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Blood ferritin hyperbilirubinemia iron

Ferritin Turnover in Plasma: An Opportunistic Use of Blood Removed during Exchange Transfusion

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Extract

The concentration of plasma ferritin was measured in serial samples of blood removed from six preterm neonates undergoing exchange transfusion for hyperbilirubinemia. The average plasma ferritin concentration in the infants was 218 ng/ml compared with 47 ng/ml in the donors. The mean concentration of ferritin decreased an average of 62 ng/ml during the exchange transfusions. The plasma ferritin half-life was computed to be 2.5 and 5.5 min in the two infants weighing 2,000 and 2,500 g compared with a half-life of 4 min in the rat. In four infants weighing between 1,000 and 1,180 g, the half-life ranged from 9.1 to 34 min. These data support the concept of a rapid plasma ferritin turnover and indicate that ferritin may transport a large amount of iron through the plasma compartment in spite of its low concentration.

Speculation

Plasma ferritin appears to play an important role in iron transport in man.

In the rat, ferritin in plasma plays a major role in the transport of iron from the reticuloendothelial system to the liver parenchymal cell. Intravenously injected ^{59}Fe-labeled, heat-treated erythrocytes are rapidly sequestered by the spleen, which then releases [^{59}Fe] ferritin into the plasma (12). [^{59}Fe] Ferritin is then cleared rapidly from the circulation by the liver parenchymal cells (6, 12). Subsequently, most of the label appears in circulating hemoglobin, presumably after transport from the liver to the bone marrow via transferrin (12). This newly proposed transport function for plasma ferritin modifies the previous view that ferritin functions solely as the major tissue storage compound for iron. The iron in plasma ferritin has a rate of turnover about 20 times more rapid than that of iron that is bound to transferrin (12). Consequently, even small amounts of ferritin could transport relatively large amounts of iron.

In man, ferritin, if fully loaded with iron, can be calculated to account for 1–5% of the iron in plasma. The turnover rate of plasma ferritin has not been measured in humans. If it is rapid, as in the rat, this would favor a similarly important role for plasma ferritin in the transport of iron. The kinetic behavior of plasma ferritin may also have bearing on the basis for changes in its concentration under normal and abnormal conditions. In general, plasma ferritin reflects the concentration of iron stores (1, 3, 7, 9, 11, 13). During normal development the changes in plasma ferritin concentration closely parallel the changes in the concentration of iron stores (11), being high at birth (mean: 101 ng/ml), low during most of childhood and adolescence (30 ng/ml), and higher in the adult male (140 ng/ml) than in the female (39 ng/ml). Abnormally low and high plasma ferritin levels are associated with iron deficiency and iron overload, respectively (1, 7, 9, 11).

We devised a means of studying human plasma ferritin turnover as a byproduct of exchange transfusion in newborn infants. Neonates who underwent exchange transfusions for hyperbilirubinemia afforded a suitable model for the following reasons. (*1*) The plasma ferritin concentration of the recipient was much higher than in the donor blood, a more than fourfold difference on the average. (*2*) The exchange of blood was rapid, the equivalent of 1.4–1.9 blood volumes/hr. Thus, if there were no endogenous release of ferritin into the plasma, the ferritin in the infant's plasma would be "flushed out" and would approach values close to those of the donor blood. A rapid rate of entry of ferritin into plasma would tend to keep the ferritin concentration stable and well above that of the donor. Assuming steady state conditions, with uptake and release of ferritin in balance, the turnover of ferritin can be calculated from the changes in its concentration in the plasma removed during the exchange transfusion.

SUBJECTS AND METHODS

The six infants studied were all preterm, between 28 and 36 weeks of gestational age. They had hyperbilirubinemia of unknown cause, with prematurity undoubtedly a contributing factor. Exchange transfusions were performed between 1 and 6 days of age (Table 1). The exchange transfusion was by routine methods with careful recording of times and volumes. The blood that was removed was collected into a series of 12–43 test tubes. The exchanges were equivalent to 1.4–2.5 times the estimated blood volume (8% of body weight) and were performed in 55–90 min (Table 1). Blood was exchanged in 6–20-ml increments. On the average, the hematocrit of the neonate and the donor blood differed by 2.7%. However, this factor was not included in the calculations because a corresponding change in the plasma volume of the neonate would affect the results to only a minor degree. Deviation from the assumed blood volume, minor fluctuation in the blood volume during the exchange, and dead space in the catheter and stopcock (0.29–0.42 ml) were also calculated to have little influence on the results.

