

# Paracetamol use in late pregnancy is linked to wheezing among offspring

FREQUENT use of paracetamol in late pregnancy (after 20 weeks) may increase the risk of wheezing among offspring, researchers from King's College London and the University of Bristol report (*Thorax* 2002;57:958).

Dr Seif Shaheen and colleagues asked over 9,000 pregnant mothers who were taking part in the Avon Longitudinal Study of Parents and Children about their use of paracetamol and aspirin when they were 18 to 20 weeks pregnant and again at 32 weeks of pregnancy. The mothers were also asked about symptoms of wheeze and eczema in their children six months after giving birth and at 12-monthly intervals thereafter.

The researchers, who have previously shown a positive association between paracetamol use and asthma, considered that exposure to paracetamol in early life might influence the development of atopic disease.

They found that frequent paracetamol use and frequent aspirin use during pregnancy were associated with different wheezing patterns. For paracetamol, frequent use (on most days or daily) was reported by 1 per cent of women. In late pregnancy (20 to

32 weeks) this pattern of use, compared with no use, was associated with a doubling in the risk of wheeze in the children when they were 30–42 months old (odds ratio 2.10, 95 per cent confidence interval 1.30–3.41,  $P=0.003$ ). The association was strongest among children whose symptoms appeared before they were six months old.

There was no evidence that less frequent use, or heavy use of paracetamol before 20 weeks of pregnancy, increased the risk of wheeze in the children born to these mothers. Nor was there any evidence to suggest that frequent use of paracetamol during pregnancy was linked to subsequent eczema in the children.

Frequent use of aspirin was associated with a higher risk of transient infant wheezing, but only in children under 6 months old. This observation was unexpected, say the researchers.

They comment that the proportion of early childhood wheezing in the population that could be attributable to frequent use of these analgesics during pregnancy, assuming a causal relationship, was small (about 1 per cent for paracetamol). "We recommend

that paracetamol should remain the analgesic of choice in pregnancy, if used infrequently," they conclude.

## MCA launches web version of yellow card scheme

THE reporting of suspected adverse drug reactions using a web version of the yellow card scheme was launched this week by Health Minister Lord Hunt. The original yellow card scheme has also been extended to include reporting by all nurses, health visitors and midwives.

A spokesman for the Medicines Control Agency said that both initiatives were designed to increase reporting through the scheme.

He added that the electronic version of the yellow card on the MCA website ([www.mca.gov.uk](http://www.mca.gov.uk)) will allow for reports to be received and processed more rapidly by the MCA, thus facilitating the early detection of previously unrecognised reactions. Pharmacists and other health care professionals are encouraged to report using the electronic yellow card where possible.

The electronic yellow card scheme will not be password protected but will require reporters to give their name, address and professional affiliation. Reports received from patients will be dealt with in the same way as those received via the paper scheme. "We deal with them as an enquiry and write to the patient to encourage them to speak to a health care professional," a spokesman for the MCA said.

The MCA has prepared an educational pack on suspected ADR reporting that will be available on its website from 31 October.

## Frequent painkiller use associated with double risk of hypertension

PEOPLE who regularly use paracetamol or some non-steroidal anti-inflammatory drugs (NSAIDs) may be doubling their risk of hypertension, say researchers from Harvard Medical School and Harvard School of Public Health in Boston. However, they also say that use of aspirin is not associated with such an increased risk (*Archives of Internal Medicine* 2002;162:2204).

They conducted a prospective study of just over 80,000 women aged 31 to 50 years who had no previous history of hypertension. Frequency of aspirin, other NSAID, and paracetamol use and incidence of diag-

nosed hypertension were determined through questionnaires. The results showed that after adjusting for age and other risk factors, only paracetamol and NSAIDs other than aspirin were associated with an increased risk of hypertension ( $P<0.001$  for trend for both).

The relative risk of hypertension for women taking NSAIDs on 22 or more days each month was 1.86 (95 per cent confidence interval, 1.51–2.28) compared with that in non-users. For those taking paracetamol at this level of frequency the relative risk was 2.00 (1.52–2.62).

