HYPERCALCAEMIA
Supporting information

This guideline has been prepared with reference to the following:

NHS Evidence Clinical Knowledge Summaries. Hypercalcaemia. 2024. NICE

http://cks.nice.org.uk/hypercalcaemia

In severe hypercalcaemia (Ca>3.4 mmol/l), rehydration with sodium chloride 0.9% at the rate of 3-4 l/24 hr depending on severity, is appropriate?
Hypercalcaemia is associated with volume depletion (as a result of polyuria) and a tendency towards metabolic acidosis (Weatherall, 1996i). Volume re-expansion corrects these underlying pathologies and is regarded as a necessary first step in the management of acute cases (Pecherstorfer, 2003). Rehydration alone rarely normalises the serum calcium concentration, however, as the effects are generally mild and transient (Body, 2000). The Oxford Textbook of Medicine states “patients may require 5 to 10 litres of 0.9% sodium chloride over a 24- to 48-h period”, without quoting any source of reference (Warrell, 2010).

Body JJ. Current and future directions in medical therapy: hypercalcemia. Cancer 2000;88:3054-8

Pecherstorfer M, Brenner K, Zojer N. Current management strategies for hypercalcemia. Treat Endocrinol 2003;2:273-92

Warrell DA, Cox TM & Firth JD eds. Oxford Textbook of medicine, 5th ed. Oxford: OUP, 2010

Evidence Level: V

IV furosemide 20-40 mg over 12 hours should be given in the event of fluid overload?
Furosemide is no longer recommended owing to risks of potential excessive diuresis and lack of beneficial supportive data (Maier, 2015).

Maier J, & Levine S. Hypercalcemia in the intensive care unit: a review of pathophysiology, diagnosis, and modern therapy. J Intensive Care Med 2015; 30:235-252

Evidence Level: V

Large doses (160 mg) of furosemide are inappropriate?
Furosemide is no longer recommended owing to risks of potential excessive diuresis and lack of beneficial supportive data (Maier, 2015).

Maier J, & Levine S. Hypercalcemia in the intensive care unit: a review of pathophysiology, diagnosis, and modern therapy. J Intensive Care Med 2015; 30:235-252

Evidence Level: V

If Ca>3.4 or Ca>3.0 mmol/l with symptoms, disodium pamidronate 60 mg in 1l sodium chloride 0.9% IV over 4 hr, followed by a return to sodium chloride 0.9%, will return Ca to normal within 7 days?
Bisphosphonates inhibit osteoclastic bone resorption and are now regarded as the standard treatment for cancer hypercalcaemia, normalising calcium levels in 70% - >90% of cases (Saunders). Bisphosphonates do not, however, affect survival rates (Ross, 2004). Etidronate, clodronate and pamidronate are licensed for use in the UK (Ralston, 2004). Two double blind randomised controlled trials (Vinholes, 1997; Purohit, 1995) have found pamidronate superior to clodronate, the former having a median duration of action of 28 days compared to 14 days with clodronate. In another double blind RCT comparing different doses of pamidronate (Nussbaum, 1993), a single-dose infusion of 60 *or* 90 mg of pamidronate normalised serum calcium in 61% and 100% of patients respectively, within 7 days. A study of 25 patients randomised to receive pamidronate either by fast (4 hour) or slow (24 hour) infusion (Sawyer, 1990) found that the fast infusion led to an earlier reduction in calcium.
It has been suggested (Body, 2004) that the newer bisphosphonates ibandronate and zoledronate may be more effective than pamidronate whilst being more convenient to administer. A 2022 review identified two RCTs which showed that zoledronic acid has superior efficacy to pamidronate for treating hypercalcemia of malignancy (Walker, 2022). Pooled data from the two RCTs in patients with

hypercalcemia of malignancy (n = 287) demonstrated that 1 dose of 4 mg of zoledronic acid reduced serum calcium to 10.8 mg/dL or lower by day 10 in 88.4% of patients, compared with 86.7% with 8 mg of zoledronic acid and 69.7% with 90 mg of pamidronate. Zoledronic acid achieved reduction in calcium for longer (30 and 40 days for 4-mg and 8-mg doses, respectively, compared with 17 days for pamidronate). The reviewers also found that there was no evidence to suggest that pamidronate does not have a lower risk of nephrotoxicity than zoledronic acid.

Body JJ. Hypercalcemia of malignancy. Semin Nephrol 2004;24:48-54

Nussbaum SR, Younger J, Vandepol CJ, et al. Single-dose intravenous therapy with pamidronate for the treatment of hypercalcemia of malignancy: comparison of 30-, 60-, and 90-mg dosages. Am J Med 1993;95:297-304

Purohit OP, Radstone CR, Anthony C, et al. A randomised double-blind comparison of intravenous pamidronate and clodronate in the hypercalcaemia of malignancy. Br J Cancer 1995;72:1289-93
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2033943/pdf/brjcancer00045-0229.pdf