Plasma ferritin was measured by radioimmunoassay (11). Three electrophoretically distinct but immunologically cross-reactive forms of ferritin have been identified in man: spleen, liver, and reticulocyte ferritin (2). It is not known which form or forms are present in plasma. A fetal form of liver ferritin has been identified in the rat (8), but there is no evidence for a developmental change in the structure of ferritin in man.

Table 1. *Conditions of exchange transfusion*

Case	Birth wt, g	Age, days	Vol. exchanged/blood vol.	Duration of exchange, min	Hematocrit, %	
					Initial	Final
1	2,000	6	2.0	60	48	47
2	2,500	4	1.4	60	45	45
3	1,180	3	2.1	70	39	43
4	1,080	5	1.5	90	40	39
5	1,130	4	2.2	90	45	35
6	1,100	1	1.9	55	43	43

ESTIMATION OF PLASMA FERRITIN HALF-LIFE

The rate of change of the amount of ferritin (P) in neonatal plasma is a function of the difference between the rates of its delivery and removal. The rate of delivery has two components, the rate of endogenous release (K) and the rate of exogenous delivery (vp_d), because of the exchange transfusion, where v is the amount of plasma exchanged in 1 min and p_d is the donor's plasma ferritin concentration. The rate of removal is also composed of two components, an endogenous rate of removal (kP), proportional to the amount of ferritin in the plasma, and an exogenous removal rate (vp), where p is the subject's plasma ferritin concentration. In defining an exchange rate coefficient $\epsilon = v/V$ (V is the infant's plasma volume), the rate of change in the total amount of plasma ferritin is

$$\frac{dP}{dt} = K + \epsilon V p_d - (k + \epsilon)P \qquad (1)$$

and the rate of change in the concentration of plasma ferritin (assuming that the total plasma volume remains constant) is

$$\frac{dp}{dt} = \frac{K}{V} + \epsilon p_d - (k + \epsilon)p \qquad (2)$$

Since the infant's initial plasma ferritin concentration is the steady state of the above differential equation, its value before the exchange, *i.e.*, when $\epsilon = 0$, is

$$p(0) = \frac{K}{Vk} \qquad (3)$$

Integration of the differential *equation 2* then yields the infant's plasma ferritin concentration at anytime during the exchange, *viz.*,

$$p(t) = \frac{kp(0) + \epsilon p_d}{k + \epsilon} + \frac{\epsilon[p(0) - p_d]e^{-(k+\epsilon)t}}{k + \epsilon} \qquad (4)$$

The time course of the plasma ferritin concentration is shown in Figure 1.

For each infant the values of his and the donor's plasma ferritin concentration, [p(t)] and [p_d], are known, as is the value of the exchange rate coefficient of plasma ferritin removal (ϵ). Hence, the only unknown parameter, the rate coefficient of endogenous ferritin removal (k), can be calculated. For this purpose a nonlinear least squares fitting procedure (program BMD 85x) on the University of California digital computer IBM 360/50 was employed (4). The mean values of k and their standard deviations were obtained (Table 2). The half-life of plasma ferritin is calculated by the formula, $t_{0.5} = \ln 2/k$.

The rate of release of ferritin from tissue to the circulation and the rate of its disappearance from the circulation are equal under steady state conditions. The calculations assume that these rates are not altered by the exchange transfusion. In addition, it was assumed that there is negligible diffusion of ferritin into or out of the intravascular compartment during the exchange transfusion. The latter assumption is supported by the observation in the rat that continuous intravenous infusion of ^{59}Fe-labeled ferritin at a rate equal to its rate of disappearance over a period of 60 min results in almost all (97%) of the radioactivity accumulating in the liver (12). Furthermore, a factor against a rapid rate of passive diffusion is the large molecular weight of ferritin, 600,000–900,000, depending on the iron content.

RESULTS

The plasma ferritin concentration in this group of neonates averaged 218 ng/ml in contrast to 47 ng/ml in the donor blood (Table 2). During the six exchange transfusions the mean concentration of ferritin decreased an average of 62 ng/ml in the neonate. Fluctuation of the individual values was in all cases greater than the error of the assay would suggest as indicated by the standard deviation of k (Table 2).

