COMPARATIVE EFFECTS OF CALCIUM CHLORIDE AND CALCIUM GLUCEPTATE

L. J. DROP and D. J. CULLEN

SUMMARY

Calcium chloride and calcium gluceptate were compared in their ability to increase plasma ionized calcium concentrations ([Ca\(^{2+}\)]. To correct a low ionized calcium concentration, each of 10 critically ill patients received both calcium chloride (10 ml of a 10% solution, containing elemental calcium 27 mg ml\(^{-1}\)) and calcium gluceptate (20 ml, containing elemental calcium 18 mg ml\(^{-1}\)) over a 5-min period in randomized order approximately 6 h apart. [Ca\(^{2+}\)] and haemodynamic variables (mean arterial pressure (MAP), mean right atrial pressure (RAP) and heart rate (HR)) were monitored for a 30-min period following completion of calcium infusion. Infusion of either calcium preparation was associated with similar increases in [Ca\(^{2+}\)] (5 min after infusion of calcium chloride: 33 ± 3.1%; calcium gluceptate: 32 ± 4.3% (mean ± SEM)) and the effects on MAP were similar for each solution (11.1 ± 1.8% and 9.7 ± 2.4%, respectively).

Calcium preparations may be infused i.v. during anaesthesia or in the critical care unit (Drop and Laver, 1975; Taylor et al., 1978). However, we do not know the effect on plasma ionized calcium concentration ([Ca\(^{2+}\)]) following either i.v. calcium chloride or calcium gluceptate administration. These two commonly used preparations differ in their elemental calcium content (calcium chloride: 27 mg ml\(^{-1}\); calcium gluceptate: 18 mg ml\(^{-1}\)) and in the availability of the calcium ion. Calcium chloride is completely dissociated in solution and calcium is present in the free, ionized form. In calcium gluceptate, not all of the calcium is in free ionized form because a complex with the gluceptate radical is formed.

We have compared changes in [Ca\(^{2+}\)] and in haemodynamic variables following i.v. administration of 10% calcium chloride 10 ml and calcium gluceptate 20 ml in patients in whom initial [Ca\(^{2+}\)] values were substantially less than normal.

PATIENTS AND METHODS

Ten patients who required artificial ventilation of the lungs following major abdominal or vascular surgery were studied. The age range was 27–90 yr, body weight 48.6–76.9 kg. In each patient, surgery had been completed at least 12 h before the time of study; no blood or blood products had been administered in the preceding 4-h period. In view of the potentially serious complications that may arise following calcium infusion in patients with abnormalities in potassium balance (Surawicz, 1967a) or those receiving digitalis (Eliot and Blount, 1961), such patients were excluded from the study.

During the study period, i.v. fluids were restricted to 25 ml h\(^{-1}\). Haemodynamic measurements were obtained at zero airway pressure. Intra-arterial and right atrial pressures were recorded as part of routine monitoring employed in these patients from appropriate indwelling catheters via Statham P23 AA transducers. Mean pressures were determined by electronic integration. Lead II of the e.c.g. was recorded at a paper speed of 25 mm s\(^{-1}\) to determine heart rate (HR).

Plasma ionized calcium concentration ([Ca\(^{2+}\)]) was measured with a calcium-selective electrode system, calibrated before and after passage of each plasma sample with aqueous solutions of known [Ca\(^{2+}\)] (Drop and Laver, 1975). Arterial \(P_{O_{2}}\), \(P_{CO_{2}}\) and pH were measured with standard commercial electrodes at 37 °C and corrected for body temperature when required. Total calcium concentration ([Ca]), sodium (Na\(^{+}\)), potassium (K\(^{+}\)), inorganic phosphorus (P\(_{i}\)) and total protein (TP) concentrations were determined by standard methods.

Immediately before infusion of calcium because of hypocalcaemia, an arterial sample was obtained for
determination of biochemical variables. In all patients, PO₂ ranged from 10.67 to 34.67 kPa, PCO₂ from 4.27 to 6.13 kPa, pH from 7.35 to 7.49, Na⁺ from 132 to 145 mmol litre⁻¹, K⁺ from 3.9 to 4.9 mmol litre⁻¹ and total protein from 46 to 57 g litre⁻¹. These values were known for each patient before each calcium infusion. Sinus rhythm was present in each patient, and heart rate ranged from 68 to 108 beat min⁻¹.

Each patient received infusions of both calcium chloride (10 ml of a 10% solution, containing elemental calcium 27 mg ml⁻¹) (Goodman and Gilman, 1970) and calcium gluceptate (20 ml, containing elemental calcium 18 mg ml⁻¹ as specified on the label) over a 5-min period in randomized order approximately 6 h apart. Heparinized arterial blood specimens were withdrawn and haemodynamic measurements made immediately before the calcium infusion and 5, 10, 20 and 30 min following completion of the calcium infusion.

