AN ESSAY ON NEONATAL HYPOCALCEMIA

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BY

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بسم الله الرحمن الرحيم

سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ.

صدق الله العظيم

بسم الله الرحمن الرحيم

TO MY PARENTS FOR THEIR

PATIENCE, SUPPORT, AND UNDERSTANDING

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C O N T E N T S

INTRODUCTION

Calcium is present in the body in larger amounts than any other mineral element. During pregnancy there is rapid transfer of calcium from mother to fetus via an active placental pump. In the last trimester of pregnancy there is a net transfer of calcium of 100 to 150 mg/Kg of fetal body weight.

Ionised calcium levels in the blood of mammalian fetuses are high and nearly always greater than that of the mother. At birth there is abrupt termination of the maternal to fetal calcium supply. Since dietary calcium in the first few days of life is significantly less than the amount normally received through maternal to fetal transfer, a fall in serum calcium would be expected to occur. High risk newborns show many changes in serum electrolytes. Neonatal hypocalcemia affects 30% - 50 % of these high risk infants.

This study aims to throw light on recent understanding for this subject.

Definition of neonatal hypocalcemia:

An infant can be considered hypocalcemic when serum calcium concentrations are below the lower limit of normal serum calcium level. Gittleman and Pincus, (1951) considered 8 mg % (4 m Eq./L) as the lower limit for full term and low birth weight , while Root and Harrison, (1976) defined neonatal hypocalcemia as a total calcium concentration below 7.5 mg%. Howover, Bruck and Weintraub, (1955) considered 7 mg% (3.5 m Eq./L) as the lower limit of normal calcium level in low birth weight infants.

Definitions vary as regards the level of serum calcium required for diagnosis of hypocalcemia, but most authors agree that when serum calcium falls below 7 mg%, the infant should be considered hypocalcemic At 7 mg %, ionized calcium levels are low, and body mechanisms for conservation of calcium are activated.

Recently, with the advent of ionized calcium determinations in clinical laboratories, the definition of neonatal hypocalcemia should be revised to include conditions where the level of ionized calcium in serum falls below 3 to 3.5 mg/dL (Tsang and steichen, 1983).

CALCIUM

Calcium represents one of the most important minerals to newborn infants and neonates. It has a basic role in the permeability of membranes, the activation or inhibition of many enzymes, the action of several hormones, blood coagulation, and nerve transmission. In vertebrates it is preferentially involved in the bone mineralization (Root and Harrison, 1976). At all ages 99% of the body's calcium is stored in bones. The body contents of calcium in infants and adults approximate 400 and 950 m Eq/Kg of body weight respectively (Behrman et al., 1983 b,).

Calcium in blood circulates as three important fractions, a protein bound fraction,a complexed fraction (complexed with bicarbonate, phosphate or citrate) and as an ionized fraction. The later 2 fractions are also termed ultra-filterable calcium (or non protein bound calcium). The ionized fraction is the only physiologically active fraction of the blood calcium. Thus total calcium levels in the blood might be reduced as the result of low plasma protein, however, if ionized calcium remains normal, there may be no physiological changes. On the other hand total calcium levels may be unchanged when chelating agents are used, such as the citrate in acid-citrated blood, in this instance ionized calcium is lowered, with potentially significant physiologic effects (Tsang and Steichen, 1983).

SOURCES OF CALCIUM :

By far the major source of calcium in the diet is milk or milk products (Guyton, 1982). Human milk contains insufficient amounts of calcium (Heird et al,1983). Calcium content of formulas and human milk ranges from 35 to 85 mg/100 ml. Intrauterine calcium accumulation rates of 130 to 150 mg/Kg/day cannot be achieved in the premature infant unless additional calcium is incorporated in all formulas and milk feedings, (Fomon et al, 1977).

Human milk was fractionated and analyzed for the distribution of copper, zinc, calcium and magnesium among various fractions. In whole milk the concentration of calcium was 241.2 $\pm$ 61.9 ug/ml. Most Ca was found in the skimmed milk, but significant amount of Ca was found in the fat, most likely associated with the fat globule membrane. Less than 4% of Ca was found in the casein. A low molecular weight fraction contained 34% of total Ca. The unique distribution and binding of Ca in the milk may, in part, explain the known high bioavailability of Ca in human milk (Fransson and Lonnerdal, 1982).

REQUIREMENTS:

Since the newborn infant begins rapid ossification soon after birth, so he needs a ready supply of calcium throughout infancy (Guyton, 1982). The recommended practical requirements have been set out by a group of experts of WHO-FAO for the period of postnatal development of the skeleton. These are:- 500 -600 mg/day from 0-12 months, 400-500 mg/day from 1-9 years, 600-700 mg/day from 10-15 years and 500-700 mg from 16-19 years. The above recommended levels represent an optimum (OMS-FAO, 1962).

There is difficulty to meet the enormous calcium and phosphorus needs of the rapidly growing premature, as these substances can be provided in only limited concentrations in I.V. fluids (intravenous fluids) without being precipitated (Usher, 1981). Growth of infant of 30 g/day requires 0.7% calcium uptake in new tissue or 210 mg of calcium deposition/day in absolute terms, most of which goes to bone mineralization. A 3000-g, full-term infant, if also growing 30 g/day, can absorb up to 240 mg, and will need 210 of that for growth. The 1,000 g extreme premature will, on the other hand, absorb only 80 mg and still require 210 mg for growth if maintaining 30 g/ day (Widdowson and Spray , 1951) .