## Rotahalers to be discontinued next year

ROTAHALER devices (Becotide Rotahaler, Ventolin Rotahaler and Ventide Rotahaler) along with all Rotacap and Ventide medicines are to be discontinued by Allen & Hanburys.

The company has written to health care professionals telling them of the decision and says it plans to discontinue the devices in 12 months time in order to allow patients to be transferred to alternative medication.

Allen & Hanburys says the decision follows a fall in the demand for Rotahalers and Ventide metered dose inhalers.

However, it maintains that there is a range of alternative devices suitable for use by patients currently using Becotide, Ven-

tolin or Ventide Rotahalers. Anna Murphy, consultant respiratory pharmacist at University Hospitals of Leicester NHS Trust, said that although there had been a reduction in use of Rotahalers, some patients had been using these devices for many years with good effect.

"I cannot see it being a large scale problem but, saying that, pharmacists from the community, hospital and primary care trusts must ensure that patients are told of the change and that the best device for them as an individual is chosen.

"Patients must have good instruction on how to use them and adequate follow up," she added.

# Euro-MPs reject proposals to reform availability of medicines information

PROPOSALS to allow pharmaceutical companies to provide information directly to the public on medicines to treat AIDS, asthma and diabetes have been rejected by the European Parliament (*P7*, 19 October, p560).

MEPs voted against the plan by 504 to 30, with 16 abstentions.

European legislators are currently consolidating and updating European Directives on pharmaceutical products at the instigation of the European Commission.

The commission has also proposed that all new medicines should be centrally licensed by the European Agency for the Evaluation of Medicinal Products. This met with the European Parliament's approval.

The amended proposals will now go to the European Union's Council of Ministers to be considered before returning to the parliament for a second reading.

The MEPs' decision has been welcomed by the Pharmaceutical Group of the European Union, which said that MEPs had confirmed the view that medicines were not to be treated as consumer goods.

Erkki Liikanen, European Commissioner for Enterprise, said that the overall package of proposals would increase the availability of innovative medicines while favouring competition with generics. He added that the central authorisation proce-

dures meant that new medicines would be available throughout Europe more quickly than was currently the case.

Commenting on the rejection of the information proposal, Mr Liikanen said: "Our proposal would not allow unsolicited advertising [of medicines for AIDS, asthma or diabetes] as is the case in the United States. But it would enable these patients to get good, appropriate and officially authorised information if they so request."

Patients who want information on medicines generally get it from websites in the US, the commissioner went on. But not all Europeans have access to the internet or understand English. Also, US medicines are not always the same as European ones even when they share the same name and this poses a health risk.

"Nothing is further from our minds than introducing advertising for prescription medicines in Europe," he added.

A series of four articles assessing the pharmaceutical industry's role in the provision of information about medicines starts this week in *The Lancet*. The authors of the first article are critical of the way in which multinational pharmaceutical companies manipulate the provision of information, and say that this contributes to a distortion of medical research.

## High-dose chemotherapy for breast cancer no better than normal

THERE is no difference in survival or relapse rate among breast cancer patients receiving high-dose and conventional chemotherapy, according to the early results of a trial comparing two regimens.

The Anglo-Celtic I study, which has recruited over 600 women with breast cancer involving the lymph nodes, has recorded 120 cancer relapses in each arm of the trial and five treatment-related deaths, all in the high-dose chemotherapy treatment arm, after an average follow-up of five years. Meanwhile, cancer deaths in the two treatment groups are comparable — 86 among the high-dose group and 84 among those receiving conventionally dosed adjuvant chemotherapy.

Study leader Dr John Crown, of St Vincent's University Hospital in Dublin, said: "In truth, the results of conventional-dose chemotherapy were better than expected. However, we must keep an open mind for the rest of the data, although our results already indicate that any benefits that emerge from high-dose chemotherapy will be, at best, modest. I believe that these results show us how far we can go with chemotherapy."

The data were presented at the European Society for Medical Oncology con-

gress, which was held in Nice, last month.

The meeting also heard that adding oxaliplatin (Eloxatin) to 5-fluorouracil (5-FU) and calcium folinate, can delay tumour progression in patients with colorectal cancer by 70 per cent.

