Clinical Chemistry 55:3
533–540 (2009)

Reducing Routine Ionized Calcium Measurement

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BACKGROUND: Ionized calcium (iCa) is measured frequently in hospitalized patients, and hypocalcemia is frequently found, seemingly supporting the practice.

METHODS: We retrieved the results of 58 040 iCa tests and records of intravenous (IV) and oral calcium supplementation from laboratory and hospital information systems and evaluated them for frequency of testing, frequency of hypocalcemia, and effects of calcium supplementation.

RESULTS: Serial and daily iCa testing was common and responsible for a substantial fraction of all iCa tests ordered. Half of all patients tested had iCa values below the reference interval. IV, but not oral, calcium therapy increased mean iCa concentrations, but the effect of calcium administration was small compared with the spontaneous increase in iCa that occurred in similar patients who received no calcium treatment. A retrospective analysis suggested that a low total calcium (tCa) concentration (<2.00 mmol/L, <8 mg/dL) could identify most patients with low iCa (<1.0 mmol/L). Introduction of a reflexive strategy reduced iCa testing by 72%–76% and reduced IV calcium gluconate therapy by 45%–81%.

CONCLUSIONS: Testing for iCa and IV calcium supplementation were significantly reduced with a reflexive calcium testing strategy that provided iCa testing only to patients with low tCa. Adverse clinical outcomes possibly associated with hypocalcemia did not increase.

Calcium is a ubiquitous mineral in the human body, found as hydroxyapatite in bone, in solution complexes with proteins and small anions, and as a "free" hydrated ion *(1)*. This last species, the free ion, is measured in clinical laboratories as whole blood, plasma, or serum "ionized calcium" (iCa).[2] Measurement of iCa has been advocated for clinical monitoring because free calcium is the physiologically relevant species that interacts with homeostatic receptors and ion channels, and it is the free calcium concentration, not the total calcium (tCa) concentration, that is tightly regulated by the body.

Ionized hypocalcemia is common in critically ill *(2–9)* and septic *(8, 10–14)* patients, and iCa monitoring and calcium supplementation are undertaken in such patients to avoid the effects of low calcium, which can include cardiovascular and neuromuscular compromise. Ionized hypocalcemia caused by massive blood transfusion and plasmapheresis transiently reduces the iCa fraction in serum or plasma by virtue of the chelating action of the citrate contained in blood products. In contrast, the ionized hypocalcemia prevalent in most critically ill patients is of unclear etiology. Dysfunction of the parathyroid and vitamin D axes has been postulated as a causal factor in some critically ill patients *(13)*, but there is no consensus as to the cause of the majority of hypocalcemia in the critically ill.

Consensus is likewise lacking as to what iCa values should prompt action in the form of oral or intravenous (IV) calcium supplementation. Severe ionized hypocalcemia (<0.80 mmol/L) can be associated with symptoms and is generally treated with IV calcium therapy *(1)*. Successful treatment of severe hypocalcemia, however, is difficult *(15)*. Mild hypocalcemia (1.00–1.12 mmol/L) is more amenable to treatment *(15)*, but treating these concentrations has not been proved to benefit patients. In fact, there is some evidence in animal models that calcium supplementation in severe sepsis is actually detrimental to survival *(16, 17)*, raising the question of whether hypocalcemia is an adaptive response with protective benefits.

Given the ongoing controversy about the role of calcium replacement in critically ill patients, we were surprised to find in our own hospital that iCa testing was frequently ordered as a daily test, and not just for critically ill patients or patients with signs or symptoms consistent with hypocalcemia. We hypothesized that

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Received August 21, 2008; accepted December 22, 2008.
Previously published online at DOI: 10.1373/clinchem.2008.116707

[2] Nonstandard abbreviations: iCa, ionized calcium; tCa, total calcium; TP, serum total protein; Alb, serum albumin; tCO_2, serum total CO_2, IV, intravenous; ICD, International Classification of Diseases.

iCa monitoring in hospitalized patients occurred more frequently than necessary and that a reduction in testing could be achieved by introducing a reflexive test panel that performed iCa testing only if the result of a less expensive tCa test was abnormal. Because iCa testing is a relatively expensive manual laboratory test, we suspected a reduction in tests could yield substantial cost savings, not only by reducing the amount of testing itself, but also by reducing the frequency of calcium supplementation given in response to low test results. We wished to assure ourselves, however, that a reduction in testing frequency would not result in a failure to provide treatment (principally calcium supplementation) to patients who would benefit from such treatment.