Fommon and associates,(1977) and Day and associates,(1975) have shown that premature infants may require and benefit from calcium intake in the range of 180 to 220 mg/kg/day. Considering that calcium retension rates are 50 to 60% of the intake, the intrauterine accumulation rates (130 to 150 mg/kg/day) are approached but not met even at these intake levels. Such levels of calcium intake are rarely achieved in the premature infant who is fed enterally.

Atkinson et al., (1983) have found that neither the premature infant's own mother's milk (preterm milk) nor the modified infant formula (SMA) supplies adequate calcium and phosphorus for the rapidly growing very low birth weight infant.

In all those situations (prematurity; babies born of high - risk pregnancy; small-for dates babies in whom there may be a reduction or difficulty in acquiring an adequate intake of calories) there will be a reduction in the alimentary intake of calcium. (Fomon et al., 1963).

ABSORPTION and TRANSPORT of CALCIUM :

Calcium is poorly absorbed from the intestinal tract because bivalent cations are poorly absorbed through the intestinal mucosa (Guyton, 1982). Calcium is absorbed by an active transport machanism in the upper small intestine. A calcium-magnesium-dependent ATP ase pump facilitates its entry into the mucosal cells where it is attached to a specific calcium-binding protein. (Shafer, 1971).

Between 20% and 60% of dietary calcium is absorbed depending on a variety of factors. Vitamin D, parathromone and perhaps growth hormone increase calcium uptake (Hanna et al, 1961). Above all the availability of cholecalciferol is the factor that markedly increases absorption (Royer, 1981).

Decreased absorption of calcium results from the presence of phytate, oxalate, and citrate (all of which complex the dietary calcium) in the gastrointestinal tract; from increased gastric motility ; from reduction of bowel length; and also from protein depletion which may cause a deficiency of the calcium binding protein in the intestinal mucosa.(Behrman, et al; 1983) Williams et al;(1970) have found that faecal loss of calcium in the newborn is influenced by the fatty acid composition of the milk lipid. A high level of stearate and of palmitate increases the calcium loss. On the other hand, oleate favour absorption. Thus it may be important in the neonatal period to take into consideration of this possible cause of tetany, when studying the new milks often described as "adapted"or" humanised".

In the normal breast-fed fullterm baby, it seems that the percentage absorption (or the cofficient of net digestive utilisation) of calcium undergoes a progressive maturation. Thus the percentages are 27.8 $\pm$ 16.5 % for babies from 4-7 days old, and 43.9 $\pm$ 13.2% for those between 7 and 10 days (Williams et al, 1970). This figure can reach 60% or more after a month (Royer, 1981) .By contrast, the absorption of calcium is much less with cows milk or with modified formulae (Williams et al., 1970) Thus the net coefficient of digestive utilisation of calcium (CDU), varies with age; it is strikingly higher in children (30-40%) than in adults (20%). It depends on the nature of the foodstuffs being more than 60% in the suckling child fed with mother's milk and between 20 and 30 % in the baby fed with cow's milk. It is much influenced by the other constituents of the diet, but above all by the availability of cholecalciferol which markedly increases absorption (Royer , 1981). Finally, it depends on factors concerned with adaptation to the alimentary supply of calcium .It has been established in various circumstances that the net CDU for calcium varies inversely with the usual alimentary supply. Further, it has been demonstrated in the adult that in an individual, a rapid or a slow adaptation to variations of alimentary supply can be observed (Malm, 1958). After a period of low calcium intake (less than 50 mg/ day) or during the period of recovery from deficiency rickets, the net CDU of calcium in the child may surpass 60%. This phenomenon may be prolonged one or two weeks untill the metabolic needs for calcium have been met (Royer, 1981). However the mechanisms responsible for this adaptation are not know (Behrman et al; 1983b). The existence of a signal governing the relationship between metabolic needs for calcium and the percentage of alimentary calcium absorbed by the intestine has been hypothesised for a long time, and has been given the name"endogenous factor" (Nicolaysen , 1943).

EXCRETION :

About 90% of the dietary calcium is excreted in the faeces, the remaining 10% is excreted in the urine. The faecal excretion represents, to a large extent, calcium added to the gut by intestinal secretion. In the kidney about 99% of the filtered calcium is reabsorbed throughout the nephron mainly by the proximal convoluted tubules. The absorption which occurs in the proximal tubules (50- 55%), and in the loop of Henle (20-30%) appears to parallel sodium reabsorption. Factors influencing transport of one of these cations also simulataneously affect the other. Calcium reabsorption is stimulated specifically by 1,25-dihydroxy vitamin D_3 and inhibited by thyrocalcitonin. Urinary excretion of calcium is also increased by many nonspecific mechanisms These include expansion of extracellular fluid volume; the administration of osmotic diuretics, furosemide, thiazides, growth hormone, thyroid hormone, or glucagon; metabolic acidosis; prolonged fasting; and an increase in serum phosphate (Winters, 1973).

There is a diurnal variation in the excretion of calcium , which peaks at the middle of the day. Alterations in dietary calcium result in only small changes in urinary excretion of calcium, probably reflecting adaptive changes in intestinal absorption of calcium. Physical inactivity is associated with increased urinary excretion of calcium and, if prolonged, may result in formation of renal stones (Behrman et al; 1983b).