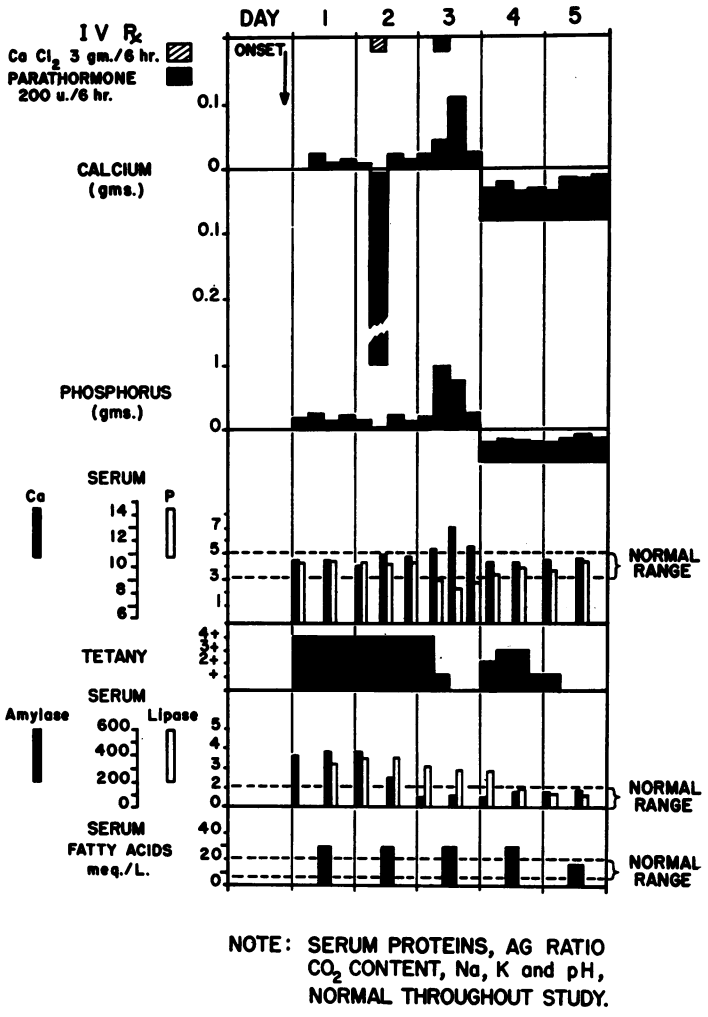

FIG. 1. (Patient #1) Tetany occurring early in acute pancreatitis with normocalcemia and refractory to calcium salt therapy. See text for explanation.

given four equal feedings, each at the beginning of a six hour period, and containing one-fourth the daily allowance of calcium, as well as the other food elements. One patient received a daily total of 320 mg. of calcium; the other was restricted to 160 mg. daily. During the period of study, urinary excretion of calcium[1, 7] and phosphorus[3] was measured for each of the four periods of every day. Serum calcium,[1, 7] phosphorus,[3] amylase,[12] lipase,[6] and fatty acids[10] were measured at frequent intervals and recorded graphically in Figures 1 and 2. Determinations of serum proteins, A/G ratio,[14] carbon dioxide content,[13] sodium,[4] potassium[4] and pH[2] were made twice daily.

During the period of tetany associated with normal serum calcium levels, a six hour intravenous infusion of 3 Gm. of calcium chloride in one liter of 5 per cent glucose in distilled water was given; such an infusion vehicle was employed for the administration of 200 units of parathyroid hormone over an equal period of time. In the one patient displaying a delayed recurrence of tetany associated with hypocalcemia, the intravenous infusion of calcium chloride was repeated.

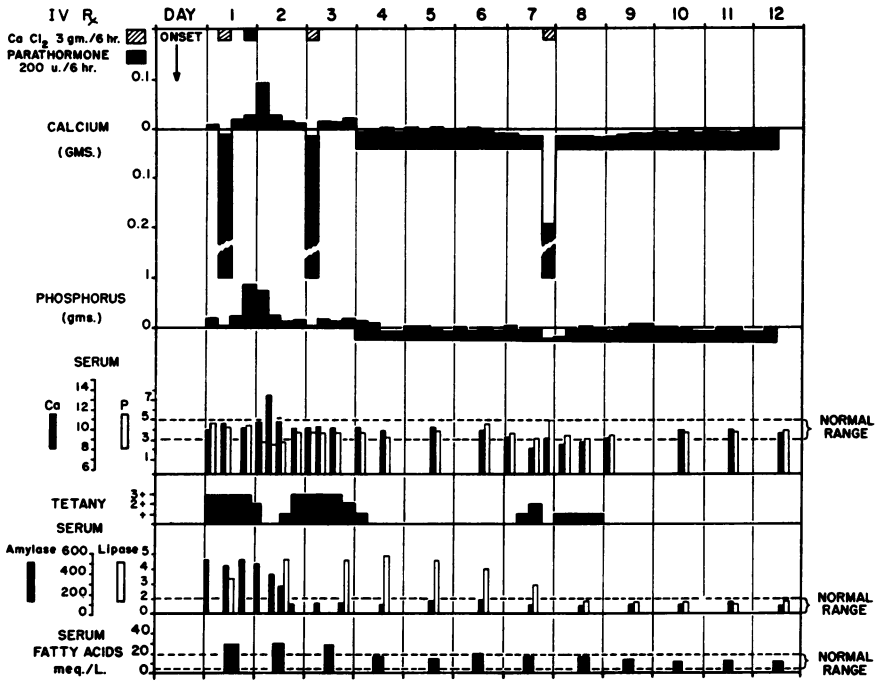

FIG. 2. (Patient #2) Tetany occurring early and late in acute pancreatitis. The early tetany occurs with normocalcemia and is refractory to therapy with calcium salts. The late tetany is associated with hypocalcemia and responds temporarily to therapy with calcium salts. See text for details.