Therefore, we undertook to characterize the patterns and results of testing in our institutions. We investigated reflexive testing strategies that could reduce the overall frequency of iCa testing without missing any patients with critically low iCa concentrations. Because reducing such testing would likely reduce calcium-supplementation rates, we then attempted to assess the effects of oral and IV calcium supplementation on iCa concentrations in patients. Finally, after implementing the reflexive test strategy, we monitored several discharge diagnoses to understand what overall effects our intervention may have had on clinical outcomes.

Materials and Methods

As part of an ongoing quality-assurance study, we searched the laboratory information system serving 2 academic medical centers (430 and 415 beds) for all iCa results generated over a 9-month period in 2006. We collected 58 040 iCa results from 8726 patients, as well as any additional chemistry-panel test results produced from the same blood draw. We then queried the pharmacy database of one of the hospitals over the same time period for all instances of IV or oral calcium distribution, including date and time of issue, size of dose, calcium formulation, and route of administration. Institutional review board approval was obtained for this study.

We produced summary statistics describing the distribution of results of iCa testing and examined the time intervals between tests, the ordering locations of tests, and the results of concurrent tests for serum total protein (TP), serum albumin (Alb), serum total carbon dioxide (tCO_2), and tCa. We assessed the ability of tCa measurements to screen for ionized hypocalcemia by determining the diagnostic sensitivity and specificity of tCa concentrations for detecting iCa below specified target values. The results were compared with ROC curves generated for several iCa target values.

Serum iCa was measured with an ion-sensitive electrode on a Radiometer ABL 725 or a Roche Diagnostics AVL 9180 instrument without correcting for pH. tCa and tCO_2 were measured with ion-sensitive electrodes on Beckman Coulter LX 20 or DxC instruments. TP and Alb were measured on Beckman Coulter LX 20 or DxC instruments by means of commercial spectrophotometric methods based on dye–protein complex formation.

We combined iCa-test data and pharmacy-derived calcium-dose data in a correlated database consisting of patient iCa results at particular times and the amount and route of the calcium dose administered between measurements. We did not exclude or partition patients in this study because the physicians in our hospitals appeared to be testing most patients every day with no apparent regard for individual characteristics; this is the behavior we wished to model. Therefore, we queried the entire patient database by selecting a subpopulation of patients who had 2 iCa tests no more than 24 h apart and who had a calcium dose administered between the tests at least 12 h before the second iCa measurement. The initial iCa concentration, the size of the administered calcium dose, and the change in iCa concentration were fit to a multiple linear regression model that used calcium dose and starting iCa concentration as the independent variables. Correction of dose for patient weight was not performed because weight data were not readily available.

The initial results of this study prompted the introduction of an iCa reflexive test in both medical centers for "routine" monitoring of calcium status. The test consisted of a tCa test, with an iCa test reflexively performed whenever the results of the tCa test were outside of preset cutoff values ($<$2.00 mmol/L or $>$2.55 mmol/L, equivalent to $<$8.0 mg/dL or $>$10.2 mg/dL). Nonreflexive iCa testing was left available as a "write-in" test, but preprinted order sheets with nonreflexive iCa testing were incrementally removed from the hospital wards. We monitored the frequencies of iCa testing and IV calcium gluconate administration before and after the implementation of the reflexive panel by examining test tallies in the laboratory information system and usage records in the pharmacy system database.

To evaluate the possible adverse clinical outcomes of this laboratory intervention, we queried the information systems of both hospitals for in-hospital deaths and searched for selected International Classification of Diseases (ICD-9) codes occurring as secondary diagnoses in discharge summaries. We chose secondary discharge diagnoses because they reflect events that occurred during the hospitalization period, rather than primary diagnoses, which are most often present at admission. ICD-9 codes were grouped as follows: cardiac

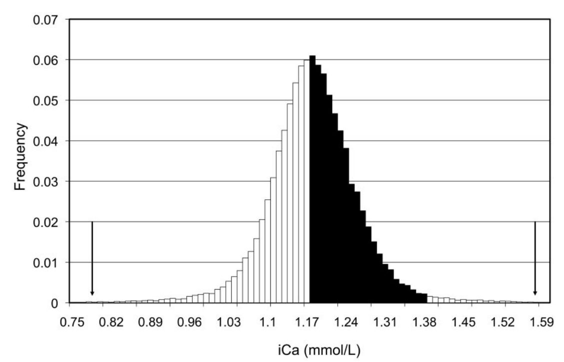

Fig. 1. Histogram of 58 040 iCa results.

