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RADIOCHROMATE RBC SURVIVAL KINETICS IN THE NORMAL HUMAN ADULT

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The measurement of RBC survival represents an important tool in both clinical medicine and research. From 1911 until 1950, transfusion of donor cells (with the accompanying risk of hepatitis) provided the only reliable means of measuring the intravascular survival of RBCs (*1,2*). In 1950 Gray and Sterling introduced the radiochromate tagging of RBC (*3*). Because of its simplicity and safety, this method has virtually replaced the more tedious Ashby method (*2*). The results of radiochromate studies, however, differ considerably from the Ashby curves. Although in the case of the Ashby method the donor cells disappeared linearly from the peripheral blood, the radiochromate curve appeared to be exponential. The rather marked differences between the actual intravascular life span of the RBCs and the radiochromate half-time have been explained on the basis of loss of the radionuclide from the cells (*4*). This loss is in addition to that caused by physiologic removal of labeled RBCs from the peripheral blood. The observed disappearance of the radioactivity can be roughly approximated by an exponential relationship; the results are usually expressed as the "disappearance half-time." Although a wide range of hematologic disorders are associated with changes in the half-times, the radiochromate RBC survival study is sometimes viewed with suspicion because it does not estimate the actual intravascular life span of the erythrocyte. Of several mathematical models that have been proposed to relate the radiochromate curve to the agglutination (Ashby) results (*4,5*), the model developed by Eadie and Brown (*4*) seemed to have considerable merit. In this paper we report the results of studies designed to evaluate this model for human subjects. To test the model, radiochromate RBC survival studies were performed on 23 healthy volunteers. A digital computer was used to fit the model to the data.

The results show that we were able to obtain estimates of the parameters (intravascular RBC life span and fraction of radiochromate lost per day) in the Eadie and Brown model for approximately 75% of the volunteers.

METHODS

A group of 23 healthy adult volunteers, 21 men and 2 women, with ages ranging from 21 to 43 years were studied. Each volunteer had a blood count (hemoglobin, hematocrit, WBC count, and WBC differential). They were questioned closely about personal or familial blood disorders. Since none of the candidates had either historical or laboratory abnormalities, all were included in the study.

Each person received an intravenous injection of 20 cc of his own red cells which were tagged with approximately 40 μCi of ^{51}Cr-chromate. The activity of the radiochromate (Abbott) was 168 μCi/ml. The amount of "cold" chromium in each dose was less than 0.1 μg. At 24 hr, 3, 7, 14, 21, 28, 35, 42, 49, and 56 days postinjection, blood samples were collected and microhematocrits measured. The RBC radioactivity was measured with a Nuclear-Chicago well counter which was equipped with a single-channel pulse-height analyzer. The results were expressed as percent of RBC activity in the 24-hr sample.

Each volunteer was counted in the University of Arkansas Medical Center whole-body counter facility. The counting room is shielded with pre-World War II ship armor plate. The detector is a Harshaw NaI(Tl) crystal 20 cm in diam and 10 cm thick. The unit is equipped with a Nuclear Data 512 Channel Analyzer. The photopeak activity was used as a measure of the total-body activity. To do this the activity was summed in those channels (57–76) corresponding to the photopeak (330 keV). Daily checks

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with the standard showed the position of the photopeak to be stable. These counts were compared with the counts of the ^{51}Cr standard (in the same channels). Since the study was concerned only with relative activity, the standard was counted as a point source instead of in a phantom.

When counting the volunteers, the crystal was placed 120 cm above the subjects who were counted for 5 min in the prone position and 5 min in the supine.

All data (blood measurements and whole-body counts) were punched onto cards for computer processing. A CDC 3300 computer was used for all calculations.

RESULTS AND DISCUSSION

The Eadie and Brown model mathematically relates the intravascular life span with the rate loss of the radiochromate from the RBCs (*4*). The model is given (in somewhat different notation) by

$$P(t) = P(0)(1 - t/L)e^{-Kt} \qquad (1)$$

in which P(0) is the percent of the radiochromium present at t = 0 and P(t) is the percent present at time t. The parameters L and K have units of days and days^{-1}, respectively. L is the intravascular RBC life span while K is the fraction of radiochromate lost by the RBCs per day.

Since the results are expressed as percent of initial measurement, the Eadie and Brown equation reduces to

$$P(t) = 100\ (1 - t/L)e^{-Kt}. \qquad (2)$$

Since we consider the 24-hr sample to represent *end* of the zero day period instead of the *start* of Day 1, this representation is valid. Calculations using either representation carry less than a few percent variation of the estimates of the half-times.

Virtually the same equation was used by Cline and Berlin to study radiochromate data in patients with hematologic disease (*6*). If, indeed, the Eadie and Brown model could be fitted to data from routine radiochromate studies, estimates of both the rate of radionuclide loss and the intravascular RBC life span could be made from a single study with a single radionuclide.

To this end, we developed a digital computer program to fit Eq. 2 to the results of the peripheral blood measurements (*7*). The results of the computations provided estimates of K and L. Also disappearance half-times, $T_{1/2}$, for Eq. 2 were calculated by solving for that value so that

$$P(T_{1/2})/P(0) = 0.50.$$

In addition, the RBC survival half-times and the whole-body half-times were estimated by fitting exponential equations of the form

$$Y = Y_0e^{-\alpha t} \qquad (3)$$

to the peripheral blood measurements and the whole-body counts. The curves were fitted by the method of least squares with a digital computer. The disappearance half-time was calculated by

$$T_{1/2} = 0.693/\alpha.$$

As a result of these calculations, we obtained two estimates of the peripheral blood disappearance half-times and one of the whole-body disappearance half-times. Table 1 contains these values.

