

The Effect of Exchange Transfusion on Serum Ionized Calcium

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ABSTRACT. The effect of exchange transfusion on serum ionized calcium concentration was studied during 27 exchange transfusions on 18 newborn infants. When heparinized blood is used negligible changes in serum calcium ion concentration occur, whereas with acid citrate dextrose (ACD) blood a profound fall in ionized calcium occurs which is not prevented by the infusion of calcium gluconate in the usually recommended amount. Ionized calcium levels could not be correlated with the infant's clinical state during the exchange transfusion. *Pediatrics*, 53:683, 1974, EXCHANGE TRANSFUSION, IONIZED CALCIUM, NEWBORN INFANTS.

Calcium is carried in the plasma in three forms—the first is bound to plasma protein, the second complexed to various anions and the third, which represents about 50% of the total calcium, is in the form of free ions. The ionized form is biologically active and, therefore, changes in ionized calcium are of primary concern during the newborn period.

It has long been the recommended practice¹ when doing exchange transfusions with acid citrate dextrose (ACD) blood, to infuse calcium gluconate at intervals during the procedure, in order to counteract the known binding effect of citrate on the calcium ion. In spite of wide acceptance of this procedure, there is no experimental evidence to indicate that the use of calcium gluconate has any beneficial effect on calcium ion homeostasis during exchange transfusions. The recent development of a calcium ion-selective electrode² has made it possible to do rapid and precise measurements of serum ionized calcium and we have thus been able to study the effect of exchange transfusion and of added calcium gluconate on the serum ionized calcium concentration.

METHODS

Eighteen newborn infants were studied during 27 exchange transfusions and divided into four groups as shown in Table I. Groups 1 and 2 were full-term infants and group 3 premature infants who received exchange transfusions with nonbuffered ACD blood. In groups 1 and 3, 1 ml of 10% calcium gluconate was infused for every 100 ml of blood exchanged. Group 2 received no calcium gluconate. Group 4 consisted of three premature and two full-term infants who received exchange transfusions using fresh heparinized blood. Exchange transfusion was performed according to standard techniques.¹ Fourteen infants had hemolytic disease (Rh and ABO incompatibility); three had hyaline membrane disease (one in group 3 and two in group 4) and one infant (group 1) had no obvious cause for jaundice.

Blood samples were taken via the umbilical vein catheter immediately before the exchange, after every 100 ml exchanged, and two hours and four hours after the exchange. Great care was exercised in flushing the catheter to remove any trace of admixed donor blood and the first 5 ml withdrawn for sampling was discarded. Serum ionized calcium was measured potentiometrically using a calcium ion-selective electrode in a flow-through configuration (Model 99-20 Serum Calcium Flow-Thru System, Orion Research, Inc., Cambridge, Massachusetts).

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TABLE I
CLINICAL AND LABORATORY DATA IN THE GROUPS OF INFANTS STUDIED

Group	No. of Infants	Type of Exchange	No. of Exchanges	Gestation (weeks)*	Birthweight (gm)*	Initial Serum Ionized Ca ⁺⁺ (mEq/liter)*	Initial Serum Total Ca (mEq/liter)*
1	4	ACD + calcium gluconate	6	40 ± 0.25	3,589 ± 74	2.25 ± 0.12	4.17 ± 0.13
2	6	ACD	6	40 ± 0.40	3,131 ± 280	2.24 ± 0.10	4.23 ± 0.13
3	4	ACD + calcium gluconate	7	34 ± 0.75	1,818 ± 343	1.64 ± 0.21	3.51 ± 0.17
4	5	Heparin	8	36 ± 1.63	2,271 ± 3.77	2.16 ± 0.17	3.96 ± 0.21

* Mean ± standard error.

setts 02139). The method has been described previously in detail.³ The standard deviation of the analysis was ± 0.02 mEq Ca⁺⁺/liter. Total serum calcium was measured by atomic absorption spectroscopy (Model 303 Atomic Absorption Spectrophotometer, Perkin-Elmer Corp., Norwalk, Connecticut 06852). Total serum protein was determined by refractometry.⁴

RESULTS

A profound fall in calcium ion occurred during exchange transfusions with ACD blood (Figs. 1 and 2). This was present whether or not calcium gluconate was added. When heparinized blood was used (Fig. 2), the changes in calcium ion concentration were negligible. The groups were compared by analysis of variance. Premature infants (group 3) showed significantly lower values for ionized