The reference interval (shaded in black) is 1.18–1.38 mmol/L, and high and low critical values (1.58 mmol/L and 0.78 mmol/L) are indicated by black arrows.

arrest, 427.5; hypocalcemia, 275.41; tetany, 781.7; seizures not associated with epilepsy or stroke, 780.39. The total numbers of diagnoses, as well as the numbers of patients who were discharged or died, were collected for the 12 months before the institution of reflexive testing and for the most recent 12 months after the intervention. Patients <1 year of age were excluded from this analysis because very few children are seen at these hospitals. Even with the neonatal ICD-9 coding system, the number of diagnoses falling into these categories during the study period was too small to derive meaningful statistics.

We assessed the significance of differences between populations with the Student *t*-test or the Fisher exact test and assessed correlations with the Pearson product–moment correlation coefficient (r). We used Microsoft Excel for linear regression analyses.

Results

iCa CONCENTRATIONS IN HOSPITALIZED PATIENTS

The institutional reference interval for iCa was 1.18–1.38 mmol/L, which was established from 56 healthy adult volunteers by means of a sampling methodology similar to that used in patients. The results of 58 043 iCa tests on patients were approximately normally distributed, with a mean (SD) of 1.18 (0.09) mmol/L, and a median and mode both equal to 1.18 mmol/L (Fig. 1). The difference in iCa values between patients and healthy controls was highly significant ($P < 0.001$), and approximately half of all iCa results for patients were below the reference interval. Critical values, defined institutionally as values <0.78 mmol/L or >1.58 mmol/L, were rare, accounting for 0.09% (critically low) and 0.17% (critically high) of test results.

iCa ASSAY FREQUENCY

The 2 hospitals investigated in this study had a mean of 3326 and 4440 iCa tests per month between January 2001 and December 2006 (mean of 109 and 146 tests/day, respectively). Testing of hospitalized patients accounted for 95% of all testing, with the remainder originating from outpatient clinics and emergency rooms. A prior test result existed in the database for 85% of the newly requested tests.

For the repeat tests, the median time difference between tests was 23.5 h, and 42% of the repeat tests were performed within 24 h (±2.4 h) of a previous test. Patients in the data set received a mean of 6.7 tests, and those who underwent daily testing [defined as an interval between tests of 24 h (±2.4 h)] had a mean of 5.9 tests. The distribution of test frequencies indicated that a few patients received a large number of consecutive tests, with 51.5% of all iCa testing performed on patients who received ≥14 serial iCa tests. We identified several instances of serial testing extending for 60–200 consecutive tests, corresponding to daily testing for 2–7 months. The distribution of the number of iCa tests per patient is very similar to the distribution of lengths of stay in the hospital over the same time period (data not shown).

iCa CORRELATION WITH OTHER LABORATORY RESULTS

To assess whether abnormal iCa results could be anticipated from other laboratory results in a possible reflexive panel, we first evaluated whether iCa results were correlated with those for other commonly monitored laboratory tests (TP, Alb, tCO_2, and tCa) by examining 9409 instances in which all 5 tests were run on a patient sample simultaneously. The highest correlation was between iCa and tCa ($r = 0.74$), and there were weak correlations between iCa and Alb ($r = 0.21$) or TP ($r = 0.30$). The latter 2 correlations may be indirect, transitive reflections of the strong correlations of these 2 variables with tCa. We then used multiple linear regression analysis to develop models to predict iCa concentration from other measured variables. One multivariate equation [$\text{iCa} = 0.5(\text{tCa}) - 0.005(\text{Alb}) - 0.002(tCO_2) + 0.2934$, where iCa, tCa, and tCO_2 are in millimoles per liter and *Alb* is in grams per liter] was the best predictor of iCa concentration ($r^2 = 0.537$, predicted vs actual), but a simpler formula [$\text{iCa} = 0.5(\text{tCa}) + 0.115$ mmol/L] was nearly as predictive ($r^2 = 0.534$; Fig. 2).