Ralston SH, Coleman R, Fraser WD, et al. Medical management of hypercalcemia. Calcif Tissue Int 2004;74:1-11
http://www.researchgate.net/profile/William_Fraser/publication/9067613_Medical_management_of_hypercalcemia/links/09e4150f3d6f05abaf000000.pdf

Ross JR, Saunders Y, Edmonds PM, et al. A systematic review of the role of bisphosphonates in metastatic disease. Health Technol Assess 2004;8:1-176
http://www.journalslibrary.nihr.ac.uk/__data/assets/pdf_file/0008/64997/FullReport-hta8040.pdf

Saunders Y, Ross JR, Broadley KE. Systematic review of bisphosphonates for hypercalcaemia of malignancy. Palliat Med 2004;18:418-31

Sawyer N, Newstead C, Drummond A et al Fast (4-h) or slow (24-h) infusions of pamidronate disodium (aminohydroxypropylidene diphosphonate (APD)) as single shot treatment of hypercalcaemia. Bone & Mineral 1990;9:121-8

Vinholes J, Guo CY, Purohit OP, et al. Evaluation of new bone resorption markers in a randomized comparison of pamidronate or clodronate for hypercalcemia of malignancy. J Clin Oncol 1997;15:131-8

Walker MD & Shane E. Hypercalcemia: A Review. JAMA. 2022;328:1624-36

Evidence Level: I

Calcitonin is only useful during the first 24 hours if symptoms are deemed to be life-threatening?

Calcitonin leads to rapid though modest (0.5 mmol/l) inhibition of osteoclast-induced bone resorption, but the effect is short-lived (2-3 days at most) (Watters, 1996). Bisphosphonates are used in conjunction with calcitonin to compensate for this (Chisholm, 1996; Ralston, 2004), as pamidronate takes effect 24-48 hours post-infusion, reaching a peak at 5-6 days. In a small series of 8 patients treated with 100 unit/8 hrly (Ralston, 1986), serum calcium concentration fell from a median of 3.6 mmol/l to a median of 2.7 mmol/l in the first 24 hours. Calcitonin thus takes effect rapidly (Sekine, 1998) and is indicated in emergency situations.

Chisholm MA, Mulloy AL, Taylor AT. Acute management of cancer-related hypercalcemia. Ann Pharmacother 1996;30:507-13

Ralston SH, Coleman R, Fraser WD, et al. Medical management of hypercalcemia. Calcif Tissue Int 2004;74:1-11
http://www.researchgate.net/profile/William_Fraser/publication/9067613_Medical_management_of_hypercalcemia/links/09e4150f3d6f05abaf000000.pdf

Ralston SH, Alzaid AA, Gardner MD, et al. Treatment of cancer associated hypercalcaemia with combined aminohydroxypropylidene diphosphonate and calcitonin.. BMJ 1986;292:1549-50
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1340556/pdf/bmjcred00238-0009.pdf

Sekine M, Takami H Combination of calcitonin and pamidronate for emergency treatment of malignant hypercalcemia. Oncol Rep 1998;5:197-9

Watters J, Gerrard G, Dodwell D. The management of malignant hypercalcaemia. Drugs 1996;52:837-48

Evidence Level: V

Is intravenous administration of calcitonin superior to intramuscular for life-threatening disease?

Only one comparative study of IV and IM calcitonin has been identified, and that is in the context of hypercalcaemia caused by primary hyperparathyroidism (Stone, 1992).This randomised open parallel study in 20 patients found that a dose of 100 U/d was more effective in the IV than the IM group, both in peak (0.31 +/- 0.035 mmol/L vs 0.13 +/- 0.034 mmol/L) and overall (0.073 +/- 0.016 mmol/L vs 0.018 +/- 0.016 mmol/L) hypocalcaemic response.

Stone MD, Marshall DH, Hosking DJ, et al. Comparison of low-dose intramuscular and intravenous salcatonin in the treatment of primary hyperparathyroidism. Bone 1992;13:265-71

Evidence Level: III (single small RCT)

If the hypercalcaemia is known to have been caused by granulomatous disease or calcitriol excess, appropriate treatment is hydrocortisone 100 mg IV 8 hrly (or prednisolone 40 mg orally daily)?

Granulomatous disease (e.g. sarcoidosis) can cause hypercalcaemia due to over-production of calcitriol by activated macrophages trapped in pulmonary alveoli and granulomatous inflammation (Sharma, 1996). This may be corrected rapidly as demonstrated in a series of 6 patients with sarcoidosis treated with 40 mg per day (or less) of oral prednisolone (Sandler, 1984). Corticosteroids are regarded as first-line treatment in these cases, despite the lack of clinical trials demonstrating improved long-term outcome (Newman, 1997), and a number of case reports (Bosch, 1998; Sharma, 1996) show them to be effective in both sarcoidosis and Crohn's disease. Hypercalcaemia may also result from an unexplained increase in serum calcitriol (Evron, 1997) which rapidly responded to oral prednisolone in the 3 patients presented. Daily low-dose prednisolone was necessary in 2 of these patients in order to maintain normal calcium levels.

