# Hypocalcemia & Hypercalcemia Perioperative Management

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# CALCIUM HOMEOSTASIS

Serum calcium concentrations are normally maintained within the very narrow range that is required for the optimal activity of the many extracellular and intracellular processes calcium regulates.

Calcium in the blood is transported:

- Partly bound to plasma proteins (about 45 percent), notably albumin
- Partly bound to small anions such as phosphate and citrate (about 15 percent)
- Partly in the free or ionized state (about 40 percent)

# Calcium Action

Extracellular calcium ions regulate numerous biological processes, including:

- Intracellular signaling for secretion of many hormones
- Muscle contraction
- The coagulation cascade

It is therefore important that serum ionized calcium concentrations be maintained within a very narrow range, which is achieved by the close interrelationship between serum ionized calcium, PTH, and vitaminD, Calcitonin,…

# CALCIUM HOMEOSTASIS

Although only the ionized calcium is metabolically active (ie, subject to transport into cells) most laboratories report total serum calcium concentrations.

Ionized calcium concentration in the cytoplasm is at least 10000 times lower than in extracellular fluid.

The normal range of ionized calcium is 4.65 to 5.25 mg/dL (1.16 to 1.31 mmol/L)

Concentrations of total calcium in normal serum generally range between 8.5 and 10.5 mg/dL (2.12 to 2.62 mmol/L) and levels below this are considered to be consistent with hypocalcemia.

# Change in total but not ionized calcium

An abnormal total serum calcium concentration in the presence of a normal ionized calcium concentration can occur in patients with :

- Hypoalbuminemia
- Hyperalbuminemia extracellular volume depletion or by fluid movement out of the vascular space due, for example, to a tight tourniqueta
- Multiple myeloma monoclonal myeloma protein binds calcium with high affinity, potentially leading to a marked elevation in the total serum calcium concentration

Pseudohypocalcemia

Pseudohypercalcemia

# Hypoalbuminemia

The serum total calcium concentration falls approximately 0.8 mg/dL for every 1 g/dL reduction in the serum albumin concentration

# Acid-base disturbances

Even in the presence of a normal serum albumin, changes in blood pH can alter the equilibrium constant of the albumin-calcium complex,

- Acidosis reducing the binding
- Alkalosis enhancing binding .( fall in ionized calcium with acute respiratory alkalosis is approximately 0.16 mg/dL (0.04 mmol/L or 0.08 mEq/L) for each 0.1 unit increase in pH)
- Thus, acute respiratory alkalosis, as in the hyperventilation syndrome, can induce symptoms of hypocalcemia, including cramps, paresthesias, tetany, and seizures, although the alkalosis is likely to be of primary importance.

- There is also a significant fall in the ionized calcium concentration in chronic respiratory alkalosis due to ,hypoparathyroidism and to renal resistance to PTH, with resultant hypercalciuria

# Acid-base disturbances

Thus, in critically ill or post-surgical patients, correcting total calcium for albumin is not necessarily accurate because of changes in pH and affinity of calcium binding .

In one study, for example, the use of the formula that corrected the calcium concentration based upon albumin level had a sensitivity of only 5 percent .

Consequently, when major shifts in pH are present, it is most prudent to directly measure the ionized calcium level in order to determine the presence of hypocalcemia

# Chronic metabolic acidosis

- In chronic metabolic acidosis, the increase in ionized calcium due to less albumin binding may not be recognized by measurement of total calcium concentrations.
- The binding of calcium to albumin that is induced by an elevation in extracellular pH may be

  important in patients with severe CKD who often have both hypocalcemia and metabolic acidosis, which will tend to raise the ionized calcium concentration.
- Treatment of the metabolic acidosis with bicarbonate therapy or dialysis can lower the ionized calcium concentration, which may exacerbate preexisting hypocalcemia and precipitate symptoms such as tetany.

# Hypocalcemia in CKD

In patients with reduced GFR who have a low serum bicarbonate and/or a low serum albumin, measuring the ***ionized calcium*** is preferable to measuring the total calcium in order to diagnose hypocalcemia or hypercalcemia.

