

*Teaching Point*  
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## Hypocalcaemia and a low cardiac output after intravenous codeine phosphate injection: need for an additional mechanism to remove ionized calcium

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### Introduction

A severe degree of hypotension in children followed the intravenous administration of codeine phosphate in several case reports—histamine release was its presumed root cause [1–3]. We also report cardiovascular collapse following accidental bolus intravenous injection of 30 mg (74  $\mu$ mol) codeine phosphate, but it was associated with a surprising profound degree of hypocalcaemia. A quantitative analysis is provided along with a novel hypothesis to explain the timing and the profound degree of hypocalcaemia that followed the administration of codeine phosphate.

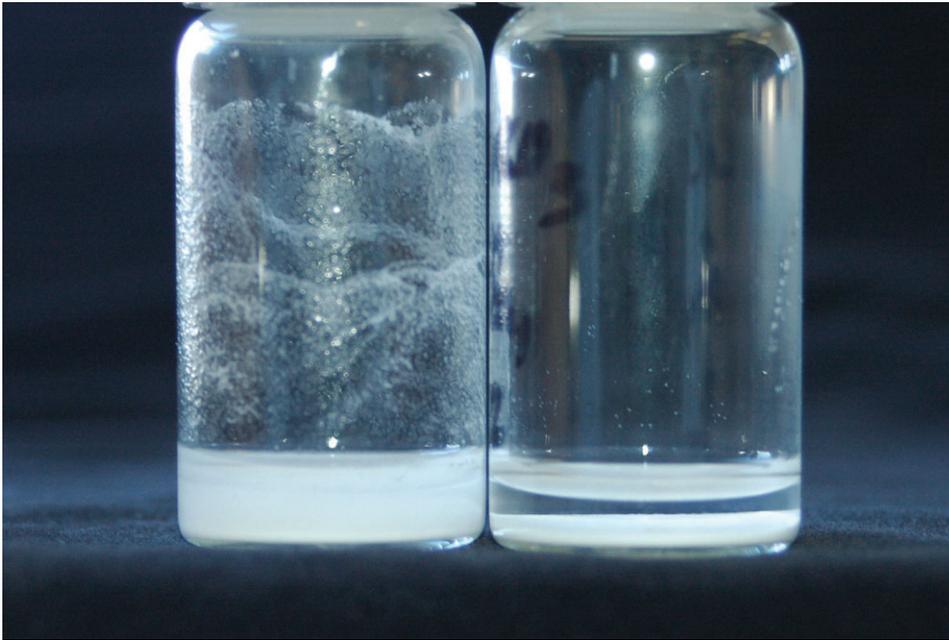
We extend this observation to the initiation of kidney stone formation. The conundrum is that while calcium oxalate deposits grow progressively to form Randall's plaque, calcium oxalate does not precipitate *in vitro* at prevailing concentrations of ionized  $\text{Ca}^{2+}$  and oxalate [4]. Since the nidus of the commonest type of kidney stone, calcium oxalate, is hydroxyapatite, it has been postulated that this nidus permits the precipitation of calcium oxalate [5]. However, it is not known how the initial deposit of hydroxyapatite can occur on the basolateral aspect of the ascending thin limb of the loop of Henle in the inner medulla in patients with idiopathic hypocalciuria. We speculate that the first deposit is a precipitate of calcium carbonate ( $\text{CaCO}_3$ ).

### Case description

A 5-year-old, 21 kg boy had elective tonsillectomy and adenoidectomy to remedy obstructive breathing during sleep.

He did not have other medical problems or known allergies, nor was he taking medications. The family history revealed a possible allergy to morphine. Anaesthesia was induced with sevoflurane. An intravenous access was established, and atropine (5  $\mu$ g/kg), fentanyl (1  $\mu$ g/kg), propofol (2.5 mg/kg), dexamethasone (0.2 mg/kg) and ondansetron (0.1 mg/kg) were administered. The trachea was intubated, and he was mechanically ventilated. Acetaminophen (40 mg/kg) was administered per rectum. Surgery and emergence from anaesthesia were uneventful. After extubation in the operating room, he was restless, and 30 mg (74  $\mu$ mol) of codeine phosphate was administered inadvertently by intravenous push into the injection port in a dorsal hand vein. Almost immediately, he coughed, became grey and unresponsive. The EKG revealed sinus rhythm, but the femoral pulses were not palpable. Accordingly, he was ventilated with 100% oxygen, the trachea was re-intubated and cardiac massage was briefly implemented. Resuscitation proceeded with atropine administration and epinephrine infusion (0.05  $\mu$ g/kg/min). Upon the return of femoral pulses, a femoral arterial blood gas was drawn. Urticaria along the venous injection site was noted, as was cutaneous flushing over the trunk, leading to a presumptive diagnosis of anaphylaxis, and intravenous Solu-Cortef (5 mg/kg), ventolin and diphenhydramine (1 mg/kg) were administered. The child was rapidly weaned off epinephrine, and he was extubated within 50 min of the administration of codeine phosphate. He made a full recovery.