Student's t test was used to test for statistical significance; values are given as mean ± SEM.

RESULTS

Details of the patients are in table I. Mean initial [Ca²⁺] before each calcium infusion was less than normal (1.12 ± 0.03 mmol litre⁻¹) (Drop et al., 1978) and less than predicted by the McLean-Hastings nomogram (McLean and Hastings, 1935) (fig. 1). Calcium infusion resulted in a sustained increase in [Ca²⁺] (table II) and in mean arterial pressure (table III); changes in these variables were not materially influenced by the choice of calcium preparation. No significant changes were recorded in mean right atrial pressure, heart rate or cardiac rhythm. For the same increase in [Ca²⁺], [Ca] increased more following calcium gluceptate than after calcium chloride (table II). Other biochemical variables did not change during the periods of observation.

DISCUSSION

In critically ill patients with ionized hypocalcaemia, calcium chloride 10 ml (elemental calcium 27 mg ml⁻¹) is equivalent to calcium gluceptate 20 ml (elemental calcium 18 mg ml⁻¹), both infused i.v. over a 5-min period, in terms of the increase in [Ca²⁺]. The changes in haemodynamic variables associated with infusion of these amounts of calcium were also similar.

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Sex</th>
<th>Condition</th>
<th>Operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>82</td>
<td>M</td>
<td>Pelvic abscess, sepsis</td>
<td>Drainage of abscess</td>
</tr>
<tr>
<td>68</td>
<td>M</td>
<td>Peripheral obstructive vascular disease</td>
<td>Aorto-femoral graft</td>
</tr>
<tr>
<td>27</td>
<td>F</td>
<td>Ulcerative colitis</td>
<td>Subtotal colectomy</td>
</tr>
<tr>
<td>61</td>
<td>M</td>
<td>Gastric varices, liver cirrhosis</td>
<td>Partial gastrectomy</td>
</tr>
<tr>
<td>63</td>
<td>M</td>
<td>Perforated colon, sepsis</td>
<td>Partial colectomy, small bowel resection</td>
</tr>
<tr>
<td>56</td>
<td>M</td>
<td>Small bowel obstruction</td>
<td>Small bowel resection</td>
</tr>
<tr>
<td>55</td>
<td>M</td>
<td>Bleeding gastric ulcer</td>
<td>Subtotal gastrectomy, splenectomy</td>
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<tr>
<td>90</td>
<td>F</td>
<td>Subhepatic abscess</td>
<td>Small bowel resection, drainage of abscess</td>
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<tr>
<td>57</td>
<td>M</td>
<td>Bleeding gastric ulcer</td>
<td>Subtotal gastrectomy, splenectomy</td>
</tr>
<tr>
<td>60</td>
<td>F</td>
<td>Multiple injury after motor vehicle accident</td>
<td>Abdominal exploration</td>
</tr>
</tbody>
</table>

Fig. 1. Ionized calcium values predicted by use of the McLean-Hastings nomogram plotted against those directly measured by electrode in 10 critically ill patients before infusion of either calcium solution. The solid line represents the line of perfect agreement. All data points are positioned to the left of this line, that is measured [Ca²⁺] values were smaller than predicted. To predict [Ca²⁺] by use of the McLean-Hastings nomogram, two variables are known (total calcium and total protein); other values are assumed to be as follows: albumin/globulin ratio = 1.8, pH = 7.35 and temperature = 25 °C.
CALCIUM SOLUTIONS AND IONIZED CALCIUM

TABLE II. Effects of calcium solutions on indices of calcium homeostasis (mean ± SEM). 

* * * P < 0.001; ** P < 0.01. [Ca²⁺] = ionized calcium; [Ca] = total calcium; P_i = inorganic phosphorous concentrations (mmol litre⁻¹)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>5</th>
<th>10</th>
<th>20</th>
<th>30</th>
</tr>
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<tbody>
<tr>
<td>Calcium chloride</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10 ml in 5 min)</td>
<td>[Ca²⁺]</td>
<td>0.79 ± 0.04</td>
<td>1.06 ± 0.05**</td>
<td>1.00 ± 0.05***</td>
<td>0.98 ± 0.04***</td>
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<tr>
<td></td>
<td>[Ca]</td>
<td>2.08 ± 0.10</td>
<td>2.44 ± 0.11***</td>
<td>2.43 ± 0.14***</td>
<td>2.39 ± 0.12***</td>
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<tr>
<td></td>
<td>P_i</td>
<td>0.57 ± 0.13</td>
<td>0.66 ± 0.13</td>
<td>0.66 ± 0.13</td>
<td>0.67 ± 0.13</td>
</tr>
<tr>
<td>Calcium gluceptate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(20 ml in 5 min)</td>
<td>[Ca²⁺]</td>
<td>0.79 ± 0.04</td>
<td>1.04 ± 0.05***</td>
<td>1.00 ± 0.05***</td>
<td>0.95 ± 0.04***</td>
</tr>
<tr>
<td></td>
<td>[Ca]</td>
<td>2.08 ± 0.05</td>
<td>2.71 ± 0.14***</td>
<td>2.57 ± 0.11***</td>
<td>2.51 ± 0.10***</td>
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<tr>
<td></td>
<td>P_i</td>
<td>0.66 ± 0.15</td>
<td>0.62 ± 0.13</td>
<td>0.62 ± 0.16</td>
<td>0.69 ± 0.16</td>
</tr>
</tbody>
</table>