The results show that the two neonates weighing 2,000 and 2,500 g had a plasma ferritin half-life of 2.5 and 5.5 min, respectively, similar to the value of 4 min in the rat (12). In the four infants weighing 1,000–1,180 g, the half-life ranged from 9.1–34 min (Table 2).

DISCUSSION

The present results indicate that plasma ferritin in man has a rapid rate of turnover and plays a larger role in iron transport than its low concentration would suggest. In the rat, the liver clears almost all of the ferritin from plasma. The figures for turnover in the neonate were variable and probably reflect incomplete development of liver function, which is likely to be exaggerated in this group of infants who required exchange transfusion for hyperbilirubinemia. This may explain why the slowest turnovers were obtained in the smaller premature

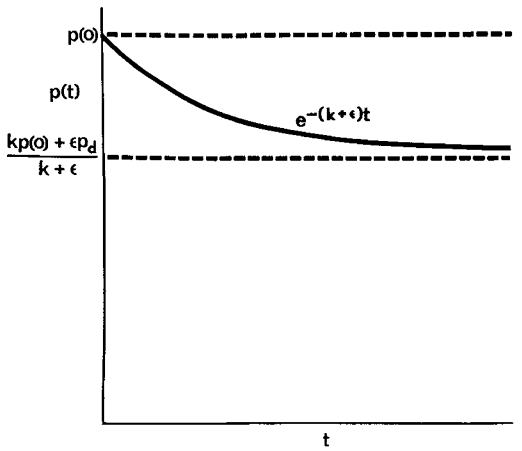

Fig. 1. Theoretical curve for decrease in plasma ferritin concentration during exchange transfusion.

Table 2. *Plasma ferritin half-life in six infants during exchange transfusion*

Case	Ferritin in donor plasma, ng/ml	Ferritin in recipient plasma, ng/ml		k^1 (±SD), min^{-1}	Ferritin half-life, min
		Initial	Final		
1	64	375	280	0.278 ± 0.074	2.5
2	24	250	215	0.127 ± 0.038	5.5
3	27	185	91	0.0764 ± 0.022	9.1
4	32	150	75	0.0207 ± 0.0039	34
5	88	270	203	0.0509 ± 0.0074	13
6	46	80	69	0.0459 ± 0.034	15

[1] Rate coefficient of endogenous ferritin removal.

infants. None of our values for ferritin turnover can be accepted as normal for man. They simply indicate an order of magnitude until a more direct method can be developed for safely measuring plasma ferritin turnover. Unfortunately, routine ferrokinetic studies in patients did not prove helpful in studying the turnover of plasma ferritin since the latter does not become significantly labeled with the injected ^{59}Fe (10). The half-life for plasma ferritin under circumstances that should lead to a falsely high estimate was considerably less than the normal half-life of 60–100 min in adults for transferrin-bound iron (5). A rough approximation of the amount of iron that could be carried by plasma ferritin can be made as follows. If serum ferritin contains 20% iron by weight and has half-life of 4 min, then the ferritin iron turnover is about 0.25 mg/100 ml whole blood/24 hr. This figure is more than one-third of the total plasma iron turnover of approximately 0.70 mg/100 ml whole blood/24 hr in the adult male (5). Thus, plasma ferritin is likely to account for a significant portion of the iron carried through the vascular compartment.

SUMMARY

Ferritin, an iron storage protein located primarily in solid tissues, is also present in the plasma in a low concentration. In the rat, plasma ferritin has so rapid a turnover that it is likely to account for a large proportion of the iron transported by plasma. We used a nonisotopic technique to estimate the turnover of plasma ferritin in newborn infants undergoing exchange transfusion. The method was based on the more than fourfold difference between the high initial concentration of plasma ferritin in the neonates (mean: 218 ng/ml) and in the ferritin-poor donor blood (47 ng/ml). The concentration of plasma ferritin was measured in serial samples of the blood removed at exchange transfusion. The more rapid the plasma ferritin turnover, the greater the tendency of the infant to maintain a stable plasma ferritin concentration in spite of "flush out" with plasma ferritin-poor blood. The computed plasma ferritin half-life in the two neonates weighing 2,000 and 2,500 g was 2.5 and 5.5 min, respectively, compared with the value of 4 min in the rat. In the four infants weighing 1,000–1,180 g, the half-life ranged from 9.1–34 min. The findings indicate that ferritin in man can transport a large amount of iron through the plasma compartment in spite of its low concentration.

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