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Ionization and Hemodynamic Effects of Calcium Chloride and Calcium Gluconate in the Absence of Hepatic Function

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Serial serum ionized calcium concentrations were measured before and after administration of either calcium chloride or calcium gluconate during the anhepatic stage of liver transplantation in 15 patients to determine the release of ionized calcium in the absence of hepatic function. When hypocalcemia (Ca^{++} < 0.8 mM) occurred during the anhepatic stage, patients were randomly assigned to treatment with chemically equivalent doses of either calcium chloride (10 mg/kg, n = 8) or calcium gluconate (30 mg/kg, n = 7). Serum concentrations of ionized calcium and citrate, hematocrit, arterial blood gas tensions, acid–base state, and hemodynamic profiles were determined before and up to 10 min after calcium therapy. In both groups of patients initial similar and rapid increases in Ca^{++} (0.98 ± 0.14 mM in the calcium chloride group and 1.05 ± 0.10 mM in the calcium gluconate group) were followed by gradual decreases over the next 10 min. Measured hemodynamic values were similar in the two groups, and neither group showed improvement in cardiovascular function after calcium therapy, possibly because of the decrease in preload that occurred during the anhepatic stage. Equally rapid increases in Ca^{++} after administration of calcium chloride and gluconate in the anheptic state suggest that calcium gluconate does not require hepatic metabolism for the release of Ca^{++} and is as effective as calcium chloride in treating ionic hypocalcemia in the absence of hepatic function. (Key words: Complications: hypocalcemia. Ions: calcium. Surgery: liver transplantation. Transfusion.)

CITRATE-INDUCED ionic hypocalcemia invariably occurs during liver transplantation because of massive blood transfusion and inadequate citrate metabolism by the liver.[1] Therefore, frequent monitoring of serum ionized calcium concentration and correction of ionic hypocalcemia are required to restore cardiovascular stability.[2–5] For the treatment of acute ionic hypocalcemia in adults, calcium chloride ($CaCl_2$) has been preferred over calcium gluconate. $CaCl_2$ is reported to produce a more rapid and predictable increase in serum ionized calcium (Ca^{++})[6] and have more positive inotropic effect.[7] Also, a greater and more predictable amount of administered $CaCl_2$ is retained in the body because urinary calcium excretion is more rapid with calcium gluconate.[8] Calcium gluconate, however, may depend on hepatic metabolism for the liberation of Ca^{++},[9] and gluconate metabolism produces CO_2, which may increase ventilatory requirement.[10]

However, recent studies *in vitro*,[11] in animals,[12,13] and in humans with normal hepatic function[13] have shown equal and rapid dissociation of Ca^{++} from $CaCl_2$ and calcium gluconate, suggesting that Ca^{++} release from gluconate is independent of hepatic metabolism. To test the hypothesis that the release of Ca^{++} from calcium gluconate is independent of hepatic metabolism, the pharmacokinetics and hemodynamic effects of equivalent doses of $CaCl_2$ and calcium gluconate were compared during the anhepatic stage in patients undergoing liver transplantation.

Methods

With the approval of the Institutional Research Review Board, informed consent was obtained from 24 adult patients undergoing liver transplantation. Anesthesia was induced with thiopental (3–4 mg/kg), and succinylcholine (1.5 mg/kg) was used to facilitate tracheal intubation. Anesthesia was maintained with isoflurane (inspired concentration, 0.3–1%), fentanyl (mean dose, 3 $\mu g \cdot kg^{-1} \cdot h^{-1}$), pancuronium (mean dose, 0.04 $mg \cdot kg^{-1} \cdot h^{-1}$), and lorazepam (mean dose, 6.1 ± 3 mg). Patients' lungs were ventilated with an oxygen/air mixture (FI_{O_2}, 0.5), and PEEP (5 cm H_2O) was added. Two indwelling radial arterial catheters were inserted. One was used for arterial pressure monitoring, and the other for blood sampling. A flow-directed pulmonary artery catheter was inserted *via* the right internal jugular vein. Two additional 8.5-Fr catheters were inserted for blood and fluid administration: one in the right antecubital vein and one in the left external or internal jugular vein. All intravenous (iv) catheters were kept open with calcium-free balanced electrolyte solution (Plasma-lyte A, Travenol, Deerfield, IL). Administration of fluid was guided by hemodynamic profile and urine output. A rapid infusion system (Haemonetics Inc., Braintree, Massachusetts) was

