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Treatment of hypercalcaemia associated with malignancy

Hypercalcaemia is found in about 5% of patients in hospital with malignant disease, though the exact prevalence varies with the frequency of estimation of serum concentrations of calcium and the site of the primary tumour.[1] Only occasionally is the hypercalcaemia life threatening, but commonly it causes symptoms. The symptoms are, however, non-specific —nausea, vomiting, anorexia, weakness, constipation, and mental changes—so that they may be thought to be due to the underlying malignant disease or to be side effects of treatment with cytotoxic drugs or radiotherapy.

If the serum calcium concentration is raised these symptoms may be relieved by treating the hypercalcaemia. Such treatment is not given as often as it should be: in one series of 219 hospital patients with hypercalcaemia associated with malignancy less than a fifth received any treatment which may have lowered their serum calcium concentrations, and of the 45 patients with concentrations greater than 3·5 mmol/l (greater than 14 mg/100 ml; the group more than likely to have symptoms) only 19 received any treatment designed to lower calcium and only nine patients received intravenous fluids.[1]

The hypercalcaemia of malignancy is usually due to increased bone resorption exceeding the kidney's capacity to excrete calcium; hence the serum calcium concentration rises —a "throughput" hypercalcaemia.[2] Dehydration may make the hypercalcaemia worse. Increased bone resorption is most commonly due to local osteolysis by the tumour invading the bone, but a humoral hypercalcaemia may also occur, due to secretion by a tumour remote from bone of circulating factors which increase bone resorption. The mainstays of the treatment of an acute hypercalcaemic crisis are rehydration[3] and forced saline diuresis with intravenous saline and frusemide[4] to optimise and increase the renal excretion of calcium. This topic has recently been reviewed in the *BMJ* and will not be considered further.[5]

Despite logical long term treatment intended to eliminate the underlying tumour symptomatic hypercalcaemia often persists even though the patient can take treatment by mouth. A high oral intake of fluid should be encouraged to maintain optimum renal excretion of calcium. Limiting the intake of calcium has no place in the management of patients with hypercalcaemia of malignancy; they have a low absorption of calcium.[6] The correct therapeutic approach is to use agents which inhibit calcium resorption from bone.

The ideal drug would be one which reliably decreases serum concentrations of calcium and can be taken by mouth—for treatment may have to continue for several weeks or months. There is no universally effective and specific calcium lowering agent. Few comparative controlled trials of the drugs have been carried out, and their evaluation is complicated because patients are often taking different anticancer treatments and usually have different primary tumours. Glucocorticoids are probably the most widely used agents, yet they are effective in fewer than half of the cases.[7 8] They work by inhibiting osteoclastic bone resorption[9] and may be effective in myeloma by interfering with the action of osteoclastic activating factors.[10] Unfortunately, it is impossible to predict the patients in whom steroids will be effective. There is usually a delay of four to five days or more before any substantial response is seen, and side effects are common.

Calcitonin is a potent inhibitor of osteoclastic bone resorption and has a direct calciuric effect on the kidney.[11] Although it has a rapid action, has no serious side effects, and can be given safely in patients with renal and cardiac insufficiency, calcitonin has proved disappointing: the response is commonly variable and incomplete, with a mean fall in the calcium concentration of 0·6 mmol/l (2·4 mg/100 ml) at 24 hours irrespective of the degree of hypercalcaemia.[11] The effect is often transient, wearing off after two to three days despite continuing administration—which has the disadvantage of having to be parenteral. Recently a combination of calcitonin and steroids has been shown to be more effective than either agent alone—indeed, steroids may prevent the escape from calcitonin treatment[12]—but no study has assessed the effectiveness of this combination for longer than four days.

Prostaglandins may play a part in the pathogenesis of the hypercalcaemia produced by some tumours, and indomethacin and other prostaglandin synthetase inhibitors have been advocated as treatment. Even when plasma prostaglandin assays are used, however, they cannot predict which patients will respond to these drugs,[13] which are effective only in occasional patients and cannot be recommended as clinically useful.[8 13]

Mithramycin is a potent cytotoxic antibiotic which inhibits osteoclastic bone resorption.[14] It is the only available uniformly effective drug for treating hypercalcaemia,[14 16] but it has to be given intravenously and is usually used only in severe hypercalcaemia. A single dose of 25 μg/kg body weight is recommended, and this will lower the serum concentration of calcium into the normal range in 24-48 hours. Repeated doses carry a risk of marrow suppression or of damage to the kidneys or liver. The duration of effect is unpredictable: in some patients the response lasts several days and in others several weeks.