PREDICTION OF LOW iCa FROM tCa

Because our models predicting iCa from tCa did not yield precise estimates of the iCa concentration, we investigated the ability of tCa to screen for iCa values below a certain cutoff. We derived diagnostic sensitivity and specificity values and used them to con-

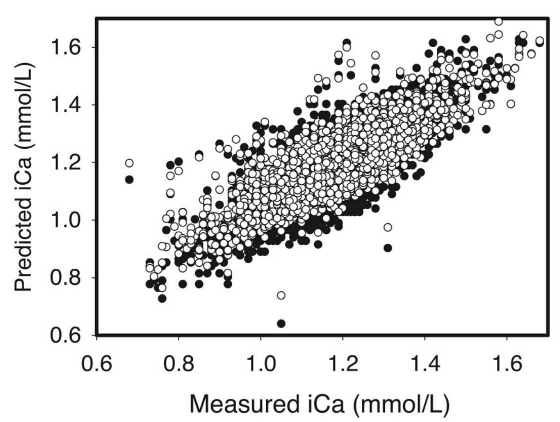

Fig. 2. iCa concentration predicted by tCa concentration alone (black circles) and by tCa, Alb, and tCO_2 concentrations (open circles).

struct ROC curves for the identification of samples with iCa results below various thresholds (Fig. 3). Although tCa was only moderately effective at detecting iCa values below the 1.18-mmol/L lower limit of the reference interval, it was much more effective at detecting values below lower thresholds. For example, if iCa testing had been performed only on samples with tCa concentrations <2.00 mmol/L (<8.0 mg/dL), 88% of patients with iCa concentrations <1.0 mmol/L would be detected, with only 2 tests with iCa values <1.0 mmol/L missed per month per hospital in our study (88% sensitivity, 74% specificity, 7% positive predictive value, 99.6% negative predictive value). Although the 2.00-mmol/L (8.0-mg/dL) tCa threshold missed a small number of iCa results below the critical notification value (<0.79 mmol/L), a review of individual medical records revealed that all of these critical iCa values were very likely to be erroneous, because concurrent measurements of electrolyte concentrations indicated likely dilution of samples by IV fluids administered via an indwelling catheter (data not shown). Therefore, limiting iCa measurement to samples with tCa values <2.00 mmol/L (<8.0 mg/dL) could have eliminated 73% of iCa testing without compromising the ability to detect serious hypocalcemia.

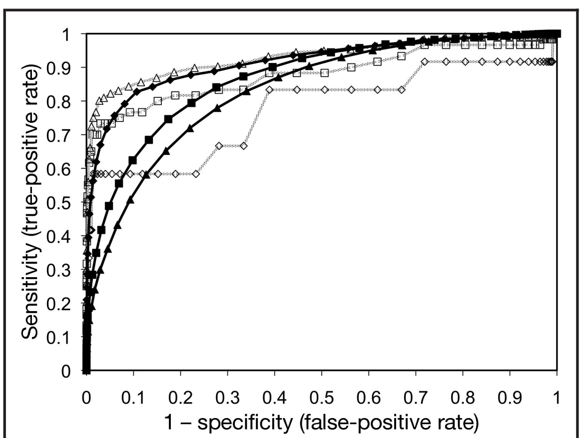

Fig. 3. ROC curves showing the ability of tCa cutoffs to predict varying levels of ionized hypocalcemia.

iCa concentration: <0.70 mmol/L (◇), <0.80 mmol/L (□), <0.90 mmol/L (△), <1.00 mmol/L (◆), <1.10 mmol/L (■), <1.18 mmol/L (▲).

EFFECTS OF CALCIUM SUPPLEMENTATION

We investigated the effects of calcium supplementation on subsequent iCa concentrations. Two-dimensional regression analysis demonstrated significant correlation between the calcium dose and the iCa response after 12–24 h for both oral and IV calcium administration (Fig. 4, A and B). Regardless of whether calcium was administered between tests, however, mean iCa concentrations in hypocalcemic patients increased to a degree directly proportional to the difference between the starting iCa concentration and the population mean of 1.18 mmol/L (Fig. 4C). Therefore, multiple linear regression was performed by modeling iCa change as a dependent variable with both starting iCa concentration and calcium dose as independent variables. For oral calcium supplementation, the model showed no dependence of iCa change on the size of the calcium dose but showed a significant dependence on the starting iCa concentration ($P < 0.001$). Therefore, oral calcium did not significantly alter iCa concentrations 12–24 h after a dose. Applying the same regression model to the data set consisting of patients who received IV calcium dosing identified a small dose-dependent increase in iCa concentration 12–24 h after calcium administration (0.0009 mmol/L per millimole IV calcium gluconate, $P < 0.001$), as well as a dependence on the starting iCa concentration similar to that seen in the oral-calcium model. Only 0.008 mmol/L of the expected iCa change after a typical IV dose of calcium gluconate (9.0 mmol) could be attributed to the dose itself.

