SHORT REPORTS

Simple rule for calculating normal erythrocyte sedimentation rate

Measurement of the erythrocyte sedimentation rate is a commonly performed blood test, so it might be expected that the reference range would have been well established. Several surveys¹⁻³ suggest that the upper limit of normal in a person aged under 50 may be as high as 15-20 mm in the first hour in men and 25-30 mm in the first hour in women, whereas a recent authoritative review⁴ recommended, on the basis of results "derived from several publications," values of 10 and 12 mm in the first hour respectively. Even so, the haematology departments at 10 London teaching hospitals quote the reference ranges as only 0-5 and 0-7 mm in the first hour in men and women respectively, following a standard textbook.⁵ We set out to clarify the upper limit of the normal range on the basis of a wide survey.

Subjects, methods, and results

The erythrocyte sedimentation rate was measured by the Westergren method⁴ in 27 912 adults (26 836 men and 1076 non-pregnant women) aged 20-65 as part of a routine health screening. None of the subjects was anaemic. Results, expressed to the nearest mm in the first hour, were stored on computer and subsequently analysed. A series of curves of erythrocyte sedimentation rate versus age (in blocks of five years) was constructed separately for men and women; these are shown in the figure, with maximum values for 50% (the median) and 98% of the population, and the mean values.

Erythrocyte sedimentation rates in men and women, with mean values and maximum values for 50% and 98% of the population. Broken lines are given by formulae and approximate to upper limits of normal.

Comment

The data for men came from a normal population 10 times the size of that in any previous study, and confirm other observations¹⁻³ that the erythrocyte sedimentation rate rises with age. Although only 1076 women were studied, the results in these women were broadly similar to those in the men but with higher values at each age. Possibly a few of these apparently healthy men and women had occult disease

that might have contributed to some of the high values, but this is unlikely to have influenced the results materially.

The 50% and 98% levels show that the results were distributed with considerable skewness,³ and this is the reason for the difference between the mean and median curves. Statistics that assume a normal distribution^{1,2,4} are thus misleading, as are the popularly quoted normal ranges of 0-5 mm in the first hour in men and 0-7 mm in the first hour in women.⁵ Upper limits of the normal range such as those of Lewis⁴ (10 and 12 mm in the first hour in men and women respectively aged under 50, and 14 and 20 mm in the first hour in men and women respectively aged over 60) and of others¹ are more accurate but hard to remember. It would seem reasonable to define the upper limit of the normal range as that value above which less than 2% of the normal population lies. On the basis of our results we propose the following formulae for calculating the maximum normal erythrocyte sedimentation rate at a given age: in men, age in years ÷ 2; in women, (age in years + 10) ÷ 2. When these calculated values are plotted against age (the broken, straight lines in the figure) the results give a good approximation to the 98% curves. These formulae are both realistic and easy to remember.

¹ Böttiger LE, Svedberg CA. Normal erythrocyte sedimentation rate and age. *Br Med J* 1967;ii:85-7.

² Wilhelm WF, Tillisch JH. Relation of sedimentation rate to age. *Med Clin North Am* 1951;35:1209-11.

³ Rafnsson V, Bengtsson C, Laennartson J, Linquist O, Noppa H, Tibblin E. Erythrocyte sedimentation rate in a population sample of women with special reference to its clinical and prognostic significance. *Acta Med Scand* 1979;206:207-14.

⁴ Lewis SM. Erythrocyte sedimentation rate and plasma viscosity. *Association of Clinical Pathologists Broadsheet* 1980;94:1-7.

⁵ Dacie JV, Lewis SM. *Practical haematology*. Edinburgh: Churchill Livingstone, 1975.

(Accepted 13 October 1982)

St Bartholomew's Hospital, London EC1A 7BE

ANDREW MILLER, DM, DPHIL, senior medical registrar
MALCOLM GREEN, DM, FRCP, consultant physician

BUPA Medical Research, London WC1X 8DU

DAVID ROBINSON, MSC, ARCS, statistician

Acebutolol-induced hypersensitivity pneumonitis

Episodes of bronchoconstriction induced by beta-blocking agents in patients with asthma or chronic bronchitis are well known.¹ To our knowledge side effects with the features of hypersensitivity pneumonitis have not been reported. We describe a case in which hypersensitivity pneumonitis appeared to be related to administration of acebutolol.