# CALCIUM HOMEOSTASIS

- Hyperparathyroidism, which increases the ionized calcium
- Hyperphosphatemia, which increases the fraction bound to inorganic anions, decreasing ionized calcium by binding to phosphor

# Hypocalcemia

# Hypocalcemia

- The first step in the evaluation of a hypocalcemic patient without symptom is measurement of the serum albumin concentration for rule out **pseudohypocalcemia**
- A patient who has a serum albumin concentration of 2 g/dL (20 g/L), which is 2 g/dL (20 g/L) below normal, will have a fall in serum total calcium concentration of 1.6 mg/dL

# Hypocalcemia symptoms

# Neurological

- Paraesthesiae
- Chvostek's and Trousseau's signs
- Muscle cramps
- Tetany
- Muscle weakness
- Hyperactive reflexes
- Convulsions

# Respiratory& Cardiovascular

## Respiratory :

- Laryngeal spasm
- Bronchospasm

## Cardiovascular:

- Hypotension
- Impaired contractility
- Bradycardia
- Arrhythmias
- Digitalis insensitivity
- Cardiac arrest
- ECG changes:
- QT and ST prolongation
- T inversion

# Psychiatric

- Anxiety
- Dementia
- Depression
- Irritability
- Psychosis
- Confusion

# Major causes hypocalcemia

## Low PTH (hypoparathyroidism)

**Genetic disorders**

Abnormal parathyroid gland development

Abnormal PTH synthesis

Activating mutations of calcium-sensing receptor (autosomal dominant hypocalcemia or sporadic isolated hypoparathyroidism)

**Post-surgical (thyroidectomy, parathyroidectomy, radical neck dissection)**

**Autoimmune**

Autoimmune polyglandular syndrome (associated with chronic mucocutaneous candidiasis and primary adrenal insufficiency)

Isolated hypoparathyroidism due to activating antibodies to calcium-sensing receptor

**Infiltration of the parathyroid gland (granulomatous, iron overload, metastases)**

**Radiation-induced destruction parathyroid glands**

**Hungry bone syndrome (post parathyroidectomy)**

**HIV infection**

## High PTH (secondary hyperparathyroidism in response to hypocalcemia)

**Vitamin D deficiency or resistance**

Multiple causes

**Parathyroid hormone resistance**

Pseudohypoparathyroidism

Hypomagnesemia

**Renal disease**

**Loss of calcium from the circulation**

Hyperphosphatemia

Tumor lysis

Acute pancreatitis

Osteoblastic metastases

Acute respiratory alkalosis

Sepsis or acute severe illness

## Drugs

Inhibitors of bone resorption (bisphosphonates, calcitonin), especially in vitamin D deficiency

Causes of hypocalcaemia

**Medical**

- Vitamin D deficiency
- Renal insufficiency with impaired 1,25(OH)2D production
- Acute pancreatitis
- Hypoparathyroidism
- Sepsis
- Hypomagnesemia
- Acute Rhabdomyolysis

**Surgical**

- Post-parathyroidectomy
- Hungry bone syndrome after parathyroidectomy

Post-thyroidectomy

- Post-cardiopulmonary bypass

**Iatrogenic**

- Massive blood transfusion
- Infusion of phosphate, citrate or calcium-free albumin
- Radiographic contrast with Calcium chelators
- Inhibitors of bone resorption (bisphosphonates, plicamycin)

# Treatment of hypocalcemia

# Treatment of hypocalcemia

The treatment of hypocalcemia varies with its :

- Severity
- Underlying cause

The severity of symptoms (paresthesias, carpopedal spasm, tetany, seizures) and signs

(Chvostek's or Trousseau's signs, bradycardia, impaired cardiac contractility, and prolongation of the QT interval) depends upon the absolute level of calcium, as well as the rate of decrease

# Calcium gluconate & Calcium chloride

Either 10% calcium gluconate (90 mg of elemental calcium per 10 mL) or 10% calcium chloride (270 mg of elemental calcium per 10 mL) can be used to prepare the infusion solution.

Calcium gluconate is usually preferred because it is less likely to cause tissue necrosis if extravasated.

# Recommend intravenous (IV) calcium for the treatment of hypocalcemia in patients sever symptom

## Intravenous calcium dosing:

- Initially, IV calcium (1 or 2 g of calcium gluconate, equivalent to 90 or 180 mg elemental calcium, in 50 mL of 5% dextrose or normal saline) can be infused over 10 to 20 minutes.
- The calcium should not be given more rapidly, because of the risk of serious cardiac dysfunction, including systolic arrest .
- Patients receiving digoxin should be monitored closely for acute digitalis toxicity, which can develop with calcium infusion

# Maintenance dose

An IV solution containing 1 mg/mL of elemental calcium is prepared by adding 11 g of calcium gluconate (equivalent to 1000 mg elemental calcium) to normal saline or 5% dextrose water to provide a final volume of 1000 mL.