REFLEXIVE iCa TESTING

In January and February of 2007, the laboratories of both hospitals began offering reflexive iCa testing, which consisted of a tCa assay followed by an iCa assay only if the tCa value was <2.00 mmol/L (<8.0 mg/dL) or >2.55 mmol/L (>10.2 mg/dL). Direct measurement of iCa was still available as a write-in test, and the use of whole-blood samples was strongly encouraged

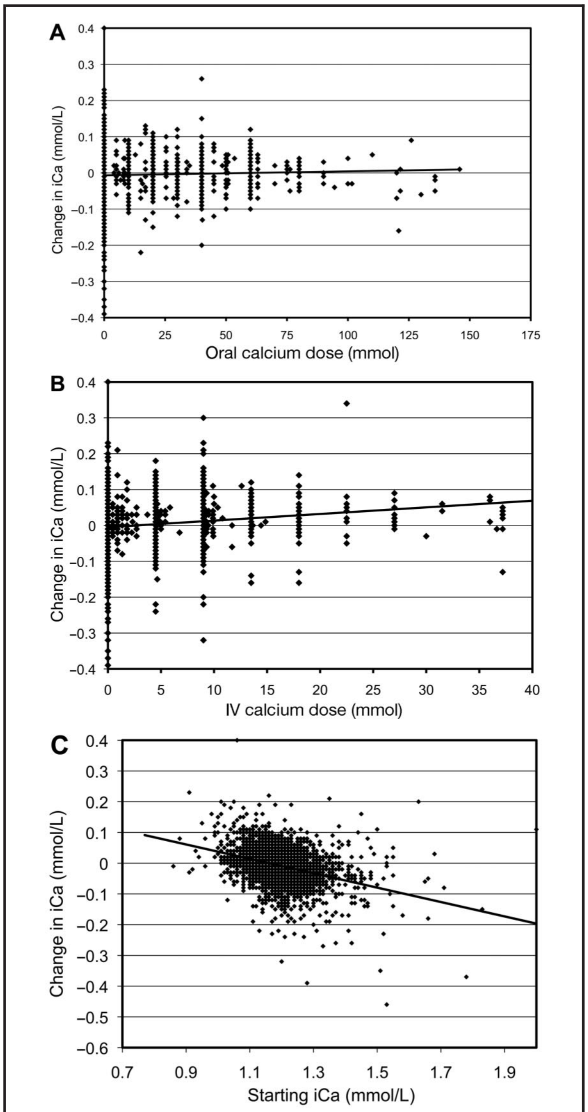

Fig. 4. Effects of calcium supplements.

(A), Response to oral calcium supplements. Regression line indicates the best-fit equation: Change in iCa = 0.00011 (Oral Calcium Dose) − 0.00675 mmol/L, where the change in iCa is in millimoles per liter and the oral calcium dose is in millimoles; $r^2 = 0.0299$. The slope is significantly different from zero ($P < 0.01$). Oral calcium was supplied as calcium carbonate, calcium acetate, or calcium citrate. (B), Response to IV calcium gluconate. Regression line indicates best-fit equation: Change in iCa = 0.0018(IV Calcium Dose) − 0.0049 mmol/L; $r^2 = 0.0299$. Slope is significantly different from zero ($P < 0.0001$). (C), Change in iCa within 12–24 h of a previous test plotted as a function of the starting iCa concentration. No oral or IV calcium was administered between tests. Regression equation: Change in iCa = −0.23 (Starting iCa) + 0.27 mmol/L; $r^2 = 0.118$. Slope is significantly different from zero ($P < 0.001$).

