Leading Article

The management of severe hypercalcaemia

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Abnormalities of extracellular fluid (ECF) calcium concentration may lead to marked changes in a variety of cellular and organ functions. These include plasma membrane excitability, with consequent changes in neuromuscular, cardiac, endocrine and exocrine functions, transport function of epithelia and bone metabolism. ECF calcium concentration depends on the balance between calcium entry from gut and bone, and its egress via the kidneys and to bone. The bidirectional movement of calcium in and out of bone is coupled and usually nearly equal, resulting in a net flux that in health is close to zero. These processes are under the control of the calcium regulating hormones, amongst which parathyroid hormone and 1,25-dihydroxyvitamin D, the active hormonal form of vitamin D, are dominant. Elevation of plasma calcium concentration reflects imbalance of these processes (see Table I).

Effective management of severe acute hypercalcaemia is of paramount importance because although many of these patients may have advanced malignant disease, this is by no means always the case (see the report by Keeling *et al.*¹) and the penalties for failing to identify and treat severe hypercalcaemia may be grave. Such patients may present with polyuria, polydipsia, vomiting, constipation, salt and water depletion, renal impairment, mental changes and coma. In severe cases treatment must be initiated immediately, with the search for underlying cause(s) proceeding in parallel. Management should be directed towards correction or amelioration of the hypercalcaemia itself, the treatment of complications of the hypercalcaemia, and finally attention should be given to the underlying cause of the hypercalcaemia and its correction.

The deleterious effect of hypercalcaemia on renal function is of particular importance as this in itself may exacerbate the problem. Hypercalcaemia reduces both glomerular filtration rate and renal tubular reabsorption of water. Urinary concentrating ability is, therefore, impaired at a time when the patient may

already be saline depleted due to vomiting, and thus additional losses occur as a result of the hypercalcaemia-induced polyuria. In turn, salt and water depletion further lowers the glomerular filtration rate, decreasing urinary calcium excretion and exacerbating the hypercalcaemia. Successful treatment depends on halting this downward spiral which, if untreated, will progress at an alarming rate.

Immediate therapy

The level of urgency will be dictated by both the clinical state of the patient and the plasma calcium concentration. In general, levels of less than 3.0 mmol/l may be regarded as non-urgent, 3.0–3.5 mmol/l as moderately urgent and when calcium exceeds 3.5 mmol/l treatment should start immediately. However, because patients differ greatly in their response to hypercalcaemia, the decision as to when to treat and how to treat should always take into account the severity of coexisting complications. Most patients with severe hypercalcaemia are profoundly salt and water depleted, often with renal impairment. The immediate objective of treatment is, therefore, the correction of the deficit by means of physiological saline (0.9% NaCl) infusion. Large volumes may be needed and if clinical assessment of the patient's volume status is in any way insecure, monitoring by means of central venous pressure measurement is advisable. The aim is to achieve a urine output of 3000–5000 ml/24 h. Once the volume deficit has been corrected, the addition of a loop diuretic such as frusemide given at doses of 40–80 mg i.v. every 2–4 hours will increase further the urinary calcium excretion, provided that the saline infusion rate is sufficient to keep the patient volume expanded.

Intravenous sodium phosphate infused at a rate of 10 mmol/h for up to 10 hours is undoubtedly highly effective, but its side effects have made its use controversial. It works by increasing the calcium phosphate product, thereby encouraging the precipitation of calcium salts in soft tissues and may increase the movement of calcium into bone. Although these

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Table I Mechanisms of hypercalcaemia

<i>Cause of hypercalcaemia</i>	<i>Bone resorption</i>	<i>Intestinal absorption</i>	<i>Tubular reabsorption</i>
Hyperparathyroidism	↑	↑	↑
Cancer -non metastatic	↑	N or ↑	↑
-metastatic	↑	↓	N or ↑
Granulomatous diseases	↑	↑	variable
Hyperabsorption (milk alkali)	N	↑	↓
Vitamin D intoxication	↑	↑	variable

effects are undesirable, the administration of intravenous phosphate may be justified if hypercalcaemia appears life-threatening, provided that plasma phosphate is normal or low and renal function is good. A much safer and equally effective alternative is emergency dialysis using a calcium-free dialysate. Either peritoneal dialysis or haemodialysis may be employed whilst waiting for supplementary measures to work.