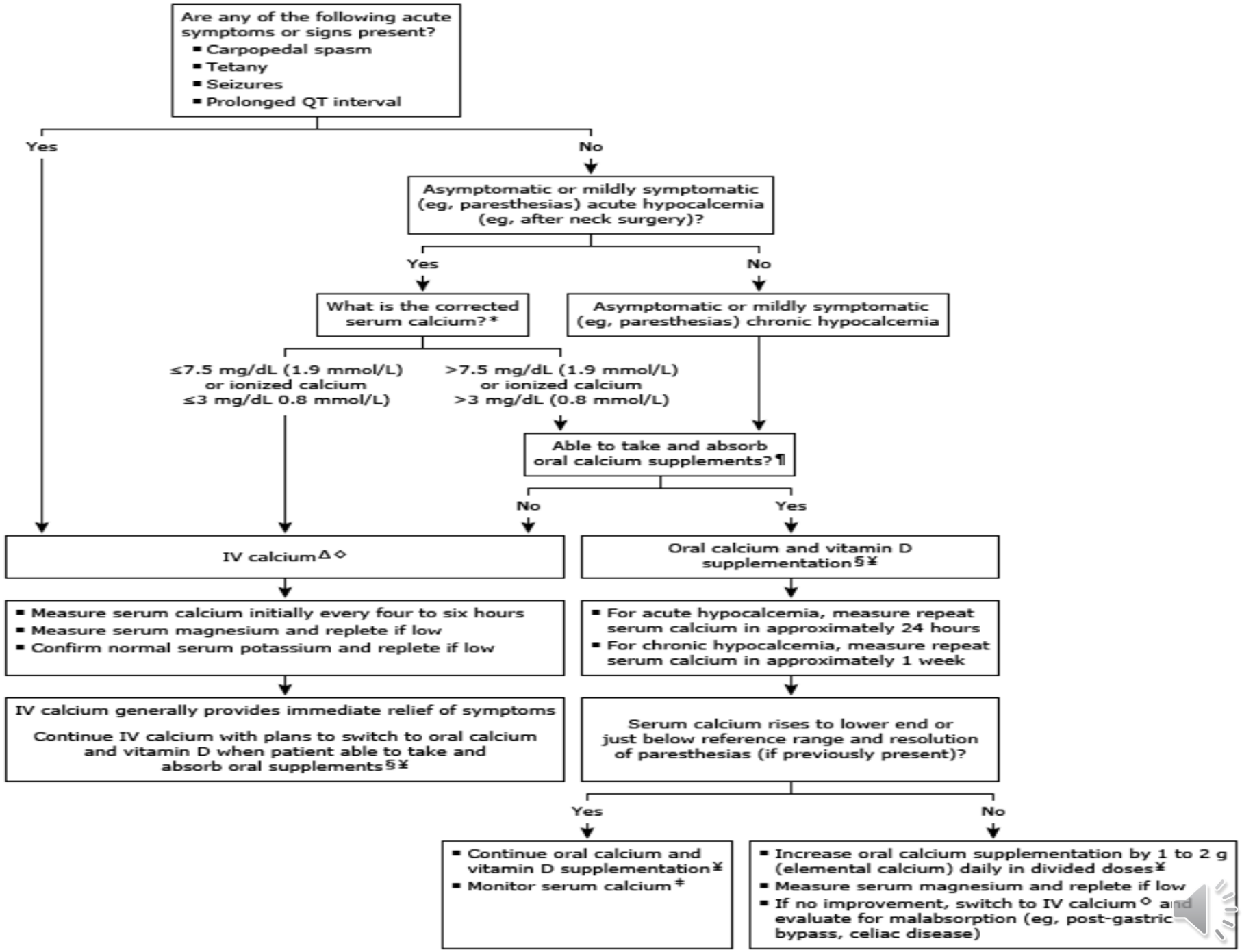
This solution is administered at an initial infusion rate of 50 mL/hour (equivalent to 50 mg elemental/hour).