Interim results for 463 patients taking part in a phase III trial to compare these two treatment regimens show that the mean time to tumour progression was 4.6 months in patients treated with all three drugs compared with 2.7 months for those given 5-fluorouracil and calcium folinate alone ( $P < 0.0001$ ).

Speaking at the meeting, Dr Mace Rothenberg, from the Vanderbilt-Ingram Cancer Centre, Nashville, and one of the study investigators, said: "Both the delay in time to progression and the reduction in tumour-related symptoms are encouraging." He added that patients suffered less from pain, weight loss and fatigue with combination therapy.

Final data from the trial are expected in about six months.

"At that point, we will know more about the impact of the oxaliplatin, 5-FU and [calcium folinate] combination on the survival of patients with recurrent colorectal cancer," said Dr Rothenberg.

## Emergency Seroxat role for pharmacists

PHARMACISTS in Ireland have been asked by the Irish Medicines Board to tell patients taking Seroxat (paroxetine) about the risk of self-harm and suicide.

Following a BBC *Panorama* programme on Seroxat and coverage in the Irish media, it emerged that GlaxoSmithKline had failed to bring information in Irish packs in line with the United Kingdom despite having been told to do so last December. The company has now been ordered to recall the product from wholesalers and to issue a clarification letter and revised patient information leaflets to pharmacists and doctors.

The decision to bring the information into line was agreed by the medicines board and the company following an expert review in the summer of 2001. A GlaxoSmithKline spokeswoman said that the suicide reference "had not been defined as critically urgent" and had been brought to the manufacturing site too late for supplies to the Irish market.

Richard Collis, president of the Irish Pharmaceutical Union, said that a significant number of Irish patients take Seroxat. "Many of them need Seroxat just to maintain everyday living," he said. "With all the publicity about the medicines board ordering a recall, they were frightened supplies were being withdrawn. We had to help calm their fears and reassure them."

# NICE makes recommendations for use of thrombolytic drugs for acute MI

BOLUS drugs should be used to treat acute myocardial infarction (MI) when patients are treated before being admitted to hospital, according to new guidance from the National Institute for Clinical Excellence.

It says that, where pre-hospital delivery of thrombolytic drugs is considered to be beneficial, for example, because of the inaccessibility of acute hospital facilities, reteplase (Rapilysin) or tenecteplase (Metalyse) should be the preferred options because they can be given by rapid intravenous (IV) bolus infusion. The two other thrombolytic agents licensed for treatment of acute MI — streptokinase and alteplase (Actilyse) — are given by IV infusion.

In hospital settings, the guidance states that the choice of which thrombolytic drug to use in acute MI should be based on patient need and the hospital's local arrangements for minimising delay in administering thrombolysis. NICE says the choice of drug should also be influenced by current practice, which accepts that people

who have already received streptokinase once should not be treated with it again.

Current spend on thrombolytics in England and Wales is estimated to be £13–26m. However, NICE says it is likely that there will be substantial costs associated with further expansion and introduction of pre-hospital thrombolysis, which it says is becoming more common.

Dr Anton Van Dellen, medical adviser to Staffordshire Ambulance Service NHS Trust, said: “[The guidance] will improve the standard of care for people who have had a heart attack. They should now be able to receive the right treatment at the right time, which could mean the difference between life and death.”

He added that Staffordshire paramedics had achieved good results with the bolus drug reteplase since they began using it two years ago.

The guidance, which provides recommendations on the use of alteplase, reteplase, tenecteplase and streptokinase in



Patients treated in the pre-hospital setting should receive reteplase or tenecteplase

patients with acute MI in pre-hospital and hospital settings, can be viewed on the NICE website ([www.nice.org.uk](http://www.nice.org.uk)).

## BRIEFLY

### DoH seeks more smallpox vaccine

The Government is looking to purchase further smallpox vaccine in addition to the batch it has already ordered from Powderject. Last week, the Department of Health placed an advertisement in the *Official Journal of the European Community* inviting bids for more supplies of the vaccine, although it did not specify the quantity required. A spokesman said that this would allow the Department to secure further supplies of smallpox vaccine from the widest possible number of suppliers, without compromising national security.