Neutral phosphate lowers serum calcium concentrations by several mechanisms, including inhibition of bone resorption and promotion of the deposition of calcium in the soft tissues.[17] Phosphate is the most effective available agent that can be given by mouth for hypercalcaemia of malignancy, producing an effect in four fifths of patients.[8 18] In about a quarter of patients, however, gastrointestinal side effects such as nausea and diarrhoea may lead to withdrawal of the drug.[8] The main disadvantage of long term treatment with oral phosphate is

extraskeletal calcification in kidneys and other major organs.

Recently the diphosphonates, which are potent inhibitors of osteoclastic bone resorption, have been used to treat hypercalcaemia associated with malignancy. Three compounds have been assessed: ethane hydroxydiphosphonate (sodium etidronate); aminohydroxypropylidene diphosphonate; and dichloromethylene diphosphonate (clodronate disodium).

Given intravenously sodium etidronate was effective in reducing serum concentrations of calcium in all 10 patients in a recent study; there was a mean delay of two days before it began to be effective, but by 10 days the serum calcium concentration was normal in eight patients.[19] Sodium etidronate for parenteral use is not generally available and oral sodium etidronate, the only diphosphonate available in Britain, is much less effective in reducing serum concentrations of calcium, doing so in fewer than one fifth of patients.[8] Aminohydroxypropylidene diphosphonate given intravenously restored serum calcium concentrations to normal in 29 out of 30 patients with tumour induced hypercalcaemia[20]; given orally it was effective in all seven patients with myeloma in whom it was used but only four of six patients with other malignancies responded.[21]

Clodronate disodium is effective when given intravenously, the calcium concentration being lowered in all 21 patients in one study, though only three quarters of them had their calcium concentrations lowered into the normal range at 10 days.[19] In another series 11 out of 12 patients responded.[22] Given orally, clodronate disodium reduced calcium in four of five patients, though in two the effect was only transient[23] and in another series calcium concentrations were reduced to normal in at least nine of 12 patients.[24]

Though diphosphonates hold great promise, they are not invariably effective and more experience is needed. Unfortunately neither aminohydroxypropylidene diphosphonate nor clodronate disodium is generally available in oral or parenteral form and further work is being held up because of questions of toxicity in either animal or human studies. In the future orally effective diphosphonate analogues may become generally available, but until then we have to continue trying empirically to select a drug which is effective in controlling hypercalcaemia in and is tolerated by each individual patient. A recent small randomised study showed that the most effective agents were oral phosphate and mithramycin, glucocorticoids and oral sodium etidronate being of only limited effectiveness and indomethacin ineffective in most patients.[8]

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Living with hydrocephalus

Hydrocephalus has many causes. Some of these are directly curable—for example, benign tumours may be excised and cysts drained internally. But in most cases of obstructive hydrocephalus the choice is between waiting for spontaneous arrest or inserting a shunt to divert cerebrospinal fluid extracranially. Neither solution is ideal. Patients with arrested hydrocephalus have varying degrees of ventricular dilatation and are dependent on an abnormal circulation of cerebrospinal fluid which is precarious at times. Those patients with shunts depend on an implanted prosthesis, which may fail.

Reliable techniques for shunting cerebrospinal fluid, either into the heart or into the peritoneal cavity, have been available for 25 years. Ventriculoatrial shunts were the first to come into general use, and for some surgeons these remain the treatment of choice for obstructive hydrocephalus.[1] The chief drawback of this technique is the need to lengthen the cardiac tube during growth in childhood. Many surgeons now prefer ventriculoperitoneal shunts, which are simpler to insert and do not need to be lengthened so often.[2] Lumbar subarachnoid peritoneal shunts are technically more difficult to establish and have limited application, although some centres favour their use for communicating hydrocephalus.[2] Many shunt operations are performed in all parts of the world. In the United States more than 150 000 shunt units are marketed each year (M Libera and R Schulte, personal communications). There are also manufacturers in several developing countries, and in India the inexpensive Upadhyaya shunt has given good service.[3]