***IV solution should not contain bicarbonate or phosphate, which can form insoluble calcium salts***

IV calcium should be continued until the patient is receiving an effective regimen of oral calcium and vitaminD.

For patients with hypoparathyroidism, calcitriol (in a dose of 0.25 to 0.5 mcg twice daily) and oral calcium (1 to 4 g of elemental calcium carbonate daily in divided doses) should be initiated as soon as possible.

# Treatment of hypocalcemia



# Management of Anesthesia in Hypocalcemia

- Symptomatic hypocalcemia must be treated prior to surgery and every effort must be made to minimize any further decrease in serum calcium intraoperatively as may occur with ***hyperventilation or administration of bicarbonate***.
- Ionized calcium levels may be decreased by massive blood transfusion of blood containing citrate or when the metabolism of citrate is impaired by hypothermia, liver disease or renal failure.
- Sudden decreases in serum calcium may be seen in the early postoperative period after thyroidectomy or parathyroidectomy and may cause laryngospasm.

# Management of Anesthesia in Hypocalcemia

- It must be remembered that greater myocardial depression and hypotension may occur and therefore, once the diagnosis has been made, calcium replacement may attenuate such responses.
- The action of muscle relaxants may be prolonged and smaller doses may be required.
- Hyperventilation should be avoided and normocapnia maintained throughout the procedure in order to prevent further decreases in ionised serum calcium.
- If hypocalcaemia develops during anaesthesia, the first indication may be the diagnostic changes in the ECG.

# Hypercalcemia

# Hypercalcemia

Hypercalcemia is a relatively common clinical problem.

Among all causes of hypercalcemia, primary hyperparathyroidism and malignancy are the most common, accounting for greater than 90 percent of cases.

# Hypercalcemia

Malignancy is often evident clinically by the time it causes hypercalcemia, and patients with hypercalcemia of malignancy usually have higher calcium concentrations and are more symptomatic from hypercalcemia than individuals with primary hyperparathyroidism.

Although hypercalcemia in otherwise healthy outpatients is usually due to primary hyperparathyroidism and malignancy is more often responsible for hypercalcemia in hospitalized patients, other potential causes of hypercalcemia must be considered

# Causes of hypercalcemia

- Hyperparathyroidis
- Malignancy&Granulomatous diseases, sarcoidosis, tuberculosis
- Thyrotoxicosis
- Vitamin D intoxication
- Medications (thiazides, vitamin A, antiestrogens)
- Alterations in CaSR* function (lithium therapy)

*CaSR, calcium sensor receptor

- Adrenal insufficiency
- Immobilization
- End-stage renal diseases
- Familial benign hypercalcemia
- Endocrine disorders (adrenal insufficiency, pheochromocytoma, VIPoma)
- Idiopathic

# Clinical features of hypercalcaemia

| | |
|---|---|
| **Gastrointestinal** | **Nausea and vomiting**<br>**Anorexia**<br>**Constipation**<br>**Dehydration** |
| **Neurological** | **Lethargy**<br>**Fatigue**<br>**Headache**<br>**Muscle weakness and hyporeflexia**<br>**Confusion**<br>**Coma** |
| **Cardiovascular** | **Hypertension**<br>**ECG changes:**<br>**Reduced QT interval**<br>**Arrhythmias**<br>**Digitalis sensitivity**<br>**Cardiac arrest** |
| **Renal** | **Polyuria**<br>**Polydipsia**<br>**↓Renal blood flow**<br>**↓ Glomerular filtration rate**<br>**Interstitial nephritis**<br>**Nephrocalcinosis**<br>**Hypercalciuria**<br>**Urolithiasis** |
| **Psychiatric** | **Anxiety**<br>**Dementia**<br>**Depression**<br>**Irritability**<br>**Psychosis** |
| **Blood** | **Thrombosis** |

# PREFERRED APPROACH
## *Mild hypercalcemia*

Patients with asymptomatic or mildly symptomatic hypercalcemia (total albumin-corrected calcium <12mg/dL [3 mmol/L] or serum ionized calcium <8 mg/dL [2 mmol/L]) do not require immediate treatment.

However, they should be advised to avoid factors that can aggravate hypercalcemia, including thiazide diuretics and lithium carbonate therapy, volume depletion, prolonged bed rest or inactivity, and a high calcium diet (>1000 mg/day).

