Correlation of Serum and Urine Vitamin B₁₂

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Summary: The relation between the serum vitamin B₁₂ level and the daily loss of vitamin B₁₂ in urine was examined in patients with normal serum vitamin B₁₂ levels and in patients suffering from vitamin B₁₂ deficiency. A linear correlation was found between the two measurements, suggesting that the serum vitamin B₁₂ level is a governing factor in the urinary loss of vitamin B₁₂. The contribution by this loss to the total loss of vitamin B₁₂ from the body is small under normal circumstances but becomes quantitatively more important with the depletion of body stores.

Introduction

Vitamin B₁₂ is lost from the body in urine and faeces. Little is known about the factors that determine the magnitude of the loss in either medium or of the relative losses in health and disease. Information on these points was sought by examining the relation between the serum vitamin B₁₂ level and the daily loss of vitamin B₁₂ in urine in subjects with normal serum vitamin B₁₂ levels and in those with vitamin B₁₂ deficiency.

Materials and Methods

Material for study was obtained from 114 male and female inpatients. Of these, 97 had diseases not known to affect vitamin B₁₂ metabolism; in particular, patients with renal, hepatic, or haematological disorders were excluded. The remaining 17 had untreated vitamin B₁₂-deficiency states subsequently diagnosed as due to pernicious anaemia (15 cases), partial gastrectomy (1 case), and dietary deficiency (1 case).

Urine was collected direct or via filter funnel into acid-washed sterile dark glass bottles. Aliquots of serum and urine were stored at -20°C. immediately after collection until assay by the method of Hutner, Bach, and Ross (1956), with *Euglena gracilis* Z strain as the test organism.

Recovery experiments with added cyanocobalamin were performed on urine samples from patients on drug therapy.

Results

Recovery experiments did not show inhibition of growth of the test organism by any sample of urine tested. A linear correlation was found between the serum vitamin B₁₂ level in pg./ml. (x) and the 24-hour urine vitamin B₁₂ in ng. (y), the regression equation being $y = 62.5784 + 0.2312x$ (Fig. 1) and the coefficient of correlation being 0.44 ($P < 0.001$). The distribution of daily urine vitamin B₁₂ values was skewed (Fig. 2).

Discussion

The correlation between the microbiological activity of serum and urine suggests that the serum vitamin B₁₂ level is a

FIG. 1.—Correlation of serum vitamin B₁₂ and daily urine vitamin B₁₂.

governing factor in the amount of vitamin B₁₂ lost in the urine. The precise nature of the relation is not clear. An obvious explanation is that vitamin B₁₂ is dissociated from the plasma-binding proteins transcobalamins I and II (Hall and Finkler, 1962, 1965), and excreted by glomerular filtration. It is also possible that the urine vitamin B₁₂ may be related to

FIG. 2.—Distribution of daily urine vitamin B₁₂ values. The shaded areas represent values for patients with vitamin B₁₂ deficiency states; the area delineated by the unbroken line represents the values for normal subjects.

the transcobalamin II-B₁₂ complex, which has a molecular weight in the region of 40,000 (Hom, Olesen, and Lous, 1966; Hom and Olesen, 1967). Neither mechanism would be incompatible with the observation that cigarette smoking has a significant effect on the urine, but not the serum vitamin B₁₂ level (Linnell, Smith, Smith, Wilson, and Matthews, 1968).

The range of daily urine vitamin B₁₂ values in this series is

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greater than that found by Register and Sarett (1951) but not out of keeping with those reported by Girdwood (1951), Mollin and Ross. (1952), Heinrich (1954), Jones, Mills, and Capps (1957), and Linnell *et al.* (1968) in smaller series of normal subjects and by Girdwood (1951), Mollin and Ross (1952), and Heinrich (1954) in patients with pernicious anaemia. The mean value of daily urine vitamin B₁₂ in the non-vitamin B₁₂-deficient subjects was 164 ng./day, which is higher than that previously found by direct measurement but less than that calculated by Hall (1964) from kinetic studies. The significance of mean values is doubtful, however, as the distribution of daily urine vitamin B₁₂ values is lognormal, as is the distribution of serum vitamin B₁₂ levels in normal subjects (Gräsbeck 1961).

The results are of interest in relation to the proportionate losses of vitamin B₁₂ from the body by the renal and intestinal routes. Serial whole-body measurements in normal and in vitamin B₁₂-deficient subjects given radioactive cobalamins orally or parenterally have shown that the daily loss of vitamin B₁₂ from the body is a function of the total body stores amounting to 0.1-0.2% of stores per day (Heyssel, Bozian, Darby, and Bell, 1966; Adams and Boddy, 1968; Boddy and Adams, 1968). Thus with stores of 2,000 µg. the daily loss will be 2-4 µg.: from the results it is clear that the contribution to this total by the urine loss will be small. With a fall in body stores to say 100 µg. and a fall in serum vitamin B₁₂ level to subnormal values the total daily loss will amount to 100 to 200 ng., and the contribution to this total by the urinary loss will be proportionately greater than in normal circumstances and may then account for half of the total loss.

The correlation between the serum and urine vitamin B₁₂ was found in normal and vitamin B₁₂-deficient subjects. Whether the measurements are correlated in disease states accompanied by a high serum vitamin-B₁₂ level, such as chronic myeloid leukaemia (Beard, Pitney and Sanneman, 1954; Mollin and Ross, 1955; Miller and Sullivan, 1958), renal failure (Matthews and Beckett, 1962), or hepatic disease (Holdsworth,

Atkinson, Dossett, and Hall, 1964; Neale, Caughey, Mollin, and Booth, 1966; Rachmilewitz and Eliakim, 1968) has not been investigated, and further study of this aspect may be necessary to comprehend the problem of vitamin B₁₂ balance in disease states.

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Effect of Ergotamine and Ergometrine on Forearm Venous Compliance in Man

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Summary: The effect of ergotamine and ergometrine on the venous compliance of the forearm has been studied in normal persons. Ergotamine tartrate (0.25 mg. intravenously) led to a fall in venous compliance amounting to 49%, on average, while ergometrine maleate (0.25 mg. intravenously) caused a reduction of 41%; these changes were statistically significant. The potent veno-constrictor action of these ergot alkaloids appears to be a major component of the circulatory response to small doses and may be important in provoking the harmful cardiovascular side-effects (such as angina and pulmonary oedema) that are sometimes observed in patients with pre-existing heart disease.

Introduction

The ergot alkaloids have been widely used in medicine and obstetrics for many years, and the risk of gangrene from excessive dosage is well recognized (Goodman and Gilman,

1965). There is, however, some risk of harmful side-effects with standard clinical doses in patients with certain cardiac abnormalities. Thus ergotamine may aggravate the symptoms of angina pectoris in patients with ischaemic heart disease (Friedman *et al.*, 1959), while ergometrine is believed to carry some risk of precipitating pulmonary oedema if given post partum to patients with mitral stenosis (Barnes, 1965). The mechanism of these untoward effects is not clear, though possible explanations have been advanced.

In analysing the circulatory side-effects of the ergot alkaloids it is important to understand their action on the peripheral circulation. The complex effect of these drugs on the arterial system has been studied in detail (Dale, 1906; Rothlin, 1947; Bluntschli and Goetz, 1948; Barcroft *et al.*, 1951), but their effect on the venous system has received little attention. We

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