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SPECIAL ARTICLE

The role of calcium in intravenous fluid therapy

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INTRODUCTION

In general, the maintenance of calcium balance is an accepted part by the fluid and electrolyte management of patients. In the medium to long term, there are clear adverse effects of consistent negative or positive calcium balance, and both hypo- and hypercalcaemia are associated with morbidity (Agus & Goldfarb, 1985). In these circumstances, monitoring of the plasma calcium concentration, and judicious use of intravenous or oral supplements, together with vitamin D analogues if required (as in renal failure), is appropriate. However, the short-term use of intravenous calcium supplementation in acutely ill patients remains a topic of controversy.

For many years, the administration of intravenous calcium was a routine part of the resuscitation regime for traumatic, haemorrhagic, or cardiogenic shock. This was based on the high incidence of acute hypocalcaemia in these conditions, and the observed beneficial effects of calcium on systemic haemodynamics (Denis *et al.*, 1985). A number of the fluid preparations available for acute intravenous use contain supplemental calcium, including crystalloids (e.g. Ringer's solution, 2.2 mmol l^{-1} calcium) and colloids (e.g. Haemaccel, 6.25 mmol l^{-1} calcium; Hoechst UK Ltd, Middlesex, UK). However, the use of intravenous calcium in these situation has been questioned, largely on the basis of the known increase in intracellular calcium concentration which occurs during ischaemic cellular injury (Trunkey *et al.*, 1976).

CELL BIOLOGY OF CALCIUM

The intracellular ionized calcium concentration — $[Ca^{2+}]_i$ — is an important determinant of vascular smooth muscle contractile activity. Contraction is produced

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by the interaction of myosin and actin, energized by the hydrolysis of ATP. This process is regulated by phosphorylation of the myosin light chain by the enzyme, myosin light chain kinase, which is activated by calcium. Protein kinase C, another calcium-activated enzyme, may also regulate muscle contraction (Dominiczak & Bohr, 1990).

$[Ca^{2+}]_i$ is normally around $0.1\,\mu mol\,l^{-1}$, as compared with a normal extracellular calcium concentration — $[Ca^{2+}]_o$ — of approximately $1.6\,mmol\,l^{-1}$. This 16 000-fold gradient across the cell plasma membrane is maintained by a complex set of regulatory systems. Calcium influx is regulated by voltage-operated calcium channels, receptor-operated channels, and 'leak' channels. Calcium efflux from cells is regulated primarily by active, ATP-dependent calcium pumps and by sodium/calcium exchange in the plasma membrane. Of primary importance in the regulation of $[Ca^{2+}]_i$ is the presence of ATP-dependent pumps in the sarcoplasmic reticulum, which restore $[Ca^{2+}]_i$ to normal after muscle contraction (Van Breemen & Saida, 1989). Mitochondrial uptake and retention of calcium only becomes substantial in the presence of a high cytosolic calcium concentration. Receptor-activated intracellular signalling increases calcium release from a hormone-sensitive pool in the sarcoplasmic reticulum and bound to cellular macromolecules, via a complex sequence of messengers, including G-proteins, inositol 1,4,5 triphosphate (IP3) and diacylglycerol (Rasmussen, 1986).

CALCIUM IN ISCHAEMIC INJURY

Under conditions of ischaemia and hypoxia, a complex sequence of cellular events occurs, including: reduced generation of ATP; intracellular acidosis; cell swelling due to reduced Na,K ATPase activity; phospholipid degeneration; activation of cellular proteases and heat shock proteins; and cytoskeletal changes. ATP-dependent exclusion of calcium from cells is reduced. There is impaired sequestration of calcium by the endoplasmic reticulum, leading to an increase in $[Ca^{2+}]_i$. Calcium accumulates in mitochondria, and this may be an important step in cell injury, although some workers have suggested that increased $[Ca^{2+}]_i$ is a late phenomenon seen during cell necrosis (Weinberg, 1991; Burke & Schrier, 1993). In some experimental models of ischaemic injury, such as the isolated rat kidney perfused with a cell-free medium, it has been shown that an increase in $[Ca^{2+}]_o$ exacerbates the cellular damage (Brezis *et al.*, 1988). In other models, however, such as the H_2O_2 model of free radical-induced injury, the complete removal of extracellular calcium from the medium has no effect on either the large increase in $[Ca^{2+}]_i$, or the degree of cellular damage, suggesting that influx of external calcium is relatively unimportant (Euda & Shah, 1992). Many studies have shown that total tissue calcium levels remain virtually unchanged during *in vivo* ischaemia (Burke & Schrier, 1993) and in models of cellular anoxic injury, no increase in total cellular calcium content can be demonstrated, again suggesting that redistribution of intracellular calcium stores is more important than calcium influx (Weinberg, 1985). Calcium channel blocking drugs are protective in some, but not all, experimental models of ischaemic injury. Their mode of action is not understood