### Green book goes online

The 1996 edition of ‘Immunisation against infectious disease’ (The Green Book) — is now available on the internet ([www.doh.gov.uk/greenbook](http://www.doh.gov.uk/greenbook)).

### Gabapentin and neuropathic pain

Gabapentin reduces pain and improves some quality-of-life measures in patients with neuropathic pain, say British and Irish researchers (*Pain* 2002;99:557). A randomised, controlled trial involving 305 adults showed that the average daily pain score decreased more for patients treated with gabapentin than for patients given placebo (7.3 to 6.3 versus 7.1 to 5.6,  $P=0.048$ ). After eight weeks of treatment gabapentin resulted in a 50 per cent or greater reduction in mean pain score in 21 per cent of patients compared with 14 per cent of patients given placebo ( $P=0.16$ ). The study was funded by Parke-Davis.

## MRC stops HRT safety trial early

A TRIAL looking at the long-term effects of hormone replacement therapy (HRT) has been stopped early, the Medical Research Council announced last week.

The Women's International Study of Long Duration Oestrogen after Menopause (WISDOM) was designed to assess the balance of risks and benefits of both oestrogen combined with progesterone and oestrogen alone, on conditions such as heart disease, breast cancer, osteoporosis and dementia.

Following the termination of a similar study — the US Women's Health Initiative (WHI) — in July (*PJ*, 13 July, p43), the MRC set up a committee of advisers to review the findings from WHI and to assess the progress of WISDOM. The committee decided that WISDOM was unlikely to

provide substantial evidence to influence clinical practice in the next 10 years and therefore recommended that the trial be halted.

Professor Ray Fitzpatrick, director of the Institute of Health Sciences, University of Oxford, and chairman of the committee of advisers, said: “When the WISDOM trial began recruiting in 1999, there were important questions about the risks and benefits of taking HRT long term that needed to be answered. But since then new findings have provided evidence in relation to those questions.”

The WISDOM study, which was funded in part by the MRC and the Department of Health, started in 1999 and was due to end in 2016.

## Study in rats suggests long-term HRT in Alzheimer's may worsen memory

MEMORY loss among postmenopausal women with Alzheimer's disease may be worsened if they take oestrogen therapy for long periods, say researchers from the University of Arizona.

The researchers trained female rats to perform a maze task and then tested whether removal of the rats ovaries and initiation of oestrogen therapy impaired the rats' memory.

They found that removal of the rats' ovaries was not enough to impair performance in the task.

However, the subsequent introduction of sustained oestrogen replacement therapy

did impair memory performance. “A therapy designed to mimic the natural cycle of hormone fluctuation may provide a more effective therapy to slow the progression of Alzheimer's disease in postmenopausal women,” say the researchers.

They add that their findings, and the results of other clinical trials, suggest a pattern of beneficial effects on cognitive function after relatively short-term HRT but that this beneficial effect is attenuated, and possibly reversed, after much longer treatment regimens.

The study is published in *Behavioral Neuroscience* (2002;116:902).

# Restrict triptans to 10 doses a month

TRIPATAN use should be restricted to a maximum of 10 single doses per month, according to researchers from Essen university hospital in Germany.

They investigated the incidence of headaches caused by overuse of acute headache drugs among 96 users of analgesics, ergots and triptans. Most patients included in the study were women who had migraine as their primary headache.

The study showed that overuse of triptans led to medication-overuse headaches (MOH) faster and at lower doses than with the other drugs studied (*Neurology* 2002;59:1011).

"[The critical intake frequency] was as low as 10 single doses per month in some patients, indicating that an intake of triptans every other or even every third day may be sufficient to develop MOH," they say.

Patients were interviewed about the history of their primary headache and about

the development of MOH. The mean duration of primary headache history was 22 years (three to 44 years) and mean duration of drug overuse was 6.5 years (0.5 to 25 years). Of the 96 taking part in the study, 46 overused analgesics, 12 overused ergots and 38 overused triptans. The researchers calculated the time taken for patients to develop MOH by subtracting the duration of MOH from the duration of drug overuse.

They found that this time was shortest in patients overusing triptans and longest in those overusing analgesics (1.7 years versus 4.8 years). They also calculated the critical dose frequency that caused MOH. This was lowest for triptans and highest for analgesics (18 versus 114 single doses per month).

