restriction of dietary calcium is beneficial. Decreased renal function or ECF depletion decreases urinary calcium excretion. In such situations, rehydration may rapidly reduce or reverse the hypercalcemia, even though increased bone resorption persists. As outlined below, the more severe the hypercalcemia, the greater the number of combined therapies that should be used. Rapid-acting (hours) approaches—rehydration, forced diuresis, and calcitonin—can be used with the most effective antiresorptive agents such as bisphosphonates (since severe hypercalcemia usually involves excessive bone resorption).

HYDRATION, INCREASED SALT INTAKE, MILD AND FORCED DIURESIS

The first principle of treatment is to restore normal hydration. Many hypercalcemic patients are dehydrated because of vomiting, inanition, and/or hypercalcemia-induced defects in urinary concentrating ability. The resultant drop in glomerular filtration rate is accompanied by an additional decrease in renal tubular sodium and calcium clearance. Restoring a normal ECF volume corrects these abnormalities and increases urine calcium excretion by 2.5–7.5 mmol/d (100–300 mg/d). Increasing urinary sodium excretion to 400–500 mmol/d increases urinary calcium excretion even further than simple rehydration. After rehydration has been achieved, saline can be administered, or furosemide or ethacrynic acid can be given twice daily to depress the tubular reabsorptive mechanism for calcium (care must be taken to prevent dehydration). The combined use of these therapies can increase urinary calcium excretion to ≥12.5 mmol/d (500 mg/d) in most hypercalcemic patients. Because this is a substantial percentage of the exchangeable calcium pool, the serum calcium concentration usually falls 0.25–0.75 mmol/L (1–3 mg/dL) within 24 h. Precautions should be taken to prevent potassium and magnesium depletion; calcium-containing renal calculi are a potential complication.

Under life-threatening circumstances, the preceding approach can be pursued more aggressively, but the availability of effective agents to block bone resorption (such as bisphosphonates) has reduced the need for extreme diuresis regimens (Table 424-4). Depletion of potassium and magnesium is inevitable unless replacements are given; pulmonary edema can be precipitated. The potential complications can be reduced by careful monitoring of central venous pressure and plasma or urine electrolytes; catheterization of the bladder may be necessary. Dialysis treatment may be needed when renal function is compromised.

BISPHOSPHONATES

The bisphosphonates are analogues of pyrophosphate, with high affinity for bone, especially in areas of increased bone turnover, where they are powerful inhibitors of bone resorption. These bone-seeking compounds are stable in vivo because phosphatase enzymes cannot hydrolyze the central carbon-phosphorus-carbon bond. The bisphosphonates are concentrated in areas of high bone turnover and are taken up by and inhibit osteoclast action; the mechanism of action is complex. The bisphosphonate molecules that contain amino groups in the side chain structure (see below) interfere with prenylation of proteins and can lead to cellular apoptosis. The highly active nonamino group–containing bisphosphonates are also metabolized to cytotoxic products.

The initial bisphosphonate widely used in clinical practice, etidronate, was effective but had several disadvantages, including the capacity to inhibit bone formation as well as blocking resorption. Subsequently, a number of second- or third-generation compounds have become the mainstays of antiresorptive therapy for treatment of hypercalcemia and osteoporosis. The newer bisphosphonates have a highly favorable ratio of blocking resorption versus inhibiting bone formation; they inhibit osteoclast-mediated skeletal resorption yet do not cause mineralization defects at ordinary doses. Although the bisphosphonates have similar structures, the routes of administration, efficacy, toxicity, and side effects vary. The potency of the compounds for inhibition of bone resorption varies more than 10,000-fold, increasing in the order of etidronate, tiludronate, pamidronate, alendronate, risedronate, and zoledronate. The IV use of pamidronate and zoledronate is approved for the treatment of hypercalcemia; between 30 and 90 mg pamidronate, given as a single IV dose over a few hours, returns serum calcium to normal within 24–48 h with an effect that lasts for weeks in 80–100% of patients. Zoledronate given in doses of 4 or 8 mg/5-min infusion has a more rapid and more sustained effect than pamidronate in direct comparison.

These drugs are used extensively in cancer patients. Absolute survival improvements are noted with pamidronate and zoledronate in multiple myeloma, for example. However, although still rare, there are increasing reports of jaw necrosis, especially after dental surgery, mainly in cancer patients treated with multiple doses of the more potent bisphosphonates.

CALCITONIN

Calcitonin acts within a few hours of its administration, principally through receptors on osteoclasts, to block bone resorption. Calcitonin, after 24 h of use, is no longer effective in lowering calcium. Tachyphylaxis, a known phenomenon with this drug, seems to explain the results, since the drug is often effective in the first 24 h of use. Therefore, in life-threatening hypercalcemia, calcitonin can be used effectively within the first 24 h in combination with rehydration and saline diuresis while waiting for more sustained effects from a simultaneously administered bisphosphonate such as pamidronate. Usual doses of calcitonin are 2–8 U/kg of body weight IV, SC, or IM every 6–12 h.

OTHER THERAPIES

Denosumab, an antibody that blocks the RANK ligand (RANKL) and dramatically reduces osteoclast number and function, is approved for therapy of osteoporosis. It also appears to be an effective treatment to reverse hypercalcemia of malignancy, but is not yet approved for this indication. *Plicamycin* (formerly mithramycin), which inhibits bone resorption, and *gallium nitrate,* which exerts a hypocalcemic action also by inhibiting bone resorption, are no longer used because of superior alternatives such as bisphosphonates.

Glucocorticoids have utility, especially in hypercalcemia complicating certain malignancies. They increase urinary calcium excretion and decrease intestinal calcium absorption when given in pharmacologic doses, but they also cause negative skeletal calcium balance. In normal individuals and in patients with primary hyperparathyroidism, glucocorticoids neither increase nor decrease the serum calcium concentration. In patients with hypercalcemia due to certain osteolytic malignancies, however, glucocorticoids may be effective as a result of antitumor effects. The malignancies in which hypercalcemia responds to glucocorticoids include multiple myeloma, leukemia, Hodgkin's disease, other lymphomas, and carcinoma of the breast, at least early in the course of the disease. Glucocorticoids are also effective in treating hypercalcemia due to vitamin D intoxication and sarcoidosis. Glucocorticoids are also useful in the rare form of hypercalcemia, now recognized in certain autoimmune disorders in which inactivating antibodies against the receptor imitate FHH. Elevated PTH and calcium levels are effectively lowered by the glucocorticoids. In all the preceding situations, the hypocalcemic effect develops over several days, and the usual glucocorticoid dosage is 40–100 mg prednisone (or its equivalent) daily in four divided doses. The side effects of chronic glucocorticoid therapy may be acceptable in some circumstances.

Dialysis is often the treatment of choice for severe hypercalcemia complicated by renal failure, which is difficult to manage medically. Peritoneal dialysis with calcium-free dialysis fluid can remove 5–12.5 mmol (200–500 mg) of calcium in 24–48 h and lower the serum calcium concentration by 0.7–3 mmol/L (3–12 mg/dL). Large quantities of phosphate are lost during dialysis, and serum inorganic phosphate concentration usually falls, potentially aggravating hypercalcemia. Therefore, the serum inorganic phosphate concentration