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used to infuse fluid with a composition of red blood cells: fresh frozen plasma: Plasma-lyte A in a ratio of 300:200: 250 ml. Transfusion of additional FFP, platelets, and cryoprecipitate was guided by thrombelastographic monitoring.[14] Venovenous bypass was used during the anhepatic stage to divert blood from the inferior vena cava and the portal vein to an axillary vein.

Baseline values of temperature, arterial blood gas tensions, acid–base status, hematocrit, arterial serum concentrations of ionized calcium and citrate, and hemodynamic measurements were made 30 min after abdominal incision. Arterial blood gas tensions were not corrected for temperature. Ionized calcium concentration was determined by use of an ICA-1 Ionized Calcium Analyzing System (Radiometer, Copenhagen) and citrate concentration with an enzymatic assay method (Berringer Mannham, Indianapolis, Indiana).[15] The hemodynamic measurements included heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), and thermodilution cardiac output in triplicate. Cardiac index (CI), left ventricular stroke work index (LVSWI), and systemic vascular resistance index (SVRI) were also calculated.

Thereafter, serum ionized calcium concentration was measured every 30–60 min. When ionic hypocalcemia occurred ($Ca^{++} < 0.8$ mM) during the anhepatic stage (nadir), all variables were determined again. Patients were then randomly assigned to one of two groups and given an equivalent dose of calcium intravenously: either $CaCl_2$ (10 mg/kg, $CaCl_2$ group) or calcium gluconate (30 mg/kg, CaGluc group). Both 10 mg of $CaCl_2$ and 30 mg of CaGluc yield approximately 1.36 mEq of Ca^{++} after dissociation.[16]

After calcium administration arterial Ca^{++} concentration was measured at 30 s, 1 min, 3 min, 5 min, and 10 min, hemodynamic measurements were made at 1 min, 5 min, and 10 min, and biochemical variables were obtained at 10 min. Plasma-lyte A solution was infused during the period between the occurrence of hypocalcemia and 10 min after calcium therapy to avoid a citrate load associated with blood transfusion.

Data are presented as mean ± SD. They were analyzed using analysis of variance of repeated measures, and differences between groups were assessed by the Student-Newman-Keuls test. $P < 0.05$ was considered statistically significant.

Results

Nine patients were excluded from the analysis: seven patients who developed hypocalcemia before or after the anhepatic stage and two patients who required vasopressor support (dopamine > 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Hypocalcemia occurred during the anhepatic stage in 15 patients: eight patients in the $CaCl_2$ group and seven in the CaGluc group. All of these patients had end-stage liver disease: five had postnecrotic cirrhosis and three cholestatic disease in the $CaCl_2$ group; five had postnecrotic cirrhosis and two cholestatic disease in the CaGluc group. The groups were similar in terms of age, weight, arterial blood gas tensions, acid–base status, Ca^{++} concentration, serum citrate concentrations, hemodynamic variables, and liver function tests at baseline, red blood cell requirement, and urine output (tables 1 and 2).

A similar degree of ionic hypocalcemia developed in the two groups of patients (0.68 ± 0.08 mM in $CaCl_2$ group and 0.74 ± 0.11 mM in CaGluc group), and the degree of hypocalcemia was inversely related to citrate concentration ($r = 0.66$, $P < 0.0002$). Serial changes in Ca^{++} concentration after calcium therapy are shown in figure 1 and table 2. Ca^{++} concentration increased rapidly after the administration of either calcium preparation. Values at 1 min were 0.98 ± 0.14 mM in the $CaCl_2$ group and 1.05 ± 0.10 mM in the CaGluc group. Ca^{++} concentration decreased gradually over the next 10 min in both groups but remained higher than the nadir value in the CaGluc group. Ca^{++} concentration was similar in the two groups of patients during the observation period. Other significant changes were increases in base deficit and citrate concentrations and a decrease in temperature compared with baseline values (table 2).

