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Eduardo L. Reyes

Robert W. Talley

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The Hypocalcemic Effects of Actinomycin D and Mithramycin

Eduardo L. Reyes, M.D.* and Robert W. Talley, M.D.**

Both actinomycin D and mithramycin are useful agents in the treatment of cancer. They can also produce hypocalcemia, a comparatively rare phenomenon in cancer. Two such cases are presented in detail. Neither patient had the classic symptoms of hypocalcemia. Instead, the clinical picture was more compatible with hypercalcemia. The mechanism of action of each drug is explained; therapeutic implications are made with regards to their synergistic effects when used in combination with the standard calcium-lowering agents. Attention is drawn to the inhibitory action of these two agents on the calcium-mobilizing effect of the parathyroid hormone. The hypocalcemic effects of these two drugs are peripheral and not due to inhibition of parathyroid hormone synthesis. Because of their potentially fatal biochemical side effects, extreme caution is advocated in their use.

Hypercalcemia is a common medical emergency in patients with neoplastic disease, either as a result of the malignancy or as a result of therapy. Hypocalcemia, however, is a relatively rare phenomenon in a patient with cancer. Conditions unrelated to cancer can give rise to hypocalcemia, eg, rickets, osteomalacia, chronic renal failure, idiopathic hypoparathyroidism as a postoperative complication of thyroidectomy, and moniliasis of the parathyroid gland.[1,2] Neoplasms may also cause hypocalcemia directly or as a result of their associated complications. For example, medullary carcinoma of the thyroid may produce hypocalcemia by secretion of large amounts of thyrocalcitonin, which is a hypocalcemic factor.[3] Hypocalcemia may also occur spontaneously in lung tumors, and has been described in carcinoma of the prostate due to sequestration of calcium into the areas of osteoblastic metastases.[4,5] Breast cancer which has responded dramatically to therapy may also result in hypocalcemia by relatively rapid deposition of calcium in lytic areas in the bone.[4] Indirectly, other conditions associated with cancer may also produce hypocalcemia, eg, hypoalbuminuria due to severe debilitation and chronic malnutrition, malabsorption syndrome which sometimes accompanies lymphomas, and chronic renal failure due to secondary metastases to the kidney.

Various drugs such as steroids,[6]

* Now at Howell State Hospital, Howell, Michigan.
** Division of Oncology, Department of Medicine.
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phosphates, sulfates, ethylene diaminetetriacetate (EDTA), and thyrocalcitonin — which lower serum calcium levels — have been used in the management of hypercalcemia.

This paper will present the complications of hypocalcemia induced by actinomycin D and mithramycin in two patients. The mechanism of action of the drugs will be discussed in relation to the homeostasis of calcium metabolism.

Case Reports

Case I

H.W., a 41-year-old white male had a thoracotomy in February, 1968, for an undifferentiated carcinoma of the right lung. Following diagnosis, the patient developed lytic osseous metastases to the left tibia and left ischium. These responded well to cobalt therapy. He had a persistent leucocytosis, with no clinical infection. In December, 1968, the patient complained of dull discomfort in the right rib cage, progressive weakness, anorexia, and weight loss. Persistence of this pain necessitated admission to the hospital on January 10, 1969.

At time of admission, pertinent physical findings revealed a thin middle-aged man complaining of weakness and pain in the right lateral rib cage. Blood pressure was 120-80, pulse 80/minute and regular, and temperature was 100.2°F. Except for tenderness in the well-healed right thoracotomy scar, a 3 x 3 cm firm tender mass over the left ischium, and prominence of the middle portion of the tibia, the physical examination was not unusual.