We did not observe cardiac arrhythmia during or following calcium infusion.

The calcium-selective electrode system enabled detection of initial ionized hypocalcaemia in our patients, present before calcium infusion. Such detection would have been impossible with the McLean–Hastings nomogram (fig. 1), the traditional method for estimating [Ca²⁺]. In the nomogram, two known variables (total calcium and total protein concentrations) are used to predict calcium ion concentration. All our directly measured data points were positioned to the left of the line of perfect agreement, indicating that hypocalcaemia was not apparent from total calcium measurement. This observation has been made previously (Drop and Laver, 1975; Drop and Scheidegger, 1979).

We had compared the increase in [Ca²⁺] following addition of different amounts of calcium gluceptate or calcium chloride to aliquots of heparinized blood drawn from a normal volunteer. Such an empirical approach appeared necessary since the elemental calcium content of a calcium solution does not provide information on its calcium ion concentration nor does it predict [Ca²⁺] increase in patients following its infusion i.v. Calcium chloride is completely dissociated in solution and calcium is present in the free, ionized form. In calcium gluceptate solution, calcium is present both in the free ionized form and as the calcium gluceptate complex. Measurement of [Ca²⁺] in the tested solutions is unhelpful since calcium ion concentration is substantially greater than the useful sensitivity range of the calcium electrode system. In addition, the pH of these solutions is unstable so that the electrode may respond, not exclusively to calcium ion activity, but to that of hydrogen ion also. Following i.v. calcium infusion, some calcium will remain in the free, ionized form and some is bound by protein and complexed to different naturally occurring anions. In the case of calcium gluceptate infusion, there is initial binding of the calcium ion by the gluceptate radical also. Thus, direct [Ca²⁺] measurement in blood from patients is essential to evaluate the effectiveness of each calcium preparation in increasing [Ca²⁺].

The calcium-selective electrode system used in this study represents a practical method for the
determination of the physiologically active portion of plasma calcium concentration in small specimens of whole blood. Madsen and Ølggaard (1977) reported that the within-day coefficient of variation for quadruple analyses was 1.8%. Data by these authors and from this laboratory (Drop, Fuchs and Stulz, 1978) have demonstrated a relatively small effect of pH throughout the physiological pH range on [Ca\(^{2+}\)] measurement while the effect of adding small amounts of heparin to the blood sample is minimal. Furthermore, the arterial-venous difference in [Ca\(^{2+}\)] is negligible. Recent data (Drop, Fuchs and Stulz, 1978) obtained concurrently in the United States (Boston, Massachusetts) and in Europe (Göttingen, Germany) have shown that [Ca\(^{2+}\)] is normally maintained within very narrow limits ([Ca\(^{2+}\)] = 1.12 ± 0.02 mmol litre\(^{-1}\), mean ± SEM, \(n = 100\)). In the case of a calibrated calcium-selective electrode system, the results of [Ca\(^{2+}\)] determinations are available approximately 3 min following initiation of the analytical procedure. We have found this feature to be of particular value in the documentation and prompt therapy of hypocalcaemic tetany during anaesthesia (Drop and Miller, 1980) and in the experimental setting allowing for study of cardiac (Drop et al., 1978; Stulz et al., 1979) and haemodynamic function (Scheidegger and Drop, 1979) during steady-state abnormalities in calcium ion balance.

In our patients, i.v. infusions of calcium chloride 10 ml and calcium gluconate 20 ml were followed by similar changes in [Ca\(^{2+}\)] and haemodynamic variable; the advantages of one form of calcium over another were not apparent. Since the calcium ion is known to be a major determinant of change in the phase 2 component of the cardiac action potential (Surawicz, 1967b), effective refractory period (Surawicz, 1967a), ventricular excitability (Surawicz, 1967a) and conduction velocity (Goodman and Gilman, 1970), it seems most likely that the safety of calcium infusion depends primarily upon the rate of [Ca\(^{2+}\)] changes in blood. In our patients, [Ca\(^{2+}\)] was adjusted to normal with calcium administration and a disturbance of cardiac rhythm was not observed. In view of the known influence of plasma potassium concentration (Surawicz, 1967a) and digitalis therapy (Eliot and Blount, 1961) on the development of calcium-induced ventricular arrhythmias, plasma K\(^+\) was ascertained to be in the normal range and patients receiving digitalis therapy were excluded. In addition, available instrumentation permitted the close monitoring of [Ca\(^{2+}\)] throughout the observation periods.

