Effect of height and weight on the in vivo recovery of transfused factor VIII C

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SUMMARY The in vivo recovery of factor VIII has been estimated on 84 occasions in 53 severely affected adolescent haemophiliacs. There was wide individual variation in recovery, which was not affected by differences in the administered dose. Recovery increased steadily with increasing surface area, and it was only over a surface area of 1.7 m² that a recovery of 2% of factor VIII per unit per kg became the norm. It is suggested that the only safe assumption to make below that surface area is an in vivo recovery of 1.5%.

The treatment of haemophilic haemarthroses with inadequate doses of factor VIII will predispose the joints to chronic synovitis, progressive arthropathy, and ultimately to crippling deformity.¹ There are, however, potentially harmful side effects associated with adequate and excessive exposure to factor VIII-containing materials,² which also strain human and financial resources.³ Clearly, the use of the correct dose of factor VIII in varying situations is of great importance.

Recent studies have identified minimum dosage schedules for bleeds of varying severity in specific sites,⁴ and in joints with or without previous and/or present damage.⁵

If the minimum effective dose is to be used efficiently, it is crucial to be able to predict the rise in factor VIII activity that is likely to follow a given dose. A rise of 2% of average normal activity per unit of factor VIII concentrate is assumed by many authors,⁶⁻⁸ but there is evidence that the response in children is lower than in adults.^{9,10} Biggs and Rizza⁶ have recommended that a rise of 1.5% of average normal factor VIII be assumed for every transfused unit per kilogram in children. No guidance is given about when to change the dosage schedule from paediatric to adult expectations.

We have presumed that any variation is likely to be related to relative plasma volumes and that the transition will probably occur during adolescence. We have, therefore, estimated the post-transfusion rise of factor VIII on 84 occasions in 53 adolescent haemophiliacs and have studied the relation to weight, height and administered dose.

Patients and methods

The subjects studied were 53 severely affected adolescent haemophiliacs (factor VIII:C < 1%) resident at the Lord Mayor Treloar College.

Blood samples were taken immediately before and between 20 and 30 minutes after infusions of factor VIII-containing material. Samples were immediately dispensed into plastic tubes containing 3.8% sodium citrate (9 vols blood to 1 vol anticoagulant). The plasma was separated within two hours by centrifuging at 2000 g at 4°C and tested immediately.

Factor VIII:C was tested by a two stage method modified from that of Denson.¹¹ During the year in which the study took place, approximately 700 factor VIII assays were undertaken in our laboratory, 10% of which were done in duplicate. Average variation between operators was never more than 10%.

All weights and heights used were obtained within two months of the relevant estimation. Height was measured with patients standing without shoes and with their heels back in contact with an upright scale. Body surface area was calculated using a nomogram based on the formula of Du Bois and Du Bois.¹²

Recovery or response was expressed as the percentage rise of factor VIII per unit of factor VIII/kg infused. The dose of factor VIII infused was based on the unit-values given by the manufacturer. These were specifically checked on 19 occasions during the study. The preparations used were fractionated by Travenol laboratories, Armour, Immuno and the Lister Institute. On 16 occasions the assayed potency deviated by less than 10% from

the manufacturer's stated potency and on no occasion was a deviation of more than 20% noted.

Haemoglobin concentrations were estimated using a Coulter model "S" counter. The relation between haemoglobin concentrations and recovery was calculated using Kendall's test of rank correlation.

Results

EFFECT OF INCREASING WEIGHT

A scattergram shows the dose response in small groups of boys with similar weights (Fig. 1). An increasing response is noted from the group weighing less than 40 kg ($\bar{x} = 1.67 \pm 0.19$) through the 40-44 kg group ($\bar{x} = 1.79 \pm 0.24$) to the 45-49 kg group ($\bar{x} = 2.16 \pm 0.43$). A similar response is seen from 55-59 kg ($\bar{x} = 1.87 \pm 0.29$) through 60-64 kg ($\bar{x} = 2.07 \pm 0.27$) to the 65-69 kg group ($\bar{x} = 2.17 \pm 0.35$). There are significant differences between the under 40 kg and the 45-49 kg groups ($p < 0.02$) and between the 40-44 kg and the 45-49 kg groups ($p < 0.005$). The difference between the 55-59 kg group and the 65-69 group is also significant ($p < 0.05$).

Fig. 1 Effect of increasing weight on the dose response.

EFFECT OF INCREASING SURFACE AREA

The dose response of small groups of boys with similar surface areas are shown in Fig. 2. The response begins to increase in the group with a surface area of 1.6 to 1.69 m² ($\bar{x} = 1.90 \pm 0.38$) through the 1.7 to 1.79 m² group ($\bar{x} = 2.04 \pm 0.21$) to the more than 1.8 m² group ($\bar{x} = 2.23 \pm 0.37$). The difference between the 1.6 to 1.69 m² group and the greater than 1.8 m² group is significant ($p < 0.05$).

Fig. 2 Effect of increasing surface area on the dose response.

EFFECT OF INCREASING DOSES OF FACTOR VIII

The scattergram shows the relation of the in vivo response to varying doses of factor VIII (Fig. 3). There is no correlation between these two parameters ($r = 0.38$).

Fig. 3 Effect of increasing doses of factor VIII on the in vivo response.

INDIVIDUAL VARIATIONS

The variations between responses of the 14 boys who had their responses estimated on more than one occasion are shown in Fig. 4.

EFFECT OF VARYING HAEMOGLOBIN CONCENTRATIONS

Haemoglobin concentrations were available on 37 occasions within one month of recovery estimations. Only one boy was found to be anaemic

Fig. 4 Varying dose response in individuals tested on more than one occasion.

(Hb 8.0 g/dl). Recoveries were estimated on three occasions at this level, and found to be 1.5, 1.6 and 1.9. The remaining 33 haemoglobin concentrations ranged between 13.0 and 16.0 g/dl. No significant correlation was found between the haemoglobin concentrations and recovery ($s = +87$, $r = 0.13$).

Discussion

The inconsistent individual variations in response rule out the possibility of predicting the recovery of factor VIII in an individual. Some of these variations may be due to inconsistencies in the factor VIII assay. It is apparent that variations in the dosage of factor VIII administered do not affect the in vivo response.

In vivo recovery of factor VIII appears to increase steadily from less than 40 kg to 49 kg, drops back, and then rises again from 55 to 69 kg. The increasing response of the larger boys is confirmed when surface area is plotted against recovery, but no early rise of recovery in the smaller boys is noted. It is apparent that a rise of 2%/unit of factor VIII/kg does not become the norm until a surface area of 1.7 m² has been reached although there is a large overlap between responses at the varying weights. The safest assumption to make below a surface area of 1.7 m² is an in vivo recovery of not more than 1.5%/unit of factor VIII/kg.

While there is some variation in the confirmation of the manufacturer's unit-value, this is usually not more than 10% and of random distribution. The consistent increase in recovery with increasing

surface area suggests that variable potency is not likely to have a significant effect on our results.

Only one boy was anaemic and while two of his recoveries were below average, one was well into the high normal range. Overall we can see no correlation between haemoglobin concentrations and recovery, but not enough anaemic patients were available to test the hypothesis that haemoglobin concentrations might influence recovery. With modern surveillance fewer patients are likely to be anaemic and surface area therefore appears to be the most reliable indication of recovery.

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