The ionized calcium (0.72 mmol/L) was very low in arterial blood drawn 18 min after codeine phosphate administration. Other values included pH 7.29,  $\text{PCO}_2$  41 mmHg,  $\text{PO}_2$  72 mmHg, calculated bicarbonate 20 mmol/L,  $\text{Na}^+$  130 mmol/L,  $\text{K}^+$  3.0 mmol/L, glucose 117 mg/dL (6.5 mmol/L), L-lactate 1.3 mmol/L and haematocrit 0.33.



**Fig. 1.** Conversion of  $\text{CaCO}_3$  to calcium phosphate *in vitro*. The objective was to illustrate that  $\text{CaCO}_3$  could be transformed to contain some calcium phosphate when exposed to inorganic phosphate at pH 7.4. Therefore, 3 mmol of calcium carbonate was added to water or 5 mmol of  $\text{K}^+$  phosphate at pH 7.4, and the suspensions were left to stand for 2 days at room temperature. The vials were shaken gently, and a picture was taken. The water controls (left image) revealed a cloudy suspension of  $\text{CaCO}_3$ , whereas a very firm precipitate was present at the bottom of the vials with the phosphate buffer (right image) with a clear aqueous solution above.

## Discussion

Although profound hypotension following intravenous codeine phosphate has been attributed to histamine release [1–3], the data in these case reports are also consistent with catastrophic but transient myocardial depression. In our case, this haemodynamic collapse was associated with profound hypocalcaemia, which suggested that phosphate rather than codeine was the root cause of this clinical emergency.

### *Quantitative analysis related to the cardiac arrest*

Very shortly after the intravenous bolus injection, all the infused phosphate could reach the pulmonary circulation in  $\sim 90$  mL of plasma. In more detail, the total blood volume in a 21 kg child is  $\sim 70$  mL/kg [6,7] (i.e.  $\sim 1500$  mL). With a haematocrit of 0.33, the plasma volume is  $\sim 1000$  mL and the pulmonary plasma volume is  $\sim 90$  mL (9% of total plasma volume). This pulmonary plasma volume plus the end-diastolic plasma volume in the right ventricle ( $\sim 1$  mL/kg) is  $\sim 110$  mL. Since the normal ionized calcium concentration is  $\sim 1200$   $\mu\text{mol/L}$ , this volume would contain  $\sim 130$   $\mu\text{mol}$  of ionized calcium. Thus, if all the added phosphate could remove 74  $\mu\text{mol}$  of ionized calcium, more than half of the ionized calcium pool would have disappeared in capillaries perfusing the myocardium. The next step is to extend this analysis to the extracellular fluid (ECF) compartment of the heart, which is 6–15 mL/100 g left ventricular mass (LVM) [8], and the LVM is  $\sim 4.7 \times \text{kg}^{0.75}$  [9,10]. In this 21 kg child, his LVM is 46 g and the volume of blood in the coronary vessels would range from 2.8 to 6.9 mL.