Our data indicate that an increase in [Ca\(^{2+}\)] was associated with increased MAP (approximately 10% at 5 min) without significant alterations in HR. Increased MAP may occur secondary to increased cardiac output or to increased systemic vascular resistance, or both. Since data on cardiac output or systemic vascular resistance were not available, the mechanism responsible for increased MAP in our patients remains uncertain. However, recent experimental data (Drop and Scheidegger, 1980) have shown that the haemodynamic response to calcium infusion was influenced by the initial [Ca\(^{2+}\)] value. When calcium was infused with the initial [Ca\(^{2+}\)] values less than normal, increased MAP was recorded principally as a result of increased cardiac output. In contrast, when calcium was infused to increase [Ca\(^{2+}\)] from normal, increased peripheral vascular resistance was the principal cause of the increase in MAP.

In this study we tested two calcium solutions available in the United States. Hempelmann and associates (1978) found that the influence of 5.5% calcium gluconate 10 ml on haemodynamic function was less than that of 10% calcium chloride 10 ml in patients subjected to cardiac operations. Although [Ca\(^{2+}\)] was not measured by these authors, it is likely that increase in [Ca\(^{2+}\)] was less following the calcium gluconate infusion as compared with calcium chloride infusion.

Finally, in our patients, [Ca\(^{2+}\)] was adjusted to normal. Caution with excessive use of calcium should be exercised since data are not available to document the benefit or possible disadvantages of [Ca\(^{2+}\)] increased to much greater than normal in patients in whom there is evidence of myocardial ischaemia.

ACKNOWLEDGEMENTS

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REFERENCES


COllUMFASSEUNGS

These two drugs were used on patients' ability to keep up with their usual medication regimen. In the case of calcium-glucuronate, the drug with the same effect, the patient was able to keep up with their usual medication regimen. However, the drug with the same effect, the patient was not able to keep up with their usual medication regimen.

ZUSAMMENFASSUNG

Die beiden Drogen wurden auf ihre Fähigkeit hin verglichen, ionisierte Kalzium-Plasmakonzentrationen [Ca++] zu erhöhen. Um eine niedrige ionisierte Kalziumkonzentration zu korrigieren, erhielten 10 schwerkranken Patienten über eine Periode von 5 Minuten in willkürlicher Reihenfolge je Chlorkalzium (10 ml einer 10%igen Lösung von 27 mg ml⁻¹ elementales Kalzium) und Kalziumgluceptat (20 ml, enthaltend 18 mg ml⁻¹ elementales Kalzium), in Abständen von etwa 6 Stunden. [Ca++] und die hämodynamischen Variablen (mittlerer arterieller Druck (MAP), mittlerer rechtsatrieller Druck (RAP) und Herzfrequenz (HR)) wurden nach Beendigung der Kalziuminfusion auf 30 Minuten überwacht. Die Infusion beider Kalziumpräparate rief ähnliche Anstiege von [Ca++] hervor (5 min nach Infusion von Chlorkalzium: 33±3,1%; Kalziumgluceptat: 32±4,3% (Mittel±SEM), und die Wirkungen auf MAP waren bei jeder der beiden Lösungen ähnlich (11,1±1,8% und 9,7±2,4%).

EFECTOS COMPARATIVOS DEL CLORURO DE CALCIO Y DEL GLUCEPTATO DE CALCIO

Se llevó a cabo una comparación de la capacidad del cloruro de calcio y del gluceptato de calcio de incrementar las concentraciones de calcio ionizado en el plasma ([Ca++]). Con el propósito de corregir una baja concentración de calcio ionizado, se administró a cada uno de 10 pacientes críticamente enfermos tanto cloruro de calcio (10 ml de una solución al 10%, que contenían calcio elemental 27 mg ml⁻¹) como gluceptato de calcio (20 ml, que contenían calcio elemental 18 mg ml⁻¹) en un periodo de 5 min en orden al azar a aproximadamente 6 h de intervalo. Se realizó un control del [Ca++] y de las variables hemodinámicas (presión arterial media (PAM), presión arterial derecha media (PAD) y del ritmo cardíaco (RC)) durante un periodo de 30 min después del término de la infusión de calcio. La infusión de cualquiera de las dos preparaciones de calcio se acompañó de aumentos similares en el [Ca++] (5 min después de la infusión del cloruro de calcio: 33±3,1%; gluceptato de calcio: 32±4,3% (promedio±SEM) y los efectos sobre el PAM fueron similares para cada solución (11,1±1,8% y 9,7±2,4%, respectivamente).