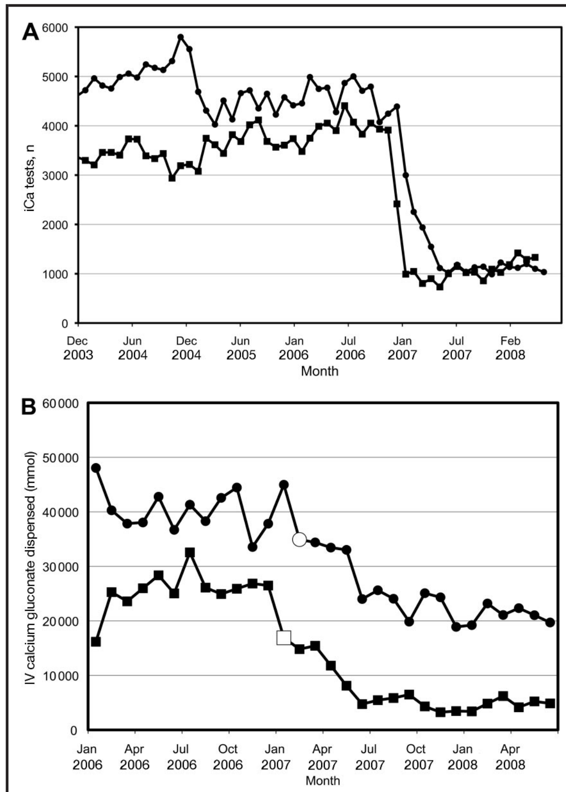

Fig. 5. Frequencies of iCa testing and IV calcium gluconate dispensed at the 2 hospitals during the study period.

(A), iCa tests ordered by month at hospital 1 (●) or hospital 2 (■). The reflexive panel was offered starting in February 2007 at hospital 1 and in January 2007 at hospital 2. (B), IV calcium gluconate (in millimoles) dispensed by each hospital pharmacy by month at hospital 1 (●) and hospital 2 (■). Open symbols denote the month that reflexive iCa testing began in each hospital.

for situations requiring direct measurement of iCa. The introduction of reflexive testing was preceded by educational sessions for the physician and nursing staff. Comparing the mean iCa test tally in the 12 months before institution of the reflexive panel to that for the 12 most recent postintervention months revealed a 72% reduction in iCa testing at one hospital and a 76% reduction at the other, a highly significant finding ($P < 0.001$; Fig. 5A) that was similar to the predicted 73% decrease. One hospital had a slower and less impressive initial decrease because of delayed implementation of the reflexive panel on some hospital units. The decreases in iCa testing have not shown any evidence to date of drifting back toward preintervention levels.

Table 1. Clinical outcomes before and after institution of reflexive iCa testing.[a]

	Total discharges and deaths, n	Deaths, n	Cardiac arrests, n	Hypocalcemia, n	Tetany, n	Seizures, n
Before reflex test intervention	36 453	1107	296	372	2	1344
After reflex test intervention	36 811	1120	307	185	1	691
P		0.96	0.73	>0.001	0.62	>0.001

[a] See Materials and Methods for how diagnoses were tabulated from ICD-9 codes. Values represent total counts for the 12 months before intervention and the 12 most recent postintervention months. *P* values are from Fisher exact tests comparing the pre- and postintervention periods.

IV CALCIUM ADMINISTRATION

We examined pharmacy records before and after January/February 2007 and found that a precipitous drop in hospital-wide IV calcium gluconate usage occurred shortly after the switch to reflexive iCa testing (Fig. 5B). Comparing usage levels for the 12 months before reflexive testing with those for the 12 most recent postintervention months revealed that IV calcium gluconate usage fell 81% at one hospital and 45% at the other ($P < 0.001$ for each comparison).

CLINICAL-OUTCOMES STUDY

We compared in-hospital deaths and selected diagnoses that occurred in the 12 months before our reflexive testing intervention with those for the most recent 12-month period after the intervention. We detected no significant increases in deaths, cardiac arrests, or tetany and found a statistically significant 51% decrease in the frequency of discharge diagnoses of hypocalcemia, as well as a significant decrease in the frequency of seizures (Table 1).

