choice for pain relief and, consequently, for overdose because selection is dictated by ready availability, sales, and prescription rates.^{2 8 9} Studies from Oxford show that, although most people who overdose know that paracetamol can be dangerous, prior knowledge of potential death and warnings on labels, however shocking, were deterrents in only a quarter of patients interviewed.^{1 2 4}

Restricting individual sales should affect the number of serious overdoses, although this is not entirely predictable.⁹ In France, where packet size is limited to 8 g, overdose is common but severe hepatotoxicity and death are rare.¹⁰ However, of people in Oxford who took more than 12 tablets, only 37% said that they would have taken smaller quantities had their packets been limited to 12 tablets.⁴ The effect of blister packs is also uncertain. Although people using them were less likely than people using loose supplies to take more than 25 tablets (40% compared to 60%), the amount ingested reflected immediate availability.⁴ The ever increasing number of formulations containing paracetamol poses practical problems for deterrent packaging, and, anyway, the new proposals on limiting pack size do not extend to effervescent tablets, granules, and sachets.⁷

Recommendations to limit the availability of designated drugs by reducing pack size or making larger amounts available only on prescription may reduce the number of serious overdoses. But given the impulsive nature of overdose, they are unlikely to reduce the total number of overdoses. The extra investment costs, if passed to the consumer, would seem an unfair financial penalty for the millions who heed recommended doses. Furthermore, selective restrictions could favour overdose with the next most available drug, or "cocktails" of unknown formulations and inferior safety record to that of paracetamol.

While we endorse the need to encourage consumers to read and heed drug safety information, we remain unconvinced, as do others,⁴ about the likely impact of any form of warnings on labels and packets as a deterrent to overdose, especially among

those who seek manipulative gain. We recommend disseminating public safety information about all the popular drugs through educational programmes in schools and via additional media such as television, radio, newspapers, and even the Internet. Information should encourage early hospital treatment after overdose, emphasising for paracetamol the high efficacy of the antidote.⁶ Any campaign that publicises the toxicity of specific drugs should be monitored carefully to watch for increases in selection of other drugs.

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Comments on the proposals (reference MLX231) should reach Dr John Price, Department of Health, Medicines Control Agency, Room 1106 Market Towers, 1 Nine Elms Lane, London SW8 5NQ, before 10 January 1997 to allow implementation of any changes by April 1997.

Thromboembolism in primary pulmonary hypertension

No clear increased risk from oral contraceptives

Premature death in patients with clinical evidence of severe right ventricular strain and no obvious predisposing condition has been recognised for over a century. In 1952 Paul Wood distinguished this syndrome of primary pulmonary hypertension from the pulmonary vascular disease that complicates some congenital heart lesions,¹ recognising the very poor prognosis that continues to characterise this rare disorder. Its yearly incidence is between 1/200 000 and 1/1 000 000, with the result that progress in understanding its pathology and interrupting its natural course has been slow. The overall mean survival remains under five years despite a variety of new treatments.

As in many systemic arterial diseases, there is increasing evidence that primary pulmonary hypertension is an endothelial disorder. The characteristic vascular obliteration that is observed as the condition progresses is thought to be the end stage of intense vasospasm and thrombosis, in different proportions in the predominantly "thromboembolic" and predominantly "plexogenic" histological types. The distinction between these as pathological or clinical entities is blurred, and it is likely that disruption of the antithrombotic and vasodilator functions of the pulmonary endothelium leads to irreversible structural pulmonary vascular disease. The endothelial products that are discussed most widely in this context are

nitric oxide and prostacyclin, both of which are vasodilators and antithrombotic agents, and endothelin-1, a powerful vasoconstrictor found in raised concentrations in the serum of the fawn hooded rat, the only animal model for the disease. Prostacyclin activity is low in patients with primary pulmonary hypertension,² but abnormalities in the basal levels of nitric oxide or endothelin-1 are less distinct.

There is no agreement as to the importance of thromboembolism, as opposed to local thrombosis in situ, in this condition. A proportion of patients have evidence of recurrent thromboembolism, and this subset can now be recognised from the characteristic appearance on a radionuclide perfusion scan.³ In patients without recognised recurrent emboli there is often histological evidence of microvascular thrombosis,⁴ and in addition there may be clot in the central pulmonary arteries that does not interfere with blood flow.⁵ The origin of such small and large vessel clots is not clear, but their occurrence supports the routine use of anticoagulants in all patients. Long term anticoagulation was shown to be associated with increased survival in the first large clinical series reported from the Mayo clinic in 1984.⁶

Most patients are women of childbearing age, and presentation during or after pregnancy is common. In established disease pregnancy is associated with rapid clinical deterioration.

