Propranolol is contraindicated in asthma

EDITOR,—The datasheet for Inderal (propranolol) states specifically that the drug is contraindicated in patients with asthma or a history of bronchospasm. Despite this, and despite the well known risks of non-selective β blockers in patients with asthma, over the past few years Zeneca has received a number of reports of cases in which an asthmatic patient died as a result of being prescribed propranolol.

Since propranolol was first marketed in 1965 the estimated exposure to it has been about 56 million patient years. The Medicines Control Agency has 51 reports of bronchospasm in its database of reports of adverse reactions to propranolol; 13 of the cases are recorded as having been fatal. Of more interest, however, are six reports in which it is stated that the patient had a history of asthma, bronchospasm, or wheeze; five of these cases were fatal. To help prevent further occurrences of this sort in asthmatic patients who might be prescribed propranolol erroneously, Zeneca has decided to highlight the warnings concerning asthma in the patient information leaflet for Inderal and related products. Pack labels will also carry warnings. Doctors should prescribe original packs so that a last line of defence against incorrect prescribing is not breached.

Current advice in the prescribing information for Inderal recommends that bronchospasm can usually be reversed with a β_2 agonist bronchodilator such as salbutamol, although large doses may be required and the dose should be titrated according to the clinical response. As β_2 adrenoreceptors are blocked by propranolol the advice will now be augmented by the statement that ipratropium and intravenous aminophylline may also be indicated.

We thank the Committee on Safety of Medicines for providing us with its information.

J M FALLOWFIELD
Medical adviser, product safety group

H F MARLOW
Senior medical adviser, clinical research group

Zeneca Pharmaceuticals,
Macclesfield SK10 4TG

Sex differences in weight in infancy

Published centile charts for weight have been updated

EDITOR,—Charlotte M Wright and colleagues report a discrepancy between the sexes in weight in infancy¹ when the British 1990 growth reference² was used to standardise the weights of infants in Newcastle upon Tyne. They suggest that this arises from a bias in the growth reference rather than a regional difference in growth.

We looked for a possible regional effect in a cohort of 7400 babies from West Sussex, who were measured between birth and 35 weeks (courtesy of Dr Ann Wallace). As in Newcastle, there was no sex difference in the standard deviation score for weight at birth, but thereafter the boys' weight centiles tended to exceed the girls' (by a mean score of 0.31, compared with 0.41 in the authors' study). Thus regional differences alone are unlikely to explain the finding, and a bias in the growth reference must exist. We believe that this bias arose during the fitting process, when several datasets were merged after adjustment for regional imbalances and secular trends. This process distorted the relation between the sexes, particularly in infancy.

We have now eliminated the bias by modifying the fitting process.³ We have also added data on a nationally representative sample of 1.5–4.5 year old children to the reference dataset.⁴ Compared with the original reference, the revised median weight for girls is reduced by a standard deviation score of up to 0.2 (180 g) at 9 months, while that for boys is unchanged. The line indicating a standard deviation score of –2.0 for girls (close to the third centile used by Wright and colleagues) is reduced by up to 0.3 (200 g), while that for boys is reduced by 0.07 (40 g), a net difference of 0.24. This accounts for about three fifths of the sex discrepancy in Newcastle and rather more in West Sussex. We are confident that the remainder is a genuine regional difference.

Wright and colleagues point out that the same imbalance between the sexes occurred with the 1966 British standards. The same is true of the 1980 Dutch standards,⁵ which were based on a large sample ($n = 8301$). This emphasises the variable nature of the sex difference in weight during infancy.

Length—often regarded as more important than weight for measuring growth—does not show the same sex discrepancy in infancy. The revised length centiles differ from the old by <4 mm, which is within measurement error at this age. The net effect on the sex difference is a score of <0.05.

These revisions have been incorporated into the published centile charts (version 1996/1) and the computer spreadsheet.

M A PREECE
Professor of child health and growth

Institute of Child Health,
University College London,
London WC1N 1EH

J V FREEMAN
Part time lecturer

Medical Care Research Unit,
Sheffield S1 4DA

T J COLE
Senior scientist

MRC Dunn Nutrition Centre,
Cambridge CB4 1XJ

- 1 Wright CM, Corbett SS, Drewett RF. Sex differences in weight in infancy and the British 1990 national growth standards. *BMJ* 1996;313:513–4. (31 August.)
- 2 Freeman JV, Cole TJ, Chinn S, Jones PRM, White EM, Preece MA. Cross sectional stature and weight reference curves for the UK, 1990. *Arch Dis Child* 1995;73:17–24.
- 3 Cole TJ, Freeman JV, Preece MA. British 1990 growth reference centiles for weight, height, body mass index and head circumference fitted by maximum penalized likelihood. *Statistics in Medicine* (in press).
- 4 Gregory JR, Collins DL, Davies PSW, Hughes JM, Clarke PC. *National diet and nutrition survey: children aged 1.5 to 4.5 years*. Vol 1. London: HMSO, 1995.
- 5 Roede MJ, Van Wieringen JC. Growth diagrams 1980. Netherlands third nation-wide survey. *Tijdschrift voor Sociale Gezondheidszorg* 1985;63(suppl):1–34.