HR and MAP did not change in either group during the study period. CVP and PCWP did not change in the $CaCl_2$ group, whereas CVP increased and PCWP decreased from baseline values in the CaGluc group. CI and LVSWI were lower and SVRI was greater than baseline values in both groups of patients. All hemodynamic variables remained unchanged after calcium administration compared with nadir values, and they were similar in the two groups of patients except for greater CI in the $CaCl_2$ group at 1 min after calcium administration.

TABLE 1. Clinical Data of the 2 Groups of Patients

Variable	$CaCl_2$ Group (n = 8)	Calcium Gluconate Group (n = 7)
Age (yr)	47.4 ± 17.4	40.0 ± 11.8
Weight (kg)	74.1 ± 15.7	70.7 ± 10.2
Total bilirubin (mg/dl)	14.1 ± 15.8	7.9 ± 9.5
Serum glutamic oxaloacetic transaminase (IU)	112.5 ± 125.7	97.3 ± 73.8
Serum glutamic pyruvic transaminase (IU)	60.3 ± 98.4	48.1 ± 20.5
Prothrombin time (s)	15.9 ± 2.4	15.2 ± 2.3
RBC requirement (unit)	18.9 ± 13.4	10.1 ± 3.6
Urine output (ml/h)	138 ± 57	148 ± 94

Values are mean ± SD. No difference was found between groups.

TABLE 2. Laboratory Values and Hemodynamic Profiles before and after Administration of an Equivalent Dose of Calcium: $CaCl_2$ (10 mg/kg) or Calcium Gluconate (30 mg/kg)