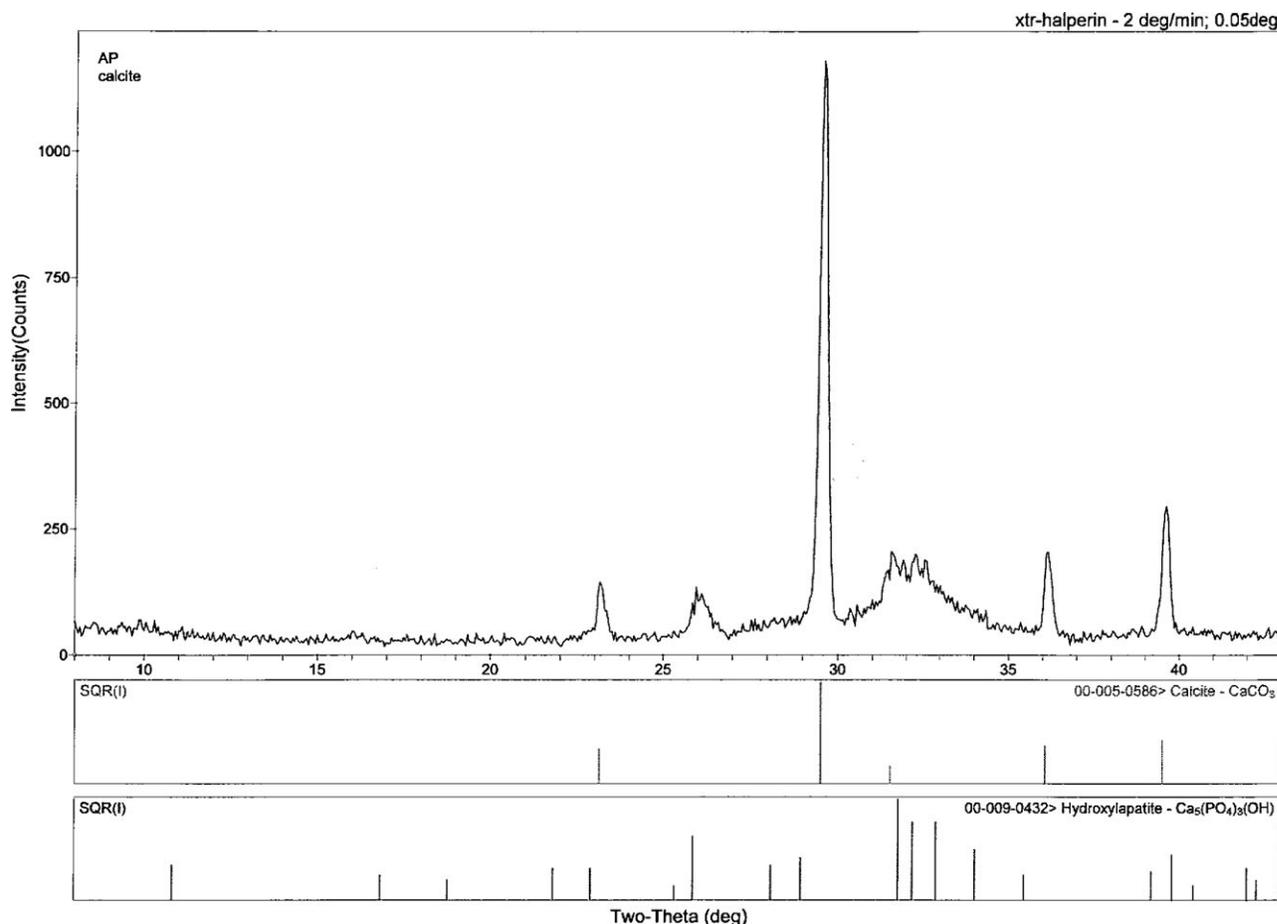
Thus, the estimated myocardial interstitial fluid volume is small enough to permit a large fall in its ionized calcium concentration after diffusion occurs. In fact, this diffusion is into myocardial capillaries, and it can be rapid because of the ‘stirring action’ produced by the beating heart.

Once the vigour of myocardial contraction is depressed by hypocalcaemia, however, movement of calcium back into the myocardial interstitial compartment should be much slower. The inotropic action of the administered epinephrine and the resuscitation procedure may have helped raise the ionized calcium concentration in the interstitial compartment of the heart during therapy.

One other clinical observation may be relevant. It is tempting to imply that the very low concentration of ionized calcium in plasma might cause a decrease in the arteriolar tone and thereby cause vasodilatation and the observed flushing in addition to, or instead of, this being due to actions of histamine [1–3].

### *Conundrum*

The total body pool of ionized calcium in plasma of this patient is  $\sim 1200$   $\mu\text{mol}$  (i.e. 1.2  $\mu\text{mol/mL}$  times the plasma volume of  $\sim 1000$  mL). This quantity is likely to be 4-fold larger after mixing plasma with the pool of ionized calcium in the entire ECF compartment. Therefore, this pool size is too much large for 74  $\mu\text{mol}$  of phosphate to cause such a large decline in the ionized calcium concentration. The problem is even greater because calcium should have been released from its bound form on circulating albumin. In quantitative terms, this bound calcium pool is almost equal to the amount of ionized calcium in plasma. Moreover,



**Fig. 2.** X-ray diffraction analysis of the precipitate formed in Figure 1. The X-ray diffraction pattern of this precipitate was generated using a powder diffractometer (Rigaku MultiFlex, The Woodlands, TX, USA) and with Jade 6 (Materials Data, Rigaku). The powder specimen was scanned from 6 to 46° 2θ at a scan speed of 2° 2θ/min (step size 0.05° 2θ, 40 kV, 30 mA, Cu Kα radiation). Crystal structure identification was done using the Jade 6 program and the mineral powder diffraction database of the International Center for diffraction data (ICDD).

since this deficit was present 18 min after receiving the intravenous bolus of codeine phosphate, there should have been mixing of plasma with the pool of ionized calcium in the entire ECF compartment. Therefore an occult factor must have contributed to this pathophysiology.

