QUESTION 44

A 47yo woman with advanced cancer is admitted at 3am with a four-day history of weakness, nausea, vomiting and constipation. Her serum calcium is 3.8mmol/L [2.2-2.6] and albumin is 32g/L [31-44].

The most appropriate initial step in her management is:

A. Intravenous rehydration
B. Diuretics
C. Steroids
D. Bisphosphonates
E. Calcitonin

CAUSES OF HYPERCALCEMIA

Increased Bone Resorption

- Primary and secondary hyperparathyroidism
- Malignancy
- Hyperthyroidism
- Other – Paget’s disease, oestrogens or anti-oestrogens in metastatic breast cancer, hypervitaminosis A, retinoic acid

Increased Intestinal Calcium Absorption

- Increased calcium intake
  - Renal failure (often with vitamin D supplementation)
  - Milk-alkali syndrome
- Hypervitaminosis D
  - Enhanced intake of vitamin D or metabolites
  - Chronic granulomatous disease
  - Malignant lymphoma
  - Acromegaly

Miscellaneous

- Chronic lithium intake
- Thiazide diuretics
- Pheochromocytoma
- Adrenal insufficiency
- Rhabdomyolysis and acute renal failure
- Theophylline toxicity
- Familial hypocalciuric hypercalcaemia
- Immobilisation
- TPN
Malignancy and hyperparathyroidism are most common causes.

In sarcoid and other granulomatous disease hypercalcaemia is due to enhanced intestinal absorption due to increased endogenous calcitriol production.

Calcium elevation in hyperparathyroidism is usually mild so treatment is aimed at correcting the hyperparathyroidism.

Hypercalcaemia in patients with familial hypocalciuric hypercalcaemia is also mild and produces few symptoms.

**CLINICAL MANIFESTATIONS**

- Central nervous system dysfunction
- Muscle weakness
- Constipation
- Increased gastrin secretion
- Pancreatitis
- Acute and chronic renal insufficiency
- Nephrogenic diabetes insipidus
- Distal renal tubular acidosis
- Nephrolithiasis
- Shortening of QT interval
- Corneal calcium deposition (band keratopathy)

**TREATMENT**

There are 5 approaches:

1) Increase urinary calcium excretion
   - Isotonic saline with or without a loop diuretic

2) Diminished bone resorption
   - Calcitonin
   - Bisphosphonates
   - Gallium nitrate
   - Plicamycin (rarely used)

3) Decreased intestinal calcium absorption
   - Corticosteroids in hypervitaminosis D due to chronic granulomatous disease or increased intake and in haematological malignancies
   - Oral phosphate in chronic hypercalcaemia

4) Chelation of ionised calcium
   - EDTA or intravenous phosphate (rarely used)
   - Oral phosphate in chronic hypercalcaemia

5) Dialysis

Treatment of hypercalcaemia usually begins with normal saline administration to produce volume expansion and increase urinary calcium excretion. It rarely normalises the calcium however (unless hypercalcaemia mild).
Concurrent treatment with bisphosphonates +/- calcitonin is usually needed to treat underlying cause (most commonly malignancy).

**Increase Urinary Calcium Excretion**

- Filtered calcium is passively reabsorbed in the proximal tubule and loop of Henle
- Actively reabsorbed in the distal tubule under the influence of PTH
- Can inhibit passive reabsorption and increase excretion by increasing fluid volume with IV normal saline
- Many patients are dehydrated at presentation due to hypercalcaemic-induced salt wasting
- Aim to maintain UO 100-150mL/hr after rehydration
- Loop diuretic can be used if fluid overload develops – this also increases calcium excretion by inhibiting calcium reabsorption in the loop of Henle

**Inhibit Bone Resorption**

- Should be concurrent with volume repletion
- Options are calcitonin, bisphosphonates and gallium nitrate
- Bisphosphonates are usually used
- They interfere with the metabolic activity of osteoclasts and thus inhibit calcium release from bone
- More potent than calcitonin
- Examples are pamidronate and zoledronic acid
- Maximum effect in 2-4 days
- Gallium nitrate carries risk of nephrotoxicity

**Decreased Intestinal Absorption**

- Increased absorption is usually associated with excess administration of vitamin D or with overproduction of calcitriol (eg: sarcoid)
- Glucocorticoids decrease endogenous calcitriol production
- Oral phosphate complexes with calcium in the gut and reduces intestinal absorption

**Chelation of Ionised Calcium**

- EDTA or IV phosphate but now rarely used due to toxicity

**Dialysis**

- Last resort
- May be indicated in severe hypercalcaemia of malignancy and renal impairment or heart failure where fluids cannot be safely administered

**Mild Chronic Hypercalcaemia**

- Risk of nephrocalcinosis and nephrolithiasis
- Oral hydration
- High salt diet
- Glucocorticoids can be considered for lymphoma, granulomatous disease
- Oral phosphate
- No pharmacological treatment is common

**More Severe or Symptomatic Hypercalcaemia**

- i.e. serum calcium > 3.0
- Normal saline
- Bisphosphonate or calcitonin

**Severe Hypercalcaemia**

- Consider haemodialysis if serum calcium >4.5

This patient has severe hypercalcaemia. She will be dehydrated. The first step in the management is to rehydrate with normal saline and then continue fluids to maintain a urine output of 100-150mL/hr.

Bisphosphonates (or calcitonin) will be needed to treat this level of hypercalcaemia but is not the initial step.

Diuretics are only used if the patient becomes overloaded – use a loop diuretic as thiazides can contribute to hypercalcaemia.

Steroids are sometimes used in certain causes of hypercalcaemia, usually due to elevated calcitonin production (granulomatous disease, lymphoma).

Answer is A.