Case report

A 69 year old man with coronary heart disease was treated with acebutolol (200 mg daily) for six months; an x-ray film taken one year earlier had been normal. At the end of the six months' treatment a routine x-ray film showed bilateral pulmonary infiltrates; physical examination was normal, and a tuberculin skin test negative. There were no symptoms of cardiac failure (normal heart rate, with neither dyspnoea nor cardiac enlargement). Tests of respiratory function yielded normal values except for the carbon monoxide pulmonary diffusing capacity, which was low (transfer coefficient 0.92 mmol/min/kPa/l; 3.3 ml/min/mm Hg/l). Serum activity of angiotensin-converting enzyme was normal; and bronchial, salivary gland, and hepatic biopsy specimens showed no abnormality. In the bronchoalveolar lavage fluid the proportions of lymphocytes, macrophages, and polymorphonuclear leucocytes were respectively 83%, 13%, and 4%.

Acebutolol was withdrawn for 54 days, after which a chest x-ray film was normal and the diffusing capacity still low; the cell differential in bronchoalveolar lavage fluid showed 46% lymphocytes, 46% macrophages, and 8% polymorphonuclear leucocytes; the OKT₄:OKT₈ ratio was 0.16.

Thirty-seven days after acebutolol treatment was resumed, with the

patient's informed consent, a chest x-ray film was normal but the diffusing capacity remained low; the cell differential in bronchoalveolar lavage fluid displayed 64% lymphocytes, 34% macrophages, and 2% polymorphonuclear leucocytes and an OKT :OKT₄ ratio of 0.20.

Once again acebutolol was stopped; the diffusing capacity returned to normal 97 days later (transfer coefficient 1.10 mmol/min/kPa/l; 4 ml/min/mm Hg/l).

Comment

Several side effects of beta-blockers other than bronchospasms have been reported, including a few cases of pleuropulmonary fibrosis.² The patient reported on here had the features of hypersensitivity pneumonitis induced by acebutolol; this diagnosis is supported by the radiological disappearance of pulmonary infiltrates and decrease in the lymphocyte count in bronchoalveolar lavage fluid after acebutolol was first stopped as well as the increase in the lymphocyte count in the lavage fluid after the drug was resumed; there was no other cause for these findings. The long lapse of time before diffusing capacity returns to normal is a phenomenon well established in hypersensitivity pneumonitis.

Assessment of bronchoalveolar lavage fluid coupled with a provocation test would seem most valuable in cases in which drug-induced hypersensitivity pneumonitis is a possibility; the diagnostic importance of such assessment (particularly the lymphocyte count) has already been demonstrated in hypersensitivity pneumonitis due to organic dust.³ The reason for the low ratio of T helper to T suppressor lymphocytes in such cases has still to be elucidated; nevertheless, a similar result has been found in hypersensitivity pneumonitis due to causes other than drugs.⁴

¹ Skinner C, Palmer K, Kerridj Y. Comparison of the effects of acebutolol and practolol on airways obstruction in asthmatics. *Br J Clin Pharmacol* 1975;2:417.

² Ahmad S. Sclerosing peritonitis and propranolol. *Chest* 1980;79:361-2.

³ Reynolds HY, Fulmer JD, Kazmierowski JA, Roberts WC, Frank MM, Crystal RG. Analysis of cellular and protein content of bronchoalveolar lavage fluid from patients with idiopathic pulmonary fibrosis and chronic hypersensitivity pneumonitis. *J Clin Invest* 1977;59:165-75.

⁴ Hirata T, Nagai S, Ohshima S, Izumi T. Comparative study of T-cell subsets in BAL fluid in patients with hypersensitivity pneumonitis and sarcoidosis. *Chest* 1982;82:232.

(Accepted 12 October 1982)

Chest Disease Unit, Hôpital Tenon, 75020 Paris, France

G M AKOUN, MD, professor and head of department

D P HERMAN, MD, chef de clinique assistant

C M MAYAUD, MD, médecin, adjoint des hôpitaux

Laboratory of Applied Immunology, Hôpital de l'Hôtel-Dieu, 75004 Paris, France

J Y PERROT, MD, assistant de biologie des hôpitaux de Paris

Effects of amiodarone in thyrotoxicosis

Amiodarone is an iodine-containing antiarrhythmic and antianginal drug that also affects thyroid hormone metabolism.¹ Since patients with thyrotoxicosis may present with arrhythmias it is likely that those with undiagnosed thyrotoxicosis may receive the drug. It is important therefore to know the effects of amiodarone in thyrotoxicosis.

Patients, methods, and results

Twenty-five patients with newly diagnosed, untreated thyrotoxicosis were studied before and after two weeks' treatment with either amiodarone or iodine equivalent to that released from amiodarone.² Seventeen received 600 mg amiodarone daily and eight 18 mg iodine daily.

Free thyroxine index was measured using Thyopac 3 (Amersham International). Serum concentrations of free thyroxine, total triiodothyronine, reverse triiodothyronine, and thyroid-stimulating hormone were measured by standard radioimmunoassay methods. Thyrotrophin-releasing hormone tests were performed using 200 µg of the hormone. Statistical analyses were performed using Student's *t* test.