Short- to medium-term therapy

The establishment of a forced saline diuresis will usually improve the patient's general state and reduce plasma calcium concentration. However, it is of itself rarely able to normalize plasma calcium and is, in addition, inconvenient, and in the elderly or those with heart disease, may be dangerous. The benefits of dialysis are short lived and therefore additional measures are needed and should be introduced at an early stage on account of their delayed onset of action.

Calcitonin reduces calcium efflux from bone by inhibiting osteoclastic resorption. It is safe and can be given as an intravenous infusion or subcutaneously at a dose of up to 8 IU/kg 12 hourly. Its hypocalcaemic effects take several hours to start and unfortunately often wear off after 6–10 days. Osteoclastic bone

resorption may also be reduced by the cytotoxic drug mithramycin. Although its effects generally take 3–8 days to develop, mithramycin is an extremely effective hypocalcaemic drug and if used with care its hepatic, renal and marrow toxicity may be minimized. It is usually given as a single intravenous infusion at a dose of 25 µg/kg body weight, and repeated as necessary provided that marrow toxicity does not appear and with due note of its delayed onset of action.

Corticosteroids are frequently given to hypercalcaemic patients. However, in hyperparathyroid disorders they are usually totally ineffective and their utility in hypercalcaemia of malignancy is unreliable. Corticosteroids are most likely to be of value in conditions such as myeloma and lymphoma, in which inhibition of tumour-related osteoclast activating factors may be important,² and in vitamin D-mediated hypercalcaemia. The majority of patients with sarcoidosis or vitamin D intoxication will show a complete response to prednisolone given at a dose of 30 mg/day with subsequent tapering as dictated by the plasma calcium concentration. Inhibition of prostaglandin synthesis (aspirin and non-steroidal anti-inflammatory agents) is often tried, usually to no avail, but occasionally with success.³ This type of response probably reflects accelerated production of bone resorbing prostaglandins by certain types of tumour.

Medium- to long-term therapy

At the moment, the extended management of these patients is unsatisfactory, and if the underlying cause is not amenable to definitive correction, may depend on intermittent doses of mithramycin often with corticosteroids. Provided that hyperphosphataemia does not supervene, oral phosphate may be helpful, although diarrhoea often prevents the use of effective doses.

Future prospects

Diphosphonates are pyrophosphate analogues that bind to hydroxyapatite and inhibit osteoclastic bone resorption. At present the only one generally available in the UK is etidronate disodium in its oral formulation. This agent may be of some benefit in the medium to long-term management of certain hypercalcaemic patients but suffers from low and unpredictable bioavailability when given by mouth and a tendency to inhibit bone formation, leading to osteomalacia. Etidronate disodium is more effective when given intravenously,⁴ but unfortunately this preparation is not generally available. However, new diphosphonates are currently undergoing intensive investigation. Of these, amino-hydroxypropylidene diphosphonate (APD) and clodronate have been extremely effective in

both the short and long term management of severe hypercalcaemia, are well tolerated and show no signs of impairing bone mineralization at the doses used.^{5,6} Looking further ahead, it is likely that analogues of parathyroid hormone that antagonize its action will become available and should be of value in the emergency management of severe parathyroid dependent hypercalcaemia as well as in the long term management of patients with hyperparathyroid disorders in whom surgery may be inappropriate. In addition, the identification of bone resorbing lymphokines operating in osteolytic metastatic disease and possibly also in humorally mediated hypercalcaemia may lead to the development of further specific antagonists.

In conclusion, the current state of the management of severe hypercalcaemia is unsatisfactory, although the difficulties can be minimized by a logical approach to the problem. The emergency treatment of severe hypercalcaemia is generally effective, but may be hazardous or technically difficult, and the medium to long term management is hampered by the lack of potent and well tolerated agents to inhibit bone resorption. The anticipated arrival of the new diphosphonates will be an important advance and should improve the lot of both hypercalcaemic patients and their doctors.

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