RESULTS

The metabolic results are charted according to the method commonly employed in this laboratory[11] and graphically portrayed in Figures 1 and 2. The first patient (Fig. 1) was seen approximately 12 hours after the onset of acute pancreatitis. The diagnosis was made clinically with considerable ease, and confirmed by a serum amylase of 400 units (upper limit of normal 150 units). Chvostek's and Trousseau's signs were strongly positive. The study was begun at once, and it is readily apparent from Figure 1 that there was no alteration from normal in calcium and phosphorus excretion. The only measurement that was made which would account for the tetany on the basis of a reduction in ionic calcium was an elevation in serum fatty acids. Twelve hours later laboratory confirmation of the diagnosis was strengthened by finding the serum lipase to be elevated in amount. At this time and throughout the study on twice daily determinations, the serum proteins, calcium, phosphorus, A/G ratio, pH, CO_2 content, sodium and potassium were all within normal limits. On the second day when 3 Gm. of calcium chloride were given intravenously over a six hour period, no change was evident in clinical status of the patient or the blood chemical findings; the only alteration in the metabolic response was a slight decrease in the urinary excretion of phosphorus, and a very prompt and nearly complete urinary excretion of the administered ionic calcium. On the other hand, when parathyroid hormone

was given in a dose of 200 units over the same period of time on the third day, many changes were seen: primarily, there was a fall in the serum level and an increase in the urinary excretion of phosphorus, followed by a very significant increase in the serum level and urinary excretion of calcium. Concomitant with the rise in serum calcium there was a disappearance of the clinical tetany. These changes occurred when the serum lipase and serum fatty acids were still significantly elevated but with no other blood components altered. As soon as the metabolic effect of the hormone had disappeared, clinical tetany returned and progressively subsided as the serum lipase and serum fatty acid concentration returned to lie within the limits of normal. The positive calcium balance can be accounted for by replacement of the element loss during the metabolic effect of the parthyroid hormone. This compensatory effect was evident, though the dietary intake was a moderately generous one.

The second patient displayed essentially a similar clinical course (Fig. 2). During the early period of tetany the failure to respond to therapy with intravenous calcium chloride and the prompt response with parathyroid hormone were associated with comparable metabolic alterations insofar as urinary excretions of calcium and phosphorus, and serum levels of enzymes, fatty acids, calcium and phosphorus were concerned. When, however, the tetany recurred late in the disease it was associated with normal serum levels of fatty acids, a rapidly falling serum lipase concentration, a decreasing serum calcium concentration, and a very significant shift in calcium balance to positive, despite a restricted intake. Intravenously administered calcium chloride given at this time was associated with a slight reduction in urinary excretion of phosphorus, a restitution of the serum calcium level to normal, and a much greater retention of the calcium than before. Clinically, there was an associated absence of demonstrable neuromuscular irritability. After this brief episode, progressive spontaneous improvement in the clinical tetany was associated with positive calcium balance while still on a restricted intake, and a return of serum calcium levels to normal.

DISCUSSION

The information obtained from a study of these two patients with moderately severe acute pancreatitis suggests some interesting speculations that can be made concerning the controls of and the mechanisms involved in calcium metabolism. An adequate demonstration of increased neuromuscular irritability in the normocalcemic and in the hypocalcemic states has been made.

Though tetany with normocalcemia has been observed to occur in acute alkalotic states, no change in blood carbon dioxide content or pH was noted in these patients. The factor common to both cases (and not seen in other patients with acute pancreatitis) which could explain the decreased ionized component with normocalcemia leading to tetany was an increase in the serum level of fatty acids, associated with an elevation in level of serum lipase. An elevation in fatty acids would increase the free hydroxyl radicals of the organic acids for binding ionic calcium much as does citric acid. This binding results in a calcium complex which must be diffusible, but with a very low pK since the renal excretion of calcium must be controlled by the serum level of the diffusible complex. Ionic calcium as calcium chloride given parenterally in a large dose was promptly excreted via the urine without altering the ionized fraction in the serum enough to influence materially the exaggerated neuromuscular irritability. The administration of parathyroid hormone at this time, by essentially altering the urinary excretion rate of phosphorus, raises the total serum calcium and, with it, the ionic fraction enough to abolish the tetany. Spontaneous improvement in the tetany occurs concur-

rently with the progressive return to normal of the serum fatty acids level.

The failure of the serum phosphorus to rise during the infusion of calcium salts strongly suggests that some degree of increased parathyroid activity was present,[8, 9] and this in the presence of normocalcemia. This may be suggestive evidence that the adequate stimulus for the parathyroid gland is the ionic fraction of the serum calcium. This is further borne out by the minimal decrease in urinary phosphorus excretion and the flat serum phosphorus levels during the parenteral administration of the calcium salts.[5]

When, however, the total serum calcium and, with it, the ionized fraction is depressed by extravascular loss to sites of pancreatic fat necrosis, prompt improvement in the tetanic state is effected by the parenteral administration of calcium salts. A prelude to this situation is evident in the metabolic study when, as tetany develops, the calcium balance changes sharply towards a more positive one, even with a limited intake. When the parenteral form of calcium is now given, the major portion of it is retained as both ionic and nonionic, associated with the abolition of tetany.

SUMMARY

A form of tetany with normocalcemia occurring early in acute pancreatitis has been shown to be refractory to therapy with calcium salts, and is probably due to binding of ionic calcium by fatty acids. The tetany does respond to treatment with parathyroid hormone. Such data suggest some information on mechanisms involved in calcium hemostasis.

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