Bosch X. Hypercalcemia due to endogenous overproduction of 1,25-dihydroxyvitamin D in Crohn's disease. Gastroenterology 1998;114:1061-5

Evron E, Goland S, von der Walde J, et al. Idiopathic calcitriol-induced hypercalcemia. A new disease entity? Arch Intern Med 1997;157:2142-5

Newman LS, Rose CS, Maier LA. Sarcoidosis. N Engl J Med 1997;336:1224-34

Sandler LM, Winearls CG, Fraher LJ, et al. Studies of the hypercalcaemia of sarcoidosis: effect of steroids and exogenous vitamin d3 on the circulating concentrations of 1,25-dihydroxy vitamin d3. Quart J Med 1984;53:165-80

Sharma OP. Vitamin D, calcium, and sarcoidosis. Chest 1996;109:535-9
http://journal.publications.chestnet.org/data/Journals/CHEST/21727/535.pdf

Evidence Level: V

Mithramycin, gallium nitrate or phosphate are all toxic in hypercalcaemic states and should not be used?

Mithramycin (plicamycin) causes hepatotoxicity in approximately 20% of patients (Green, 1984) and other possible side effects are nephrotoxicity and thrombocytopaenia (Slavik, 1975). Gallium nitrate also causes nephrotoxicity, although generally at higher dosing levels than those used for hypercalcaemia. In a randomised, double-blind comparison to calcitonin (Warrell, 1988), a dose calculated to 200mg/m2 body surface caused renal failure in 8% of 164 patients. In 16 patients given a dose of 500mg/m2 (Krakoff, 1979), 3 demonstrated nephrotoxicity, but 6 of 8 suffered adverse effects at a dose of 750mg/m2. Randomised studies have shown gallium nitrate to be more effective than pamidronate, etidronate, and calcitonin in terms of response rate and duration of normocalcaemia (Leyland-Jones, 2003). Although IV phosphate reduces serum calcium rapidly, its use can result in severe hypotension (Shackney, 1967), hyperparathyroid crisis (Vernava, 1987) or soft tissue calcification (Carey, 1968).

Carey RW, Schmitt GW, Kopald HH, et al. Massive extraskeletal calcification during phosphate treatment of hypercalcemia. Arch Intern Med 1968;122:150-5

Green L, Donehower RC. Hepatic toxicity of low doses of mithramycin in hypercalcemia. Cancer Treat Rep 1984;68:1379-81

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Krakoff IH, Newman RA, Goldberg RS. Clinical toxicologic and pharmacologic studies of gallium nitrate. Cancer 1979;44:1722-7

Leyland-Jones B. Treatment of cancer-related hypercalcemia: the role of gallium nitrate. Semin Oncol 2003;30 (Suppl 5):13-9

Shackney S, Hasson J. Precipitous fall in serum calcium, hypotension, and acute renal failure after intravenous phosphate therapy for hypercalcemia: report of two cases. Ann Intern Med 1967;66:906-16

Slavik M, Carter SK. Chromomycin A3, mithramycin, and olivomycin: antitumor antibiotics of related structure. Adv Pharmacol Chemother 1975;12:1-30

Vernava AM, O'Neal LW, Palermo V. Lethal hyperparathyroid crisis: hazards of phosphate administration. Surgery 1987;102:941-8

Warrell RP, Israel R, Frisone M, et al. Gallium nitrate for acute treatment of cancer-related hypercalcemia: a randomised, double-blind comparison to calcitonin. Ann Intern Med 1988;108:669-74

Evidence Level: V

Haemodialysis can assist management if renal function is poor?

Calcium-free haemodialysis is effective where advanced renal impairment precludes the use of large volumes of intravenous fluids. (Camus, 1996; Koo, 1996; Kaiser, 1989; Strauch, 1976). In a series of 33 patients (Camus, 1996), the mean decline of calcium during haemodialysis was 1.71 (+ or – 0.54) mmol/l over a 4 hour session. Calcium rebound after 24 hours was, however, seen in all cases, and 43% of patients suffered hypotension, arrhythmia, or both. In an earlier series of 4 patients (Kaiser, 1989), the mean calcium decline was 1.25 mmol/l with only 1 case of calcium rebound and no arrhythmia. Another series of 6 patients (Koo, 1996) showed a mean decline of 0.76 mmol/l after 3 hours, with no adverse effects. Although its effects are short-lived, haemodialysis can rapidly lower calcium levels when other therapy has been ineffective or is contraindicated (Strauch, 1976).

Camus C, Charasse C, Jouannie-Montier I, et al. Calcium free hemodialysis: experience in the treatment of 33 patients with severe hypercalcemia. Intensive Care Med 1996;22:116-21

Kaiser W, Biesenbach G, Kramar R et al. Calcium free hemodialysis: an effective therapy in hypercalcemic crisis – report of 4 cases. Intensive Care Med 1989;15:471-4

Koo WS, Jeon DS, Ahn SJ, et al. Calcium-free hemodialysis for the management of hypercalcemia. Nephron, 1996;72:424-8

Strauch BS, Ball MF. Hemodialysis in the treatment of severe hypercalcemia. JAMA 1976;235:1347-8

Evidence Level: V

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