The prothrombotic effects of female sex steroids are well known, and it has been suggested that the oral contraceptives may be implicated in the development of primary pulmonary hypertension as a result of increased tendency to thrombosis or a direct proliferative effect on the intima of the pulmonary arteries.⁷ There are case reports of severe deterioration in patients with established pulmonary vascular disease coinciding with the introduction of pills containing oestrogen,⁸ and of patients presenting with primary pulmonary hypertension soon after starting such treatment.⁹ However, data from the National Heart, Lung and Blood Institute primary pulmonary hypertension registry show no difference in the frequency of use of oral contraceptives in 194 registered patients and the general population.¹⁰

The link between oestrogens and primary pulmonary hypertension is one of the issues specifically addressed in the International Primary Pulmonary Hypertension Study, which has recently reported its findings.¹¹ This case-control study of 95 prospectively enrolled patients presenting with primary pulmonary hypertension found no difference in the frequency of use of oral contraceptives between patients and controls, while confirming the increased risk associated with the use of some appetite suppressants, intravenous drug misuse, and HIV infection.

There are two established medical treatments that have been shown to be effective in improving the clinical condition, and to a limited extent prognosis, of patients in addition to anticoagulation. On haemodynamic testing, about a quarter of patients show a significant reduction in pulmonary artery pressure and pulmonary vascular resistance with high doses of calcium antagonists. These patients derive long term benefit from long term treatment.¹² The doses required are high (for example, nifedipine 240 mg/day), and there is a danger of exacerbating right ventricular dysfunction and causing haemodynamic collapse in patients who have little pulmonary vasoreactivity. Use of this treatment has been limited by the need for patients to have appropriate haemodynamic characteristics and to be able to tolerate the side effects. Prostacyclin is a potent pulmonary vasodilator in responsive patients, and its antithrombotic action is also of potential benefit. Its short half life means that long term treatment must be by continuous infusion, and this technique has been associated with an improvement in patients with advanced disease and sometimes little apparent vasoreactivity.¹³ The problems of continuous infusion limit its application to patients with severe disease, usually as a bridge to transplantation.

Transplantation at present offers the best chance of long term survival. Heart-lung, single lung, and double lung transplants are established techniques with reasonable success in patients who are hypoxic and have evidence of severe right ventricular dysfunction. It is increasingly apparent that right ventricular failure may be reversible with the reduction in

afterload that occurs after lung transplantation, and single lung transplantation increases the potential number of patients who can benefit from the limited supply of donor organs.

Possible new palliative treatments include oral prostaglandin preparations and endothelin inhibitors, inhaled nitric oxide or intravenous nitric oxide precursors, and perhaps atrial septostomy in patients with advanced right ventricular dysfunction. However, since established vascular disease is present in most cases at presentation, early recognition and prevention of progression will be the keys to substantially altering the natural course of this condition.

In conditions that predispose to pulmonary hypertension, such as systemic sclerosis or atrial septal defect, and in patients with established primary or secondary pulmonary vascular disease, there is no doubt that pregnancy is associated with clinical deterioration and high mortality. In such cases there is probably a substantial risk associated with using oral contraceptives, particularly oestrogen containing preparations. However, in other women, apart from those from rare families in which the disease seems to have a direct mendelian inheritance, the risk of primary pulmonary hypertension does not warrant refusal to provide routine oral contraception.

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Heart attacks and homocysteine

Time for a randomised controlled trial of plasma homocysteine reduction

It is now accepted that an elevated plasma concentration of homocysteine is a risk factor for atherosclerotic vascular disease affecting the coronary, cerebral, and peripheral arteries.¹ Prospective data²⁻⁴ confirm the findings of case-control studies⁵⁻⁸ and indicate that an elevated plasma homocysteine concentration precedes the development of disease and that there is a dose-response effect.

A 5 µmol/l increase in plasma homocysteine concentration has been estimated to raise the risk of coronary heart disease by as much as an increase in serum cholesterol concentration of 0.5 mmol/l.¹ Data from the European Union concerted action project, a case-control study of 750 patients with vascular disease and 800 controls, indicate that a plasma homocysteine concentration above 12 µmol/l (the top fifth of