Pertinent laboratory findings were: hemoglobin (Hgb) 10 gm/100 cc; white blood count (WBC) 17,000/cu mm; platelet count 524,-300/cu mm; polymorphonuclear leucocytes 82%, lymphocytes 17%, bands 1%; urinalysis normal; fasting blood sugar (FBS) 105 mg/100 cc; urea nitrogen 12 mg/100 cc; alkaline phosphatase 6.8 Bodansky units; total bilirubin 0.64 mg/100 cc; direct bilirubin 0.32 mg/100 cc; serum calcium 11.3 mg/100 cc, phosphate 3.6 mg/100 cc, serum glutamic oxaloacetic transaminase (SGOT) 15 units, lactic dehydrogenase (LDH) 260 units; albumin 3.07 gm/100 cc; and α_1 globulin 0.43%, α_2 globulin 1.31 gm%, β globulin 1.09 gm%, and γ globulin 1.97 gm%. Iliac crest bone marrow aspiration revealed a ME ratio of 11.2:1, and decreased normoblasts but no evidence of tumor cells. The electrocardiogram (EKG) was within normal limits. X-rays of the chest revealed a superior mediastinal mass and a postoperative deformity of the fourth right rib. Skeletal x-rays demonstrated a lytic lesion of the left ischium and left tibia.

Since the patient had extensive metastatic disease with recurrence of lesions previously radiated, he was considered a candidate for chemotherapy with vincristine and antinomycin D.[7] The program of therapy was 3.7 mg of vincristine on the first day with 0.7 mg of actinomycin D on the next three days. Late during the second day of therapy, he developed chills and fever. However, the following day his temperature returned to normal. At this time, he developed tachycardia, tachypnea and anxiety. On the fourth day, these symptoms increased in severity and the deep tendon reflexes were absent. An EKG revealed only sinus tachycardia. The serum electrolytes were: sodium 120 mEq/L, potassium 3.6 mEq/L, chlorides 86 mEq/L, carbon dioxide 17 mEq/L, and serum calcium 6.8 mg/100 cc. The serum enzymes, which had been normal prior to chemotherapy, were: SGOT of 550 units, LDH 4,750 units and creatine phosphokinase (CPK) 189 units. The Hgb was 10.4 gm/100 cc; WBC 14,700/cu mm, and platelet count 50,000/cu mm. On the fifth day (one day after completion of the course of therapy) he became weak and lethargic, and complained of nausea and dryness of the mouth. Neurological examination again revealed the absence of deep tendon reflexes but no evidence of increased muscular irritability or a positive Chvostek's sign. At this time, the serum calcium had fallen to 5.2 mg/100 cc. A few hours later, the patient lapsed into a coma. Despite therapy with 10 cc of 10% calcium gluconate hourly for four doses, he deteriorated and died. The blood pressure was normal and stable until one hour prior to death.

At autopsy no evidence of acute myocardial infarction or pulmonary embolism was found. There was a tumor in the right upper lobe infiltrating the pleura, superior mediastinum, esophageal serosa, adventitia of the aorta, and periosteum of the adjacent thoracic vertebra. There was also tumor involvement of the left ischium and left tibia. The parathyroid glands were within normal limits.

Case II

G.O., a 27-year-old white male, was re-

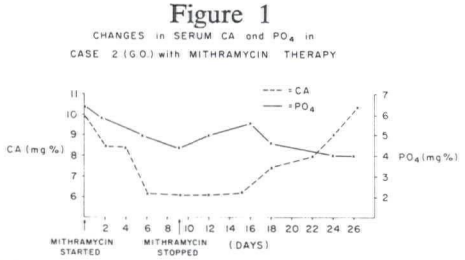
ferred to Henry Ford Hospital on June 19, 1966, for chemotherapy of metastatic embryonal carcinoma of the testis. He had undergone an orchiectomy in October, 1964, at another institution, followed by radio therapy to pelvic and para-aortic nodes. An abdominal mass and ascites developed in February, 1966, but treatment with cyclophosphamide and vinblastine resulted in a brief regression. Pertinent physical findings at time of admission were: a mass measuring 7 x 8 cm in the left supraclavicular area, dullness to percussion of the bilateral chest, hepatomegally 8 cm below the right costal margin, and a firm, hard 15 x 13 cm mass in the left upper abdomen.