The researchers comment that the pharmacological and clinical presentation of triptan-induced MOH is different from that induced by other acute headache drugs. All patients who overused analgesics and most who overused ergots developed tension-

type headaches. However, of the patients overusing triptans almost 40 per cent developed an increase in the frequency of their migraine attacks.

## Bisphosphonate can benefit cancer

A THIRD generation bisphosphonate has been shown to reduce skeletal complications among breast cancer patients.

American researchers randomised 435 women with breast cancer and bone metastases to receive 20 or 50mg ibandronate (Bondronat) or placebo daily for 96 weeks. Those taking ibandronate suffered fewer cancer-related bone complications than those taking placebo ( $P=0.017$ ). In addition, the ibandronate group suffered less pain and had an improved quality of life compared with the placebo group.

Ibandronate is currently licensed as a treatment for tumour-induced hypercalcaemia. However, the manufacturer Roche has also applied for it to be licensed for metastatic bone disease in breast cancer patients. These latest data, presented at the European Society for Medical Oncology meeting in Nice last month, have been submitted to support the application.

## Mesalazine prophylaxis could be used to prevent colorectal cancer

EVIDENCE is building that prophylaxis with mesalazine (5-aminosalicylic acid, 5-ASA) is effective in preventing colorectal cancer in patients with inflammatory bowel disease (IBD), according to a leading gastroenterologist.

Addressing the United European Gastroenterology Week congress in Geneva last week, Dr Jayne Eaden, one of the authors of the British Society of Gastroenterology guidelines on cancer surveillance in IBD, presented a review of evidence which suggests that mesalazine is the only treatment to be associated with a statistically significant reduction in the risk of developing cancer in patients with ulcerative colitis.

Odds ratios for developing cancer in IBD patients taking mesalazine were as low as 0.08, compared with 0.40 with other drugs such as sulfasalazine and olsalazine. Dr Eaden, who is a consultant gastroen-

terologist at Walsgrave Hospital in Coventry, is planning to set up a UK-wide study to examine the possibility of using the drug routinely in these patients.

She believes that being able to tell patients that the drugs they are taking for symptomatic relief of IBD symptoms are protecting them from cancer could increase compliance: "In Denmark, where ASA prophylaxis is routine in these patients, there is evidence of a very low risk of colorectal cancer and that it is even a cost-effective intervention when compared with surgery."

Dr Eaden added that current UK practice, of checking for neoplasms using colonoscopy, had little evidence to back it up. "There is no randomised controlled trial showing it works and we know that the type of neoplasms in patients with ulcerative colitis look different anyway," she told delegates.

### BRIEFLY

#### Combination therapy benefits RA

Interim results from a phase II trial involving 122 patients reveal that, after six months of treatment, 80 per cent of patients taking methotrexate plus rituximab (MabThera) showed a 20 per cent improvement in their rheumatoid arthritis, compared with only a third of those taking standard methotrexate monotherapy ( $P=0.001$ ). The data were presented at the annual American College of Rheumatology meeting in New Orleans last month.

## A daily dose of lansoprazole could reduce exacerbations in difficult to control asthma

DAILY use of the proton pump inhibitor lansoprazole reduces asthma exacerbations and improves the general well-being of patients with asthma and symptoms of acid reflux, new data shows.

Researchers randomly assigned 207 subjects with moderate to severe asthma and symptoms of acid reflux to receive lansoprazole 30mg or placebo daily. At 24 weeks, fewer patients in the treatment group had experienced one or more asthma exacerbations than in the placebo group (8 versus 22). Four subjects taking lansoprazole and 15 subjects taking placebo required pred-

nisolone for exacerbations. The researchers note that those patients requiring at least one long-term medicine for controlling their asthma in addition to inhaled corticosteroids had the greatest improvement in exacerbations and quality of life from taking lansoprazole. They conclude that lansoprazole offers the most benefit to patients with more difficult to control asthma.

Data from the study, funded by TAP Pharmaceuticals and Abbott Laboratories, were presented at the annual meeting of the American College of Gastroenterology in Seattle, Washington, last week.