Discussion

Daily laboratory testing is becoming a hallmark of inpatient medical care. When testing is done as a matter of daily routine, rather than for cause, it can be considered a form of serial screening. Screening is most useful if it can detect a condition that might otherwise be inapparent and for which there is an intervention that leads to improved outcomes; however, there is a paucity of evidence that routine monitoring of common analytes leads to benefits for unselected patients.

iCa testing has increasingly found its way into the daily testing regimen in tertiary-care medical centers. In our own hospital, this practice had become so routine that iCa tests appeared on preprinted admission order forms, allowing house staff to order daily iCa testing simply by checking a box.

Routine iCa testing poses a problem for the clinical laboratory, however, because compared with other routinely monitored laboratory results, it requires substantial manual labor. Samples must be collected and handled in such a way as to minimize the loss of CO_2 by exposure to air or to the partial vacuum of an incompletely filled tube. Because no automated instrument offers testing for iCa, samples must be assayed individually by a technologist, and with some instruments, manual entry of results into the laboratory information system may also be required.

Given the burden of frequent iCa testing on our laboratory resources, we set out to assess how frequently iCa testing was being performed in our laboratory, with a goal of determining whether the volume of testing was justified. We also investigated the correlation between iCa test results and the results of other, less labor-intensive tests to develop a reflexive iCa test that could replace a majority of iCa testing with a less demanding alternative. Finally, because calcium supplementation was the principal intervention for ionized hypocalcemia, we attempted to correlate iCa test results with calcium-administration data to understand the dose–response relationship between administered calcium and iCa to determine how beneficial such supplementation might be.

Our study indicated that daily serial iCa testing was very common in our academic medical center. The majority of iCa testing was performed on patients who received 14 or more tests, clearly indicating that serial testing is the major contributor to heavy test use. We did not segregate all patients in this study by diagnosis, but we found that the patients who received the most testing were mostly patients who had undergone solid-organ or bone marrow transplantation. Although this finding most likely reflects the long mean length of stay for these patients, the literature for these 2 fields to our knowledge does not support daily iCa testing of such patients, despite its having become standard practice.

Approximately half of all patients tested for iCa were hypocalcemic, according to a reference interval derived from healthy adults. The consistent finding of hypocalcemia in ill patients in this and other studies indicates that hypocalcemia may be a natural response to illness, akin to the alterations in other serum analytes (fibrinogen, Alb, iron, and so forth) seen during inflammation. This finding, together with animal studies that have demonstrated possible harm from calcium administration during sepsis *(16, 17)*, should prompt a reevaluation of current practices regarding calcium supplementation in hospitalized patients. Standing orders and protocols that call for frequent measurement and reflexive supplementation of calcium in patients without clinically significant hypocalcemia should be scrutinized.

With the goals of reducing unnecessary iCa testing and calcium supplementation, we attempted to find a screening strategy to reduce iCa testing. We found that simply offering iCa testing only to those patients with tCa values <2.00 mmol/L (<8 mg/dL) could be reasonably diagnostically sensitive and specific for identifying seriously low iCa concentrations, with only a small number of patients with iCa values <1.0 mmol/L being missed. It is worth noting that tCa concentrations were measured with an ion-selective electrode in this study, and the sensitivity and specificity of tCa measured with an alternative method (dye binding) might be slightly different. Although we also performed iCa testing on patients with tCa values >2.55 mmol/L (>10.2 mg/dL), we did not focus on identifying hypercalcemic patients in this investigation because the incidence of total or ionized hypercalcemia was far lower than the incidence of hypocalcemia and because the concordance between total and ionized hypercalcemia as defined by our reference intervals was much higher than for hypocalcemia (data not shown). We also continued to offer nonreflexive iCa testing as a write-in test for all patients, because such testing is clearly applicable in several clinical settings, such as parathyroid dysfunction, transfusion, apheresis, malignancy, and serum protein abnormalities.

Because many fewer iCa tests were performed after the institution of reflexive testing, we sought to quantify the cost savings associated with our intervention. We estimated that it cost the laboratory US$3.28 to perform an iCa test, including sample processing, reagents, and technologist time. Implementation of the reflexive strategy eliminated approximately 60 000 manual assays per year, for an estimated savings to the laboratory of approximately US$197 000. Because the reflexive iCa panel also reduced the number of low iCa results that would normally have triggered calcium supplementation, a large decrease in IV calcium gluconate usage occurred shortly after the panel went into effect (Fig. 5B). Considering that the cost of calcium supplementation includes the material cost of calcium gluconate, pharmacy technician time to prepare doses, nursing time to administer doses, overhead, and the indirect costs of adverse effects such as line sepsis or the need to replace IV lines (e.g., when ceftriaxone or another medication incompatible with calcium is coadministered), the overall cost savings of this intervention are likely quite substantial. Because these additional costs are not accounted for separately in patients billed under diagnosis-related groups, however, accurate estimation of these further costs is not possible.