Pertinent initial laboratory findings were as follows: Hgb 14.3 gm/100 cc; WBC 18,000/cu mm; platelet count 350,000/cu mm; neutrophils 84%; lymphocytes 9%; monocytes 1%; bands 6%. Urinalysis showed specific gravity to be 1.026, albumin +2, occasional epithelial cells, RBC 10-12. Serum alkaline phosphatase was 7.4 Bodansky units; serum bilirubin 1.6; serum calcium 10 mg/100 cc; and urea nitrogen 45 mg/100 cc. X-ray films of the chest revealed bilateral pleural effusion and enlarged mediastinal nodes. Upper gastrointestinal study revealed a complete obstruction of the fourth portion of the duodenum by a large retroperitoneal mass, and an intravenous pyelogram revealed minimal hydronephrosis bilaterally.

On June 21, 1968, the patient was started on a course of mithramycin 1.75 mg/day given in an 8-hour intravenous infusion. His serum calcium fell to 8.6 mg/100 cc the following day from an initial level of 10 mg/100 cc prior to therapy. This continued to fall steadily so mithramycin was discontinued after nine days. Even though his serum calcium level fell to 6.2 mg/100 cc, the patient manifested no increased muscular irritability or other signs and symptoms of classic hypocalcemia. The serum urea nitrogen rose progressively to 72 mg/100 cc. A slight decrease was noted in the size of the cervical and abdominal mass following mithramycin therapy. The serum calcium gradually returned to normal (Fig 1) even though the serum urea nitrogen increased slowly to 90 mg/100 cc 14 days after completion of therapy. By that time the serum calcium had returned to a normal level of 10.2 mg/100 cc. Because of the persistent intestinal obstruction the patient's condition deteriorated and he died.

The autopsy revealed bilateral bronchopneumonia and metastases to the para-aortic and mediastinal nodes, both adrenals, liver, left kidney, vertebra, and left cervical nodes. The parathyroids were normal.

Figure 1



Changes in serum calcium and phosphate in Case ♯2 (G. O.) with mithramycin therapy.

Discussion

Even though the exact etiology of the hypocalcemia in these two patients was not conclusively proven, the most likely explanation was the effect on calcium homeostasis by the two chemotherapeutic agents employed. The time relationship between drug administration and the onset of hypocalcemia favors this; also the fact that these patients had high calcium levels (Case ♯I — H.W.) and a normal serum calcium prior to therapy (Case ♯II — G.O.). In both cases, the patients had none of the signs frequently associated with hypocalcemia such as increased muscular irritability and hyperactive reflexes. On the contrary, the signs and symptoms could be confused with hypercalcemia. However, part of the symptomatology of Case ♯I could be explained on the basis of metabolic acidosis and low sodium, chlorides, and potassium which may account for the hyperventilation as well as lethargy and areflexia. Vincristine may also have contributed to the areflexia. However, there are no reported instances of hypocalcemia occurring with vincristine therapy. The markedly elevated serum enzymes may have resulted from necrosis of normal

and/or tumor tissue caused by these agents.

Actinomycin D, an antibiotic, was first discovered by Waksman and Woodruff in 1940 and found to be an effective antibacterial agent, but it is too toxic to be used clinically as an antibacterial agent.[8,9] Antinomycin produces selective toxicity to the bone marrow, lymphoid tissue, and intestinal epithelium, and in this respect is similar to other cancer chemotherapeutic agents.[8] In humans, antinomycin D has also been found to be effective in treatment of neuroblastomas, Wilm's tumor, choriocarcinoma, and testicular neoplasms.[10] The combination of antinomycin D and vincristine has been reported to be effective in the therapy of lung cancer.[7]

This agent has also been found to produce profound biochemical effects including the antagonism of the action of parathyroid hormones.[11,12] Antinomycin binds to guanine of the deoxyribonucleic acid (DNA) chain, thus inhibiting the synthesis of messenger ribonucleic acid (MRNA). With MRNA synthesis inhibited, further RNA synthesis is blocked.[13] Although the exact mechanism of interference with parathyroid hormonal action is unclear, it is believed to depend upon induction of an enzyme system which blocks parathormone or Vitamin D action.[9,12] Parathormone induces the synthesis of MRNA which regulates enzyme production. Actinomycin D probably does not interfere with the synthesis of hormones but blocks peripheral action. In animal experiments, actinomycin prevents serum calcium elevations in Vitamin D-deficient rats given either Vitamin D or parathyroid hormone.[13-16]