# ASDA to repeat 'flu vaccination offer

THE ASDA supermarket chain is to offer influenza vaccinations for a second time this year because sales on the first occasion were so successful (*PJ*, 5 October, p470). Nurses from Doctorcall will be at 80 ASDA supermarkets on 9 November from 9am to 2pm.

ASDA said that it had been astonished at the success of its first initiative, with customers queuing for vaccinations before sales started. Demand was strongest in East Anglia, where vaccine supplies were exhausted within hours of being made available. "It's clear that thousands of shoppers appreciated the convenience of picking up their 'flu jabs with their fish fingers and feta cheese," said ASDA's healthcare director David Miles.

Customers will be expected to pay for their injections at store checkouts before completing prevaccination questionnaires and seeing the Doctorcall nurses.

Letters, p643

## BRIEFLY

### MeReC Briefing update

The latest issue of the *MeReC Briefing* reviews the impact of lifestyle on cardiovascular risk. Evidence for the effects of smoking, diet, exercise and alcohol, is discussed. The publication is available from the National Prescribing Centre website ([www.npc.co.uk](http://www.npc.co.uk)) and from [www.npc.ppa.nhs.uk](http://www.npc.ppa.nhs.uk).

### LINKScripts 2 update

AAH Pharmaceuticals has launched an updated version of its LINKScripts 2 pharmacy computer system. Changes to the system include endorsements for the extended nurse formulary, monitoring of owed items, ordering capability from any wholesaler and reminders to check unusual dosage instructions.

### NPA board election

The National Pharmaceutical Association is holding an election to fill a board vacancy for its Birmingham, Coventry and West Midlands area caused by the co-option of Andy Murdock, director of pharmacy at Lloydspharmacy, to the board. Nominations for the vacancy can be made until noon on 11 November.

### Pneumovax supply problem

Aventis Pasteur MSD is experiencing problems meeting demand for its pneumococcal vaccine Pneumovax II. This follows a 40 per cent increase in demand for the vaccine in the United Kingdom in September this year compared with that for last year. A spokesman for the company explained that the increase is because of the introduction of recommendations to vaccinate all persons aged 65 years and over in Northern Ireland and Scotland.

## PSNC medicines management project enters main phase

THE Pharmaceutical Services Negotiating Committee's medicines management project — the community pharmacy medicines management project (CPMMP) — has now entered its main phase.

Helen Rhodes, project manager for the CPMMP, told *The Journal* that the pilot phase had been completed successfully and that the lessons learnt during the pilot and from feedback from participants had been used to improve the processes rolled out into the main phase.

"Many of the practices involved in the project have now written to patients on their [coronary heart disease] lists to invite them to participate in the project. The next step is for audit clerks to extract core baseline data from patients' medical notes." This information will then be sent to participating pharmacists to enable them to make initial

assessments of patients and invite them for an interview.

Ms Rhodes added that the nine pilot areas (*PJ*, 16 June 2001, p802) remain the same for the main phase and that the only difference between the pilot and main phases is that more patients are being invited to participate.

The PSNC is to hold a series of evening roadshows, planned for January and February 2003, to inform community pharmacists about medicines management in general, based upon the experiences of the project. Information on how to assess premises, identify training needs and plan and conduct a medicines management consultation will be presented at the roadshows.

Information about the project and the roadshows is available from [www.medicinesmanagement.org.uk](http://www.medicinesmanagement.org.uk).

## Industry provides CPD support

RECKITT Benckiser has launched a "CPD toolkit" for community pharmacists at a conference held in association with the National Pharmaceutical Association and the College of Pharmacy Practice in London earlier this week.

The toolkit has 10 sections, including ones for standard operating procedures, staff training and category management. Mel Smith, global professional relations manager at Reckitt Benckiser, said that the CPD toolkit was not intended to replace the Royal Pharmaceutical Society's CPD material, but to work alongside it. The company will be distributing the toolkit to independent pharmacists through its local sales representatives.

## Rural pharmacists' group wound up

THE Rural Pharmacists Association (RPA), which was formed to represent the interests of pharmacists working in rural areas, is to be wound up because its officers have decided that the need for such a group has declined.