Simply broadening the reference interval for iCa for hospitalized patients could have yielded a similar decrease in calcium usage. We did not choose this intervention, however, because it would have reduced only calcium therapy, not testing.

The next part of our study evaluated the dose–response relationship between calcium supplementation and iCa measurement to evaluate what effect the decline in calcium supplementation might have. We did not design this study as a controlled pharmacologic study, nor did we intend to interpret it as such. Rather, we chose to study population effects by relying on pharmacy and laboratory records to infer individual effects from population observations. In so doing, we found that the mean iCa increased over a 12–24 h period in hypocalcemic patients to a degree proportional to the severity of the initial hypocalcemia and that the effect was present even when no calcium was administered. Although the amount of the spontaneous rebound was small compared with the interpatient variation, the slope of the regression (Fig. 4C) was highly significant, and the spontaneous changes were more substantial than the effects of calcium supplementation. The weakness of these associations is consistent with self-regulation of iCa to individual-specific set points.

Of note is that iCa concentration tended to spontaneously increase overall when the initial concentration was <1.18 mmol/L, the approximate midpoint of the iCa distribution, and tended to decrease when initial concentrations were >1.18 mmol/L. This observation is consistent with the possibility that 1.18 mmol/L represents a mean homeostatic set point for this population of ill patients. The essentially normal distribution around this value is also consistent with this hypothesis. If this hypothesis is true, many of the "low" iCa concentrations observed in hospitalized patients may in fact be appropriate, possibly reflecting another aspect of the acute-phase response.

Because only a small fraction of the relatively weak response to IV calcium seen in patients with marked hypocalcemia (iCa values of 0.8–1.0 mmol/L) was attributable to the administered calcium itself, we predicted that the observed reduction in calcium-supplementation rates caused by decreased iCa testing would probably not affect population calcium concentrations significantly. The clinical data we collected supports this prediction, because we found no significant increase in cardiac arrests, tetany, or seizures, all of which might be expected to increase if there were increased numbers of patients with unrecognized and untreated severe hypocalcemia. The overall high frequency of seizures can be explained by the fact that one of the hospitals is a referral center for neurosurgery, but the reason for the postintervention decrease is unclear. Tetany, a classic finding in hypocalcemia, was conversely extremely rare, which could indicate either that the true frequency of tetany is low or that hospital coders rarely record the event. Most interesting, however, is that despite lowering the overall rate of calcium supplementation with our intervention, we found a significant decrease in diagnosed hypocalcemia. This finding could indicate that rather than increasing clinically significant hypocalcemia in the population, our intervention most likely prevented physicians from making a diagnosis of hypocalcemia based on laboratory data only.

The data we have collected are subject to several sources of possible error and ambiguity. First, by looking retrospectively at a large database of laboratory data, we could not completely assess individual patient characteristics that could affect calcium metabolism. Although statistically significant population trends were identified, we recognize that patients should be treated as individuals in the medical decision-making process. Second, by relying entirely on hospital data, we experienced wider variation and uncertainty in when and how samples were collected and when and how calcium supplementation was given than would be encountered in a strictly controlled clinical trial studying dose and response. To eliminate this and other sources of error and to address possible clinical outcomes other than the relatively few investigated in this report, a prospective, placebo-controlled trial is warranted to investigate the outcomes of calcium supplementation and the utility and safety of frequent calcium measurement and supplementation in hospitalized patients.

RECENTLY PUBLISHED REVIEW

A recent publication reviewed the topic of administering calcium for hypocalcemia in critically ill patients and concluded that there was a lack of evidence that parenteral calcium supplementation impacts the outcome of critically ill patients *(18)*.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.*

Authors' Disclosures of Potential Conflicts of Interest: *No authors declared any potential conflicts of interest.*

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

Acknowledgments: Portions of the data in this report were presented orally at the 2007 meeting of the Academy of Clinical Laboratory Physicians and Scientists by G.S. Baird, P.M. Rainey, and W. Chandler but were not published in written form. We thank Rick Clayton for his assistance in data retrieval.

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