Notice from Table 1 that computer fits were not obtained on all patients. This is a consequence of the estimation technique not converging to a solution (*7*). This means that after a large number of iterations the successive estimates of K and L did not approach a constant value for these individuals. We do not know the exact reason for this nonconvergence. Further investigation concerning the robustness of the model and the general applicability of the numerical fitting technique is needed.

Figure 1 summarizes the results of the study. The upper left panel shows the frequency distribution of the RBC radiochromate disappearance half-times as calculated by the Eadie and Brown model (Eq. 2). The distribution is somewhat more symmetrical than

TABLE 1. EXPERIMENTAL RESULTS

Item	Source	No. Obs.	Mean	s.d.	Range
L*	Eadie & Brown Model	17‡	114.0	20.2	90–160
K†	Eadie & Brown Model	17	0.0076	0.0033	0.0022–0.124
Peripheral blood half-time	Eadie & Brown Model	17	35.9	3.6	30–44
Peripheral blood half-time	Exponential Model	23	33.5	3.0	30–42
Whole-body half-time	Exponential Model	23	61.9	7.5	48–80

* Intravascular RBC life span (days).
† Rate of radiochromate disappearance (days^{-1}).
‡ Computer solutions could not be obtained for six individuals (see text).

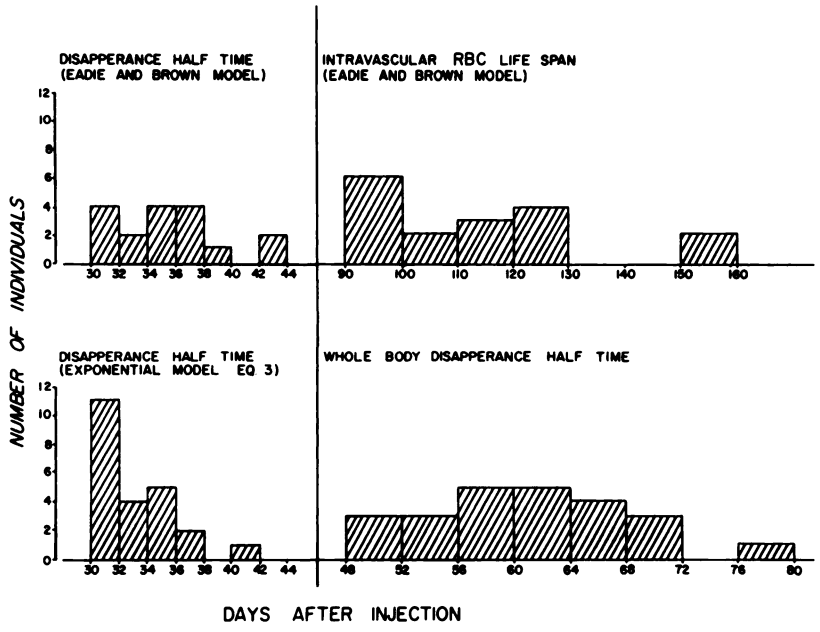

FIG. 1. Experimental results. Abscissa indicates value of estimated half-times while ordinate shows number of individuals having that value. Upper and lower panels on left show frequency distribution for RBC radiochromate disappearance half-times as calculated by Eadie and Brown model and by exponential model. Upper right panel shows frequency distribution for calculated intravascular RBC life spans. Lower right panel contains frequency distribution of whole-body radiochromate disappearance half-times.

the RBC radiochromate disappearance half-times (lower left panel) as calculated from the exponential model (Eq. 3). The mean values and the ranges of values, however, are essentially the same (see Table 1). Our results using both the Eadie and Brown model and the exponential model (Eq. 3) agree with those of Weinstein, et al who reported values of 33 ± 3.2 (s.d.) days (*8*). Also, the calculated values of K (the fraction of radiochromate lost per day), 0.0076 ± 0.0033 (s.d.) days fell within the range reported by Cline and Berlin (*6*). While most of the calculated values for the intravascular RBC life span fell between the expected 90 and 130 days, four volunteers had values of 150–160 days (upper right panel). The reason for this bimodal distribution is not known.

The right lower panel shows frequency distribution of the whole-body disappearance half-times. Since sampling (and whole-body counting) were suspended by Day 60, approximately half of these values were based on data obtained before the estimated half-times. Consequently, the accuracy of these estimates should be considered to be less than the estimates of the RBC disappearance half-times. For the latter, the half-times were well bracketed by measurements before and after the half-times. The results, with all reservations considered, indicate the total-body retention of the radiochromate to be longer than the intravascular retention. Because of the mechanism of destruction of RBCs, the reticuloendothelial system would seem to be the most likely site of this retention (*9*).

In conclusion, we believe that the Eadie and Brown model allows estimation of the intravascular RBC life span from radiochromate studies for many individuals. However, the frequency of nonconvergence of the computer solution limits its clinical effectiveness for individual patients. Perhaps methods of computer solution could be developed which would eliminate this estimation problem.

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