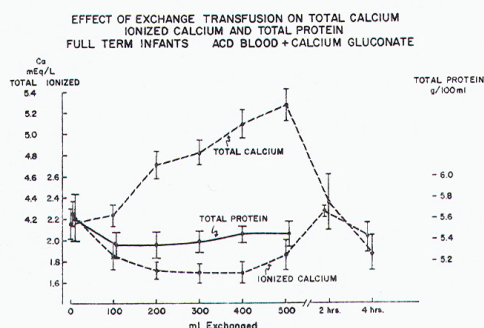


FIG. 1. Total calcium, ionized calcium and total protein concentrations in full-term infants undergoing exchange transfusion with ACD blood. One milliliter of 10% calcium gluconate was administered intravenously after each 100 ml of blood exchanged. Each point represents the mean and standard error for six exchange transfusions.

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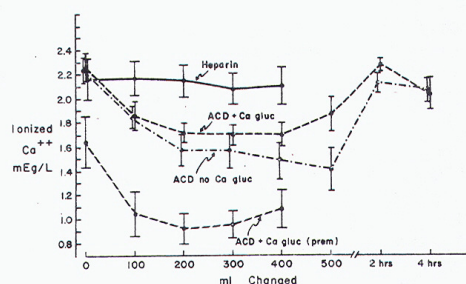


FIG. 2. Serum ionized calcium concentration during exchange transfusion on the four groups of infants studied. Each point represents the mean and standard error of the mean.

calcium initially ($p < 0.05$) and at all levels of the exchange ($p < 0.01$) than did the full-term infants (group 1).

The infants in group 1 (term, ACD, and calcium gluconate) were compared with group 2 (term, ACD, and no calcium gluconate). Ionized calcium for all measurements during the exchange (taken together) are higher in group 1 than in group 2 ($p < 0.05$). However, the values, when compared at each interval of the procedure, show no significant difference at any stage of the exchange transfusion. Serum ionized calcium returned to normal levels within two hours of the exchange transfusion (Figs. 1 to 3). This also occurred in the two premature infants in which two-hour samples were obtained.

Changes in total serum calcium are shown in Figures 1 and 3. The addition of calcium gluconate caused a significant elevation of total calcium ($p < 0.01$) but failed to prevent the simultaneous fall in ionized calcium (Fig. 1). Exchange transfusion

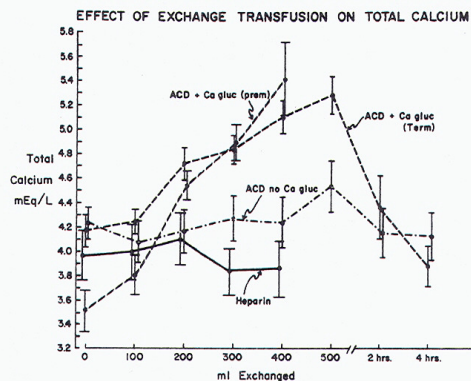


FIG. 3. Serum total calcium concentration in the four groups of infants studied. Each point represents the mean and standard error of the mean.

with heparinized blood caused minimal change in total serum calcium.

Figure 4 shows measurements of ionized and total calcium obtained at 100-ml intervals and again after the administration of calcium gluconate (10 ml of blood were exchanged after the calcium gluconate was administered and then a second sample was obtained). It is apparent (Fig. 4) that the administered calcium gluconate produces an immediate elevation of serum calcium. Although about 90% of this increase is accounted for by ionized calcium, the concentration of serum ionized calcium pursues its steady downhill course.

During exchange transfusions, crying, restlessness and irritability are commonly attributed to a low serum ionized calcium. In order to see whether these obvious clinical signs correlated with the babies' ionized calcium levels, we plotted the clinical state of the infant recorded at the time of sampling against the value for ionized calcium as shown in Figure 5. Eighty-one observations during 19 exchange transfusions were suitable for analysis. No significant difference was found between the two groups. Mean ionized calcium value for the infants recorded as sleeping was 1.52 ± 0.48 mEq/liter (SD) and for those recorded as crying or irritable was 1.50 ± 0.35 mEq/liter (SD).