Variable	Group	Baseline	Nadir	1 min	5 min	10 min
*p*H	$CaCl_2$	7.45 ± 0.06	7.42 ± 0.05	—	—	7.43 ± 0.06
	CaGlu	7.42 ± 0.04	7.39 ± 0.03	—	—	7.40 ± 0.03
Pa_{CO_2} (mmHg)	$CaCl_2$	34.9 ± 3.4	34.8 ± 3.2	—	—	34.5 ± 6.9
	CaGlu	35.4 ± 4.8	34.1 ± 3.2	—	—	32.6 ± 2.7
Pa_{O_2} (mmHg)	$CaCl_2$	182 ± 79	261 ± 72*	—	—	260 ± 62*
	CaGlu	220 ± 83	279 ± 58	—	—	287 ± 41
Base excess (mM)	$CaCl_2$	0.5 ± 2.6	−1.9 ± 2.6*	—	—	−1.6 ± 3.7*
	CaGlu	−1.9 ± 1.3	−4.1 ± 1.3	—	—	−4.0 ± 1.6
Hematocrit (%)	$CaCl_2$	28.6 ± 4.3	29.8 ± 4.1	—	—	29.4 ± 6.4
	CaGlu	28.3 ± 4.2	28.1 ± 3.8	—	—	27.7 ± 5.2
Citrate (mM)	$CaCl_2$	0.36 ± 0.28	0.99 ± 0.6*	—	—	1.26 ± 0.72*
	CaGlu	0.38 ± 0.36	1.04 ± 0.38*	—	—	0.94 ± 0.48*
Ca^{++} (mM)	$CaCl_2$	1.00 ± 0.10	0.68 ± 0.08*	0.98 ± 0.14†	0.83 ± 0.08*†	0.76 ± 0.07*
	CaGlu	1.00 ± 0.10	0.74 ± 0.11*	1.05 ± 0.10†	0.93 ± 0.10†	0.89 ± 0.09*†
Temperature (° C)	$CaCl_2$	35.8 ± 0.8	34.9 ± 0.7*	34.9 ± 0.8*	34.9 ± 0.8*	34.9 ± 0.8*
	CaGlu	36.0 ± 0.5	35.0 ± 0.9*	35.0 ± 0.9*	34.9 ± 0.9*	34.8 ± 0.8*
Heart rate (beats per min)	$CaCl_2$	92.9 ± 22.6	94.6 ± 21.4	96.4 ± 20.7	95.3 ± 20.1	96.3 ± 20.8
	CaGlu	100.1 ± 10.3	99.3 ± 12.4	100.3 ± 12.8	98.9 ± 12.6	97.9 ± 12.8
MAP (mmHg)	$CaCl_2$	69.6 ± 11.5	68.9 ± 9.8	72.3 ± 6.5	71.6 ± 8.3	67.9 ± 8.1
	CaGlu	78.1 ± 9.0	73.0 ± 13.8	75.0 ± 12.6	74.9 ± 13.4	73.3 ± 13.2
CVP (mmHg)	$CaCl_2$	11.3 ± 2.8	12.0 ± 4.2	11.9 ± 3.8	12.0 ± 3.8	11.9 ± 3.7
	CaGlu	9.7 ± 4.4	13.6 ± 4.2*	13.4 ± 4.2*	13.4 ± 4.5*	13.4 ± 4.4*
PCWP (mmHg)	$CaCl_2$	13.1 ± 3.2	12.4 ± 2.6	11.6 ± 3.7	11.6 ± 4.0	11.3 ± 2.4
	CaGlu	13.3 ± 2.0	11.9 ± 3.6	10.2 ± 1.7*	10.3 ± 2.4*	10.7 ± 2.1*
CI ($l \cdot min^{-1} \cdot m^{-2}$)	$CaCl_2$	4.4 ± 1.4	3.6 ± 1.8*	3.0 ± 0.5*	3.1 ± 0.8*	3.0 ± 0.5*
	CaGlu	3.9 ± 1.1	2.5 ± 0.5*	2.2 ± 0.4*‡	2.4 ± 0.6*	2.4 ± 0.7*
LVSWI ($g \cdot m \cdot m^{-2}$)	$CaCl_2$	36.3 ± 8.3	28.3 ± 9.3*	26.6 ± 6.5*	26.7 ± 5.6*	24.1 ± 4.6*
	CaGlu	34.1 ± 10.1	21.0 ± 8.4*	20.5 ± 9.4*	21.6 ± 7.3*	21.0 ± 6.1*
SVRI ($dyne \cdot s^{-1} \cdot cm^{-5}$)	$CaCl_2$	1,154 ± 444	1,527 ± 680*	1,671 ± 451*	1,655 ± 524*	1,564 ± 403*
	CaGlu	1,546 ± 609	2,020 ± 755*	2,360 ± 726*	2,306 ± 1,020*	2,147 ± 979*

* $P < 0.05$ *versus* baseline values within the same group.
† $P < 0.05$ *versus* nadir values within the same group.
‡ $P < 0.05$ *versus* the corresponding value of the $CaCl_2$ group.

Discussion

An inverse relationship between serum Ca^{++} and citrate concentrations was seen in this study, as has been described.[2,17,18] Both $CaCl_2$ and CaGluc administration rapidly corrected citrate-induced hypocalcemia, although a gradual decrease in Ca^{++} concentration over the 10-min period after treatment suggests that repeated doses of calcium may be required to avoid a recurrence of hypocalcemia.