clearly; it may be independent of an effect on calcium influx, and relate to other intracellular actions, such as inhibition of the calcium-binding protein, calmodulin (Weinberg, 1991). Interestingly, intracellular acidosis has recently been shown to protect cells markedly from calcium influx and the deleterious effects of an increase in $[Ca^{2+}]_i$ (Weinberg, 1985). As yet, there is no firm evidence from clinical studies to show that the short-term administration of calcium worsens ischaemic or hypoxic tissue injury in patients.

Indeed, it is known that the intracellular environment is protected from calcium overload by a mechanism whereby an increase in extracellular calcium concentration makes the membrane less permeable to calcium, and also to all other ions — the "membrane-stabilizing effect" of calcium (Webb & Bohr, 1978; Dominiczak & Bohr, 1990). This is thought to reflect increased binding of calcium to the cell plasma membrane. As $[Ca^{2+}]_o$ increases, trans-membrane fluxes of both sodium and potassium are decreased (Webb & Bohr, 1978). This may serve to limit cell swelling due to sodium influx, and could also modulate the rise in plasma potassium in critically ill patients.

CALCIUM AND CIRCULATORY FUNCTION

As one would predict on the basis of a crucial role in the coupling of stimulus and contraction in muscle cells, calcium is recognized as central to the maintenance of cardio-circulatory function (Webb & Bohr, 1978). Known cardiovascular manifestations of acute hypocalcaemia include hypotension, reduced myocardial function, ECG abnormalities, and frank heart failure (Denlinger & Nehrwold, 1976; Agus & Goldfarb, 1985). These have been documented following infusions of EDTA, after massive blood transfusion, in neonatal hypocalcaemia, after parathyroid surgery, and in idiopathic hyperparathyroidism. Intractable ventricular fibrillation and complete heart block have also been reported (Agus & Goldfarb, 1985).

It has been known for many years that the plasma total calcium concentration falls acutely in patients suffering from major trauma and/or haemorrhagic shock, and that this is not dependent on citrate infused during transfusion (Kovalik *et al.*, 1981). It is now known that there is an equivalent, or even greater, fall in ionised calcium, and that infusion of colloids such as albumin solution may disguise this decrease, by disproportionally increasing the total calcium concentration (Kovalik *et al.*, 1981). Similar data are available for patients with cardiogenic shock, and patients being resuscitated from cardio-respiratory arrest (Gando *et al.*, 1990; Erdmann & Reuschel-Janetschek, 1991). Information in sepsis and septic shock is less clear, but we have shown recently a significant decrease in plasma calcium, corrected for albumin, in an ovine experimental model of septic shock (Cumming & Linton, unpublished). In haemorrhagic shock, the hypocalcaemia may persist after resuscitation for up to 6 days, in the absence of supplementation (Kovalik *et al.*, 1981).

It has been shown that in cats infused with endotoxin, there is markedly reduced myocardial and vascular responsiveness to infusions of calcium chloride. Prior to endotoxin, calcium infusion produced a pressor response of 24 mmHg, but

had no pressor effect at all after endotoxin (McCaig & Parratt, 1980). This has been ascribed to damage to receptor-operated calcium channels, and these observations may also be relevant to other forms of shock (Parratt, 1989).