DISCUSSION

These findings are in agreement with the observations of Radde *et al.*⁵ and Friedman *et al.*⁶ and demonstrate that calcium gluconate is not effective in preventing the fall in ionized calcium which occurs during exchange transfusions with ACD blood. In particular, in premature infants, serum ionized calcium falls to extremely low levels (Fig. 2) and it

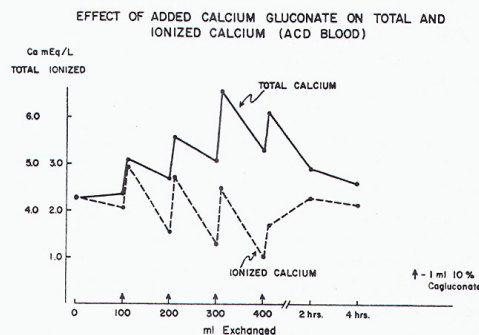


FIG. 4. Serum concentrations of total and ionized calcium immediately before and after the infusion of 1 ml of 10% calcium gluconate during an exchange transfusion using ACD blood. Ten milliliters of blood was exchanged between the two samples.

is remarkable that these infants are not symptomatic more often. As we could detect no calcium ion activity in the donor ACD blood, the fall in ionized calcium concentration may be due, in part, to dilution of the recipient's blood by calcium-ion-free donor blood.⁶ However, the chelation of the calcium ions by the infused citrate is much more likely to be the main mechanism responsible, particularly as the most significant fall in serum ionized calcium occurs very rapidly during exchange of the first 100 to 200 cc of blood and is much slower thereafter (Fig. 2), suggesting that the rate of metabolism of citrate by the liver has begun to keep pace with the rate of citrate infusion. After completion of the exchange transfusion, the levels of serum ionized calcium may return to normal within ten minutes,⁶ presumably as a result of the rapid me-

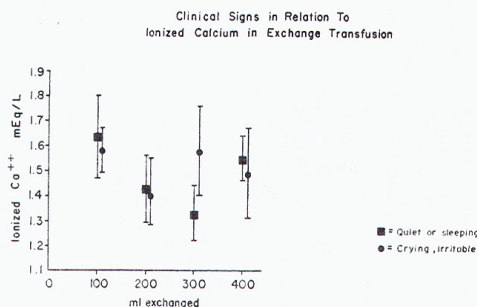


FIG. 5. Clinical signs in relation to serum ionized calcium concentration in exchange transfusion. Each point represents the mean and standard error of the mean. ■ Quiet or sleeping; ● crying, irritable.

tabolism of citrate. This is further support for the central role of citrate in the depression of serum ionized calcium concentration. It is interesting that even small premature infants demonstrate the ability to metabolize citrate quite rapidly. In two of the four premature infants in which two-hour post-exchange samples were obtained, the serum ionized calcium had returned to normal concentrations.

Studies in man and animals have demonstrated that massive infusions of ACD blood or of sodium citrate may produce high serum citrate levels and profound hemodynamic and cardiac effects.⁷⁻⁹ However, the "toxicity" of citrate has been shown to be due entirely to its binding of calcium ion and the resultant fall in serum ionized calcium.^{7,9} Considering the number of exchange transfusions which have been performed on newborn infants and the almost negligible effect exerted by calcium gluconate on the concentration of serum ionized calcium, it is remarkable that the clinical signs of hypocalcemia are not seen more frequently. Perhaps this is because the low levels of calcium ion are generally too short-lived to have any significant clinical effect. Another factor which may protect the infant against tetany is the acid load of the transfused ACD blood which tends to produce a metabolic acidosis.¹⁰ It has recently been demonstrated in dogs, that the combination of hypocalcemia and alkalosis is necessary in order to consistently produce tetany.¹¹

The finding that the levels of ionized calcium correlated poorly with clinical signs and symptoms (Fig. 5) merely emphasizes the fact that, while crying and restlessness during an exchange transfusion may, on occasion, be due to low concentrations of serum ionized calcium, this is by no means the only cause.

SUMMARY

Measurements of ionized calcium during exchange transfusions on newborn infants demonstrated that the use of ACD blood produces a profound fall in serum calcium ion concentration which is not prevented by the infusion of 0.1gm of calcium gluconate after each 100 ml of blood exchanged. When heparinized blood is used, there are negligible changes in ionized calcium concentrations.

The absence of clinical tetany in spite of very low levels of ionized calcium is consistent with the experimental observations that hypocalcemia alone

does not consistently produce tetany and suggests that the acid load of the infused blood may be protective.

There was no correlation between crying and restlessness during the exchange transfusion and hypocalcemia.

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