# PREFERRED APPROACH
## *Moderate hypercalcemia*

Asymptomatic or mildly symptomatic individuals with chronic moderate hypercalcemia (total albumincorrected calcium between 12 and 14 mg/dL [3 to 3.5 mmol/L] or ionized calcium between 8 and 10 mg/dL [2 to 2.5 mmol/L]) may not require immediate therapy.

They should follow the same precautions described above for mild hypercalcemia.

It is important to note that an acute rise to these concentrations may cause marked changes in sensorium, which requires more aggressive therapy like sever hypercalcemia.

# PREFERRED APPROACH

## *Severe hypercalcemia*

Patients with total albumin-corrected calcium >14 mg/dL (3.5 mmol/L) or ionized calcium >10 mg/dL (2.5 mmol/L) require more aggressive therapy.

patients with an acute rise in serum calcium to more moderate levels who have changes in sensorium (eg, lethargy, stupor) also require aggressive therapy.

# Immediate therapy

## Volume expansion

with isotonic saline at an initial rate of 200 to 300 mL/hour that is then adjusted to maintain the urine output at 100 to 150 mL/hour.

***In the absence of renal failure or heart failure, loop diuretic therapy to directly increase calcium excretionis not recommended, because of potential complications and the availability of drugs that inhibit bone resorption, which is primarily responsible for the hypercalcemia.***

# Immediate therapy

***Administration of salmon calcitonin***

(4 international units/kg) and repeat measurement of serum calcium in several hours.

- If a hypocalcemic response is noted, then the patient is calcitonin sensitive and the calcitonin can be repeated every 6 to 12 hours (4 to 8 international units/kg).

- Patients may develop tachyphylaxis to calcitonin after 24 to 48 hours, so therapy is usually limited to this time period and then discontinued.
- The administration of calcitonin plus saline should result in substantial reduction in serum calcium

concentrations within 12 to 48 hours.

# Immediate therapy

## ***Bisphosphonates***

The concurrent administration of zoledronic acid (ZA; 4 mg intravenously [IV] over 15 minutes) or pamidronate (60 to 90 mg over two hours).

ZA is preferable because it is superior to pamidronate in reversing hypercalcemia related to malignancy.

The bisphosphonate will be effective by the second to fourth day, thereby maintaining control of the hypercalcemia

# Bisphosphonates Side effects

Although IV bisphosphonates are generally well tolerated, side effective may include :

- Fu-like symptoms (fever, arthralgias, myalgia, fatigue, bone pain)
- Ocular inflammation (uveitis)
- Hypocalcemia
- Hypophosphatemia
- Impaired renal function
- Nephrotic syndrome
- Osteonecrosis of the jaw, and atypical femur fractures (in patients who require long-term therapy)

# Immediate therapy

## Denosumab

For patients with hypercalcemia in whom bisphosphonates are contraindicated (eg, due to severe renal impairment), denosumab can be administered concurrently with calcitonin.

bisphosphonates were treated with denosumab 60- 120 mg subcutaneously weekly for four weeks and then monthly thereafter.

# Immediate therapy

## ***Hemodialysis***

Should be considered, in addition to the above treatments, in patients who have

serum calcium concentrations in the range of 18 to 20 mg/dL (4.5 to 5 mmol/L) and neurologic symptoms but a stable circulation or in those with severe hypercalcemia complicated by renal failure.

# Disease specific approach

Hyperparathyroidism

Parathyroid carcinoma

lymphoma, sarcoidosis

ingestion of calcitriol

# Calcimimetics

Calcimimetic agents (only cinacalcet is currently available) reduces the serum calcium concentration in patients with severe hypercalcemia due to parathyroid carcinoma and in hemodialysis patients with an elevated calcium-phosphorous product and secondary hyperparathyroidism.

# Management of Anesthesia in Hypercalcemia

- The anaesthetist is particularly interested in its effects on the heart, circulation, muscle power and blood coagulation.
- Adequate pre-operative assessment and appropriate treatment should be initiated before elective surgery if the patient is symptomatic
- Particular attention must be paid to the action of muscle relaxants
- The duration of non depolarising relaxants is likely to be prolonged, especially if muscle weakness coexists.
- Patients with hypercalcemia may benefit from hyperventilation and respiratory alkalosis in an attempt to shift calcium onto the albumin molecule.
- The cardiovascular and hemodynamic changes, although potentially lethal, are not commonly seen under anesthesia

Thank you for your attention