The mean free thyroxine index and concentrations of free thyroxine and total triiodothyronine fell significantly in the 17 patients treated with amiodarone, but the concentration of reverse triiodothyronine rose slightly, though not significantly (table). Mean free thyroxine index and concentrations of free thyroxine, triiodothyronine, and reverse triiodothyronine fell significantly in the eight patients treated with iodine. The change in reverse triiodothyronine concentration induced by amiodarone was significantly different from that induced by iodine ($p < 0.001$). Thyrotrophin-releasing

Change in thyroid function in 17 patients with thyrotoxicosis treated for two weeks with 600 mg amiodarone daily and in eight patients treated for two weeks with 18 mg iodine daily. Figures are means $\pm$ 1 SD (normal values given in parentheses)

	Free thyroxine index (50-145)	Free thyroxine (pmol/l) (10-26)	Triiodothyronine (nmol/l) (0.8-3.0)	Reverse triiodothyronine (nmol/l) (0.29-0.69)
<i>Patients treated with amiodarone</i>				
Before	320 $\pm$ 138	66.9 $\pm$ 35	6.5 $\pm$ 2.8	1.05 $\pm$ 0.6*
After	174 $\pm$ 46	31.9 $\pm$ 13	3.1 $\pm$ 0.7	1.50 $\pm$ 0.6*
Significance of difference	$p < 0.001$	$p < 0.001$	$p < 0.001$	NS
<i>Patients treated with iodine</i>				
Before	303 $\pm$ 166	62.4 $\pm$ 40	7.2 $\pm$ 3.3	1.2 $\pm$ 0.4
After	124 $\pm$ 41	22.0 $\pm$ 7.7	3.1 $\pm$ 0.6	0.54 $\pm$ 0.1
Significance of difference	$p < 0.02$	$p < 0.02$	$p < 0.01$	$p < 0.001$

*Measured in only nine patients.

Conversion: SI to traditional units—Thyroxine: 1 pmol/l $\approx$ 77.7 pg/100 ml. Triiodothyronine and reverse triiodothyronine: 1 nmol/l $\approx$ 65 ng/100 ml.

hormone tests showed absent or impaired responses both before and after two weeks' treatment with either amiodarone or iodine in all patients except one. This patient, with triiodothyronine toxicosis, showed an absent response of thyroid-stimulating hormone to thyrotrophin-releasing hormone before treatment; both serum triiodothyronine concentration and the response to thyrotrophin-releasing hormone were normal after two weeks' treatment with amiodarone. Striking symptomatic improvement was noted in five patients treated with amiodarone. The response to carbimazole was delayed in five patients, whose free thyroxine index rose in the two- to four-week period after carbimazole was started immediately after amiodarone treatment.

Comment

In euthyroid subjects amiodarone reduces circulating concentrations of triiodothyronine and increases those of thyroxine and reverse triiodothyronine,¹ but iodine equivalent to that released from amiodarone does not in the short term significantly affect triiodothyronine, thyroxine, or reverse triiodothyronine concentrations.³ These effects of amiodarone thus appear to be independent of its iodine content. The increased reverse triiodothyronine and reduced triiodothyronine concentrations are due to inhibition of peripheral conversion of thyroxine to triiodothyronine with enhanced conversion of thyroxine to reverse triiodothyronine. The cause of the raised thyroxine concentration is uncertain.

In our patients with thyrotoxicosis both amiodarone and iodine significantly reduced circulating concentrations of thyroxine and triiodothyronine, due to iodine-induced inhibition of release of thyroid hormone. Whereas iodine also reduced mean circulating concentrations of reverse triiodothyronine, however, amiodarone increased these slightly. Thus, as in euthyroid subjects, in patients with thyrotoxicosis amiodarone affects peripheral thyroid hormone metabolism independently of its iodine content. In thyrotoxicosis, however, in which sensitivity to iodine is increased, the inhibitory effect of amiodarone on conversion of thyroxine to triiodothyronine was masked by its much greater, iodine-induced inhibition of release of both thyroxine and triiodothyronine. Indeed, the fall in triiodothyronine concentrations induced by amiodarone was no greater than that due to iodine.

Striking symptomatic improvement was noted in some patients after treatment with amiodarone because the drug inhibits release of thyroid hormone; the development of a normal response to thyrotrophin-releasing hormone in one patient after only two weeks' treatment, however, was surprising. Because of these and its antiarrhythmic effects amiodarone might be used in short-term management of thyrotoxicosis. It should, however, be combined with an antithyroid drug such as carbimazole to inhibit synthesis of thyroid hormone. If used alone amiodarone would be expected to deplete thyroid iodine and delay the effect of carbimazole, as was evident in some of our patients and in a patient reported on by Wimpfheimer