Previous reports have suggested that $CaCl_2$, rather than CaGluc, is the preferred calcium salt for treatment of ionic hypocalcemia, mainly because of the possibility of more rapid release of Ca^{++} from $CaCl_2$. White *et al.*[6] demonstrated a more rapid and predictable increase in serum ionized calcium concentrations following administration of $CaCl_2$ than following CaGluc. However, their study included patients on hypothermic cardiopulmonary bypass, and the pump prime solution contained 23 mEq/l of gluconate, which might have decreased ionization of calcium gluconate. Worthley and Phillips[9] suggested that hepatic metabolism was necessary to release Ca^{++} from its gluconate carrier. However, Coté *et al.*[13] observed similar peak Ca^{++} concentrations within 30 s after administration of $CaCl_2$ or CaGluc in both children and dogs. Furthermore, Bull and Band[11] demonstrated no difference in the increase in Ca^{++} when equivalent doses of $CaCl_2$ and CaGluc were added to aliquots of whole blood. Our study results demonstrate that both $CaCl_2$ and CaGluc rapidly release Ca^{++} within 30 s of administration even in the absence of hepatic function, suggesting that simple dissociation rather than hepatic metabolism is the main mechanism for the release of Ca^{++} from both $CaCl_2$ and CaGluc.

Hempelmann *et al.*[7] suggested that the positive inotropic effect of $CaCl_2$ is greater than that of CaGluc during cardiac surgery, but the difference might have been related to the chemically inequivalent doses used: their $CaCl_2$ group received 7.5 mEq of Ca^{++} and their CaGluc group received 4.5 mEq of Ca^{++}.

In this study a difference in hemodynamic effects of the two calcium preparations was not demonstrated. Neither calcium salt improved hemodynamic variables. This lack of improvement might have been related to two characteristics of our experimental design. First, the definition of hypocalcemia in this study was conservative because myocardial depression has been shown to occur during liver transplantation when serum ionized calcium

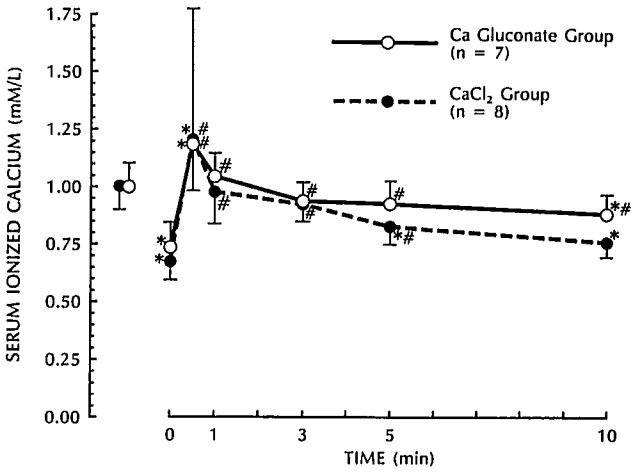

FIG. 1. Serial measurements of serum ionized calcium after administration of $CaCl_2$ or calcium gluconate. Values are mean ± SD. Solid circles represent $CaCl_2$ group (n = 8), and open circles represent calcium gluconate group patients (n = 7). *$P < 0.05$ *versus* baseline value. #$P < 0.05$ *versus* nadir value. No difference was found between the two groups.

is less than 0.56 mM.[2] Furthermore, improvement in left ventricular performance after calcium administration is greater when the initial serum ionized calcium concentration is low.[3] Second, the decrease in preload that occurs during the anhepatic stage of liver transplantation[19] might also have contributed to the lack of hemodynamic improvement. A decrease in preload from the baseline value determined during the preanhepatic stage was inevitable when the great vessels were clamped, even with the use of venovenous bypass, resulting in decreases in PCWP, CI, and LVSWI, and an increase in calculated SVRI. Thus, the failure to demonstrate hemodynamic improvement after calcium administration more likely represents an artifact of experimental design, rather than the implication that the treatment is unnecessary or ineffective.

Other potential complications associated with CaGluc do not appear clinically significant, although only a single dose was used in this study. CO_2 production and accumulation of acid were not significant, and differences in the retention of calcium due to differences in urinary excretion may not be an important consideration in the treatment of acute hypocalcemia.

In summary, chemically equivalent doses of $CaCl_2$ and CaGluc produced equally rapid and predictable increases in serum ionized calcium in humans during the anhepatic stage of liver transplantation; therefore, they are equally effective in treating acute ionic hypocalcemia even in the absence of hepatic function.

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