Data from Sheffield support authors' findings

EDITOR,—Charlotte M Wright and colleagues describe differences between the sexes in the weights of infants in Newcastle upon Tyne compared with the British 1990 national standards.¹ Some support for this sex discrepancy is found in a longitudinal prospective study of failure to thrive in a socially disadvantaged group of infants in Sheffield that is currently in progress. Table 1 shows the mean weights at birth and 3 months in

these infants compared with the standards given by the national 1990,² Tanner (1965),³ and local Sheffield weight charts (1974).⁴ Although the selection of subjects precludes any direct comparison with the mean weights of the standards, it is interesting that there is a considerable discrepancy between the 1990 standard deviation scores of the otherwise homologous boys and girls in the study group at 3 months, which, as Wright and colleagues note, places more girls than boys below the mean.

J K H WALES
Senior lecturer in paediatric endocrinology
C P A KENNEDY
PhD student

Department of Paediatrics,
University of Sheffield,
Sheffield Children's Hospital,
Sheffield S10 2TH

- 1 Wright CM, Corbett SS, Drewett RF. Sex differences in weight in infancy and the British 1990 national growth standards. *BMJ* 1996;313:513–4. (31 August.)
- 2 Freeman JV, Cole TJ, Chinn S, Jones PRM, Preece MA. Cross sectional stature and weight reference curves for the UK, 1990. *Arch Dis Child* 1995;73:17–24.
- 3 Tanner JM, Whitehouse R, Takaishi M. Standards from birth to maturity for height, weight, height velocity and weight velocity: British children 1965. Part 1. *Arch Dis Child* 1966;41:454–71.
- 4 Carpenter RG, Gardner A. *Sheffield weight charts*. London: Foundation for the Study of Infant Deaths, 1978.

Confusion over whether new technologies should be regulated at European or state level

EDITOR,—In their editorial on the Safety and Efficacy Register of New Interventional Procedures, Trevor A Sheldon and Alex Faulkner discuss regulation of the new health technologies.¹ It is true that, if drugs have to be evaluated before their widespread use is permitted, one could expect the same requirement for interventional technologies and that, because this has not been the case, new technologies have diffused through health care systems despite lack of evidence of their safety, effectiveness, and cost effectiveness.

The creation of the register is certainly an important initiative to answer these questions. Since it will concentrate exclusively on safety and efficacy, however, two questions should be discussed.

Firstly, on 1 January 1995 a new set of European rules covering practically all non-pharmaceutical products became effective in the member states of the European Union for the marketing approval of implantable medical devices—namely, CE marking, which indicates that devices meet the essential requirements of the medical device directives. After 14 June 1998 all medical devices will have to bear the CE mark. To implement these directives some countries reorganised the relevant units within their ministries of health. Others delegated authority and operational responsibilities to independent organisations. Thus many of the member states of the European Union currently have their own notified bodies dealing with the marketing approval of new medical devices.²

The fact that the new register will concentrate on safety raises the issue of how it will share this responsibility with the notified bodies. It will be

Table 1—Standard deviation scores at birth and three months for male and female infants in study in Sheffield compared with 1990 and 1965 (Tanner) national standards and 1974 local (Sheffield) standards

	Boys (n = 63)			Girls (n = 56)		
	1990	Tanner	Sheffield	1990	Tanner	Sheffield
At birth	–0.07	0.01	0.01	–0.01	–0.01	0.00
At 3 months	0.06	0.13	0.11	–0.43	0.03	0.10

an interesting way of clarifying the current debate on whether the notified bodies' role is only to serve manufacturers or also to take into account public health concerns.³ Organisations such as the new register could improve the work done by the notified bodies. But to be consistent with the European Union directives this improvement should be carried out at the European level because all the member states, being considered as a single market, need the same safety requirement.

Secondly, in addition to evaluating safety it is necessary to assess the effectiveness and cost effectiveness of the new technologies, which, as Sheldon and Faulkner point out, is not the role of the new register. Even though international collaboration can be useful in such evaluations, health policy in each country has to be taken into account, and thus such evaluation should be performed at the state level.

In terms of regulating the new technology, the debate on how to avoid confusion between these two challenges needs to be clarified.

FREDERIC FLEURETTE

Head, health technology assessment programme

Agence Nationale pour le Développement de l'Évaluation Médicale,
159 rue Nationale,
75013 Paris,
France

- 1 Sheldon TA, Faulkner A. Vetting new technologies. *BMJ* 1996;313:508. (31 August.)
- 2 Altenstetter C. Regulating healthcare technologies and medical supplies in the European Economic Area. *Health Pol* 1996;35:33-52.
- 3 Bradbury J. France extends moratorium on breast implants. *Lancet* 1996;347:1543.