It is generally accepted that the parathyroid hormone influences the kidneys, gastrointestinal tract, and (more profoundly) bone. Vitamin D has a similiar action, increasing the permeability of the intestinal mucosa to calcium[13] and also causing morphologic bone changes.[14] Actinomycin D is antagonistic to these two effects of Vitamin D because it inhibits the calcium transport system in the gastrointestinal tract[13] and suppresses hypercalcemia and morphologic bone changes induced by the vitamin.[14,15,17]

Previous experiments also have shown the inhibitory action of antinomycin D on the calcium-mobilizing effect of the parathyroid hormone.[16,18,19] It seems that actinomycin D blocks this effect on the bone but is not effective against the phosphoturic action of the parathyroid hormone. To further confirm the hypocalcemic effect of actinomycin D, it has been shown that recovery from hypocalcemia is delayed in rats treated with actinomycin D after administration of thyrocalcitonin.[16] The hypocalcemic effect of actinomycin D is usually delayed from 7 to 12 hours after administration. A hypothesis offered for this speculates that, with the inhibition of a parathyroid hormone, thyrocalcitonin and steroids would be free to exert their effects unopposed.[18]

Mithramycin, another antibiotic, also produces hypocalcemia. Historically, this drug was derived from an Actinomycete culture belonging to the genus Streptomyces. It was first shown to be active against HeLa cells in tissue culture, adenocarcinoma 755 as well as gram positive bacteria in 1960.[20] In the same year, Curreri and Ansfield published the first clinical evaluation of the drug in solid tumors, reporting regressions in two patients. Toxic effects

noted were nausea, vomiting, acute renal failure, and hematopoietic toxicity of severe thrombocytopenia.[21] There was no mention of hypocalcemia.

Parker et al gave the drug to 19 patients in 1960 and formed the same conclusions.[22] In 1963, Koffman reported the results of therapy using the drug in 84 patients, with regressions observed in six patients. Besides the usual side effects noted by previous investigators, he reported hypocalcemia in two patients.[23] In 1965, Brown and Kennedy also noted significant reduction in serum calcium and phosphorus, with one patient developing symptomatic hypocalcemia.[24] In 1966, Koons also encountered hypocalcemia in his patients.[25] In 1968, Ream reported regressions in 9 of 26 evaluable patients. Three of his patients developed hypocalcemia, two of them symptomatic and the other one asymptomatic.[26] Talley also noted hypocalcemia (less than 8 mg%) in 10 of 51 patients given this drug for all types of solid tumors.[27] Also, none of these patients had symptoms suggestive of hypocalcemia but many had symptoms that were more suggestive of hypercalcemia.

Mithramycin has also been shown to inhibit RNA synthesis. Most probably this is also accomplished by binding to DNA like antinomycin D.[28] With this inhibition, the enzyme system necessary for hormone action is also blocked. The hypocalcemic action of mithramycin has been reported in a controlled study by Parsons.[29] Patients with cancer, given mithramycin, showed a reduction in urinary calcium reflecting a decrease in serum calcium. Urinary hydroxyproline excretion was also diminished thereby ruling out the possibility of rapid bone repair.[29] He also suggested that mithramycin might block the osteolytic sterols.

Summary

Two patients are reported with hypocalcemia, one secondary to actinomycin D and one incidental to mithramycin. Neither patient had the classic symptoms of increased muscular irritability associated with hypocalcemia. Instead, the clinical picture was more compatible with hypercalcemia. The mechanism of action of these two drugs is identical. Both inhibit MRNA production which is necessary for enzyme synthesis. Such enzyme synthesis is vital for hormonal action. The hypocalcemic effects of these two drugs are peripheral and not due to inhibition of parathyroid hormone synthesis. Review of the literature shows that these drugs have an antagonistic action on the hypercalcemic effects of parathyroid hormone and Vitamin D in laboratory animals. Because of this easily unrecognized complication, attention should be directed toward biochemical side effects as well as known bone marrow toxic effects. Therapeutically, actinomycin D or mithramycin might be used cautiously in the treatment of hypercalcemia when other accepted modalities of therapy have failed.

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