#### Possible resolution to this conundrum

The addition of phosphate ‘triggered’ the disappearance of ionized calcium in the ECF compartment. The first step is likely the formation of a nidus of calcium phosphate, driven by the very high concentration of divalent phosphate in the small volume of blood in the dorsal hand vein. Second, this nidus of calcium phosphate caused CaCO<sub>3</sub> to precipitate from plasma because the ion product of ionized calcium and carbonate (CO<sub>3</sub><sup>2-</sup>) in plasma is close to or slightly exceeds the solubility product (K<sub>sp</sub>) for CaCO<sub>3</sub> [11].

#### Perspectives

The nidus of the commonest type of kidney stone, calcium oxalate, is hydroxyapatite located on the basolateral aspect

of the ascending thin limb of the loop of Henle in the inner medulla [5]. While calcium oxalate deposits grow progressively to form Randall’s plaque, calcium oxalate will not precipitate *in vitro* at the prevailing concentrations of ionized Ca<sup>2+</sup> and oxalate [4]. Moreover, owing to the very high apparent pK for trivalent phosphate (PO<sub>4</sub><sup>3-</sup>), the ion product of Ca<sup>2+</sup> and PO<sub>4</sub><sup>3-</sup> is unlikely to exceed its K<sub>sp</sub>. Accordingly, it is unclear why a nidus of hydroxyapatite would form in this location.

The implied transformation of precipitates of calcium salts from our case prompted us to carry out simple *in vitro* experiments and to suggest how hydroxyapatite could be formed *in vivo*. As shown in Figure 1, addition of CaCO<sub>3</sub> to a phosphate buffer solution at pH 7.4 *in vitro* led to an obvious change in the visual appearance and especially in the rigidity of the precipitate. When this precipitate was analysed by x-ray diffraction, it was found to be composed of a mixture of CaCO<sub>3</sub> and hydroxyapatite (Figure 2).

Our hypothesis is that the initial step in the formation of a nidus is a precipitate of CaCO<sub>3</sub> because the paracellular reabsorption of ionized Ca<sup>2+</sup> in the medullary thick ascending limb of the loop of Henle will raise the local concentration of ionized Ca<sup>2+</sup> in the basolateral region of

this nephron segment [12]. Moreover, since  $\text{HCO}_3^-$  and  $\text{K}^+$  are added to the medullary interstitial compartment by the  $\text{H}^+/\text{K}^+$ -ATPase in the medullary collecting duct [13], this will increase the concentration of  $\text{CO}_3^{2-}$  and thereby favour the formation of  $\text{CaCO}_3$  in this location. The factors that augment flux through this  $\text{H}^+/\text{K}^+$ -ATPase are primarily hypokalaemia [14] and, of note, a sudden  $\text{K}^+$  load in people who eat  $\text{K}^+$ -rich food in an intermittent fashion [13]. Thus, the initial precipitate of  $\text{CaCO}_3$  could be carried down to the inner medulla in the descending vasa recta to help initiate the formation of the nidus of hydroxyapatite by transformation reactions [4], and thereby the growth of calcium oxalate stones [15].

There is a second implication from this revised analysis of the physiology of ionized calcium. For example, when a person consumes 1 L of orange juice, there is an input of  $\sim 1500 \mu\text{mol}$  of citrate. There would be an addition of enough citrate to remove twice as much ionized calcium from plasma delivered to the heart as compared to events in our patient if the liver extracted only 90% of this citrate in a single pass. Nevertheless, drinking orange juice quickly does not create a clinical problem possibly because of 'buffering' of the ionized calcium concentration by the release of calcium bound to albumin and of far greater importance, the chelation of ionized calcium does not form a nidus for the precipitation of  $\text{CaCO}_3$ . This novel hypothesis should be followed up with experiments to examine if there are local chemical groups that will cause  $\text{CaCO}_3$  to adhere to the basolateral aspect of the ascending thin limb of the loop of Henle and to determine if calcium oxalate may deposit over time to this mixed precipitate of  $\text{CaCO}_3$  and hydroxyapatite.

### Teaching points

- (1) One must not only look at the desired component of the medication (codeine) but also recognize the potential risks due to its other ingredients (phosphate).
- (2) Bolus injections into a peripheral vein will lead to very high concentrations in plasma. Perhaps, the administration of codeine phosphate would not have produced this cardiovascular collapse if the rate of administration were much slower.
- (3) There are many other safer anions available in other preparations of codeine.
- (4) Observations from a clinical case, when examined quantitatively, may lead to unanticipated new insights.

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