Ratio of waist circumference to height is better predictor of death than body mass index

EDITOR,—The ratio of waist circumference to height has been shown to be a stronger predictor of intra-abdominal fat than the body mass index,¹ and this must partly explain why this

ratio showed a stronger association with cardiovascular risk than did body mass index in a cross sectional study.² Height, weight, and waist and hip circumference were measured in the 1984-5 health and lifestyle survey of a nationwide random stratified sample of British adults.³ All participants in the survey were flagged on the central health service register, and the survey was notified when death occurred and was sent copies of the death certificates with appropriate coding (*International Classification of Disease*, ninth revision).

Fifths of the distribution of anthropometric variables were calculated for the 3321 men and 4093 women, aged 18-97, whose measurements were valid. Figure 1 shows the 10 year all cause mortality and cardiovascular mortality by fifth for each variable for the 1158 men and 1460 women who were aged 40-64 at the time of the survey. No consistent trend was observed for body mass index, but there was a linear trend with the ratio of waist circumference to height for both all cause mortality and cardiovascular mortality in women and for cardiovascular mortality in men.

Logistic regression analysis was also carried out, with adjustment for age and smoking, in the 2184 men and 2730 women aged 30-79. This showed that body mass index did not significantly predict death from all causes or cardiovascular death whereas the ratio of waist circumference to height was a significant predictor ($P<0.01$) of both death from all causes and cardiovascular death in women and of cardiovascular death in men. Omission of people who died within four years of the survey or with pre-existing disease did not significantly alter the trends. The ratio of waist circumference to hip circumference was a predictor of similar value, but waist circumference alone, although being as good a predictor of death in women, was not as good at predicting cardiovascular death in men. Previous reports that waist circumference alone can predict cardiovascular disease have been made on the basis of cross sectional rather than prospective data.^{4,5}

This prospective study therefore supports the proposal² that the ratio of waist circumference to height should be used in a public health context because, unlike the ratio of waist circumference to hip circumference, it is an appropriate measure of the reduction in risk as well as of the risk itself.

BRIAN D COX

University lecturer

MARGARET J WHICHELOW

Senior research associate

Health and Lifestyle Survey,
Department of Community Medicine,
Institute of Public Health,
Cambridge CB2 2SR

- 1 Ashwell MA, Cole TJ, Dixon AK. Ratio of waist circumference to height is strong predictor of intra-abdominal fat. *BMJ* 1996;313:559-60. (31 August.)
- 2 Ashwell MA, LeJeune SRE, McPherson K. Ratio of waist circumference to height may be a better indicator of need for weight management. *BMJ* 1996;312:377.
- 3 Cox BD, Blaxter M, Buckle ALJ, Fenner NP, Golding JF, Gore M, et al. *The health and lifestyle survey*. London: Health Promotion Research Trust, 1987.
- 4 Hans TS, Lean MEJ, Seidell JC. Waist circumference remains useful predictor of coronary heart disease. *BMJ* 1996;312:1227-8.
- 5 Hans TS, van Leer EM, Seidell JC, Lean MEJ. Waist circumference action levels in the identification of cardiovascular risk factor: prevalence study in a random sample. *BMJ* 1995;311:1401-5.

Consensus statement on management of hypothyroidism and hyperthyroidism

Long term treatment is not safe in elderly patients with toxic nodular hyperthyroidism

EDITOR,—According to the consensus statement for good practice and audit measures in the management of hypothyroidism and hyperthyroidism, "long term treatment with 5-10 mg carbimazole seems to be safe and is an option for patients with relapsed Graves' disease or toxic nodular hyperthyroidism."¹ We have analysed the data for 28 patients aged over 60 with toxic nodular hyperthyroidism receiving long term treatment with methimazole (starting dose 3-30 mg (median 10 mg); maintenance dose 2.5-15 mg (5 mg)). The patients were treated for 6-240 months (23.5 months). During treatment 18 relapses occurred in 14 patients (five relapses of clinical hyperthyroidism and 13 of subclinical hyperthyroidism). Neither the starting dose nor the time until the patients became euthyroid predicted relapse. In most cases (nine patients) the relapse was explained by poor compliance: the patients stopped taking the drug or did not take it regularly. In three cases iatrogenic hypothyroidism occurred.

On the basis of these data we think that long term thyrostatic treatment of toxic nodular hyperthyroidism with methimazole (and probably also with carbimazole, which is not used in Hungary) is not safe in elderly patients. Radioiodine treatment, which is recommended by the consensus statement particularly for elderly people, should be the first choice.

I K TAKÁCS (research scientist),

I SZABOLCS (senior lecturer), M GÓTH (senior lecturer),

O DOHÁN (lecturer), L KOVÁCS (lecturer),

G SZILÁGYI (professor of medicine), division of endocrinology,

first department of medicine, Haynal University of Health

Sciences, Budapest, PO Box 112, H-1389 Hungary;

J FÖLDES (professor of medicine), first department of

medicine, Semmelweis Medical School, Budapest,

H-1083 Hungary

- 1 Vanderpump MJP, Ahlquist JAO, Franklyn JA, Clayton RN. Consensus statement for good practice and audit measures in the management of hypothyroidism and hyperthyroidism. *BMJ* 1996;313:539-44. (31 August.)

Fig 1—Ten year all cause mortality and cardiovascular mortality in 40-64 year old British adults by fifths of body mass index and ratio of waist circumference to height