The combination of reduced plasma ionized calcium and decreased myocardial and vascular sensitivity to calcium would be predicted to lead to circulatory compromise, at least partly reversible by calcium infusion. This is supported by observations of beneficial haemodynamic effects of calcium infusion in trauma, haemorrhagic shock, and cardiogenic shock (Harrigan *et al.*, 1983; Denis *et al.*, 1985). It is widely accepted that a normal plasma ionized calcium concentration is important for the maintenance of cardiac contractility. For example, calcium alone can increase blood pressure in hypotensive patients after coronary artery bypass grafting (Zaloga *et al.*, 1991). In a study of dogs undergoing hypotensive haemorrhage, Denis *et al.* (1985) showed beneficial effects of calcium supplementation on blood pressure and cardiac output, compared with animals given no calcium or given verapamil, a calcium channel blocking drug. They showed that without calcium supplementation, there was a significant and prolonged increase in plasma parathyroid hormone concentration during the post-resuscitation period (Denis *et al.*, 1985).

CRUSH SYNDROMES AND RHABDOMYOLYSIS

Marked hypocalcaemia is seen frequently in patients with traumatic or non-traumatic muscle damage. The pathophysiology is complex, and probably related at least in part to the attendant increase in plasma phosphate, which encourages calcium deposition in the damaged muscle and elsewhere, and suppresses production of 1,25-dihydroxycholecalciferol (Lach *et al.*, 1981). Better & Stein (1990) and others have argued that calcium supplementation should be avoided in this condition, on the basis that this will encourage tissue calcification and further damage to muscle. However, direct evidence for this is lacking. While it is clear that calcium does accumulate in acutely damaged muscle, particularly in the presence of renal failure (Meroney *et al.*, 1951), the hypothesis that infusion of exogenous calcium potentiates this phenomenon has not been tested, either in experimental or clinical studies. Indeed, it has been argued that the intense stimulation and hyperplasia of the parathyroid glands during the hypocalcaemic phase may lead to hypercalcaemia during the recovery period, and that this secondary hyperparathyroidism, together with 'rebound' high levels of 1,25-dihydroxycholecalciferol, may be the major factor in causing permanent tissue damage (Llach *et al.*, 1981; Agus & Goldfarb, 1985). The optimal strategy may be the maintenance of a normal plasma calcium concentration, together with measures to control the plasma phosphate, such as restricted intake, oral phosphate binders, and initiation of a diuresis with volume loading and mannitol, which will have a marked phosphaturic effect (Agus & Goldfarb, 1985). Whether the persistently increased parathyroid hormone levels associated with untreated hypocalcaemia in other types of circulatory failure, as described above, could have a similar effect on secondary tissue injury is not known.

CONCLUSIONS

At present, the role of calcium supplementation in the resuscitation and subsequent care of acutely ill and shocked patients remains controversial. However, it is clearly inappropriate to extrapolate directly from the fact that the intracellular calcium concentration rises in ischaemic cells, to the avoidance of calcium supplements in hypocalcaemic shocked patients. The influence of infusion of exogenous calcium on cell injury and death is not clear, and can even be argued to be beneficial, via a membrane-stabilizing effect, rather than deleterious. In contrast, the harmful circulatory effects of untreated acute hypocalcaemia, including hypotension and decreased myocardial function, have been clearly established, and seem likely to outweigh any local tissue effect in most situations.

The optimal value of ionized calcium for cardiovascular function has not been established, but has been suggested to be approximately $1.7\,mmol\,l^{-1}$ (Denis *et al.*, 1985). With appropriate equipment, the direct measurement of ionized calcium is quick and reliable, and can be performed easily by medical staff. A desirable strategy is therefore to measure ionized calcium prior to and during the course of resuscitation, and use the value as a guide in the choice of replacement fluids. Experience locally suggests that this will tend to lead to increased use of calcium-containing solutions and calcium supplementation. Even if it is only possible to measure total calcium, the available evidence suggests that a reduction in total plasma calcium is highly likely to indicate a low ionized calcium, and may indeed overestimate the ionized calcium concentration in some circumstances. In the absence of such information, it may be appropriate to err on the side of over- rather than under-replacement of calcium, particularly in patients with ongoing hypotension and/or myocardial depression.

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