The RPA was founded in by John Davies and Mervyn Madge in 1981 (*PJ*, 25 July 1981, p104) and supported rural pharmacists in the face of competition from dispensing medical practices, where professional standards often fell short of those expected of pharmacists.

Any funds remaining after the RPA is wound up will be donated to the Royal Pharmaceutical Society's Benevolent Fund.

# Thrombin inhibitor more effective than enoxaparin at preventing blood clots

A NOVEL direct thrombin inhibitor has been found to be more effective than enoxaparin (Clexane) at preventing venous thromboembolism in patients undergoing elective hip or knee replacement surgery.

The inhibitor is being developed by AstraZeneca as both a subcutaneous injection, melagatran, and in an oral formulation, ximelagatran, a prodrug of melagatran. Both will carry the brand name Exanta.

In the expanded prophylaxis evaluation surgery study (EXPRESS), researchers randomly assigned 2,764 patients undergoing surgery to receive either a regimen of melagatran 2mg immediately before surgery followed by melagatran 3mg in the evening after surgery and then ximelagatran 24mg twice daily (ximelagatran group) or enoxaparin 40mg daily started the evening before surgery. The total duration of treatment was eight to 11 days.

The researchers report that the regimen of melagatran and ximelagatran reduced the risk of proximal deep vein thrombosis (DVT) and pulmonary embolism by almost two

thirds compared with that for enoxaparin — the rate of proximal DVT and pulmonary embolism was 2.3 per cent in the ximelagatran group (n=1,138) and 6.3 per cent in the enoxaparin group (n=1,178) ( $P<0.000002$ ). The melagatran and ximelagatran regimen also reduced the risk of proximal and distal DVT, pulmonary embolism and total mortality by a quarter compared with that for enoxaparin — total rate of venous thromboembolism was 20.3 per cent in the ximelagatran group (n=1,141) and 26.6 per cent in the enoxaparin group (n=1,184) ( $P<0.0003$ ).

The number of cases of symptomatic venous thromboembolism was eight in the ximelagatran group and 13 in the enoxaparin group. Bleeding events and transfusion rates were both more common in the ximelagatran group than in the enoxaparin group.

Ximelagatran in combination with melagatran is expected to receive a licence in the United Kingdom during the latter half of next year for the prevention of venous thromboembolism in patients undergoing knee and hip replacement surgery.

Data were presented at the International Congress on Thrombosis held in Bologna last week.

## New data supports rosuvastatin

ROSUVASTATIN (Crestor) is more effective at reducing low density lipoprotein (LDL) cholesterol levels in patients with cardiovascular risk factors than atorvastatin, simvastatin and pravastatin, researchers say.

In a trial of 2,161 patients, lead researcher Professor Richard Hobbs, University of Birmingham, found that 81 per cent of high-risk patients (n=314) and 85 per cent of low-risk patients (n=75) taking rosuvastatin 10mg achieved their LDL cholesterol goal compared with 49 per cent (n=327) and 64 per cent (n=66), respectively, for patients taking atorvastatin. Rosuvastatin was also found to be more effective in both risk categories when compared with simvastatin and pravastatin.

Professor Hobbs, concludes: "It is likely that the greater intrinsic activity of rosuvastatin at starting doses will reduce the need for dose titration to achieve target levels, so improving the efficiency and convenience of this treatment across the range of patients requiring statin therapy."

In another study of 1,245 patients, Dr Anthony Wierzbicki, St Thomas' Hospital, London, and colleagues found that treatment with rosuvastatin for 12 weeks improves lipid profiles in patients with hypercholesterolaemia regardless of baseline high density lipoprotein (HDL) cholesterol levels. "Individuals with low base-line HDL cholesterol appear to gain particular benefit," they say.

Rosuvastatin is being developed by AstraZeneca. Data were presented at the Primary Care Cardiovascular Society annual meeting in Cardiff last month.

Data were presented at the 27th European Society for Medical Oncology Congress in Nice last month.

## Novel antifolate drug in combination with gemcitabine promising therapy

THE novel antifolate drug pemetrexed (Alimta) in combination with gemcitabine is promising for patients with advanced non-small cell lung cancer, phase II data show.

Pemetrexed targets specific enzymes involved in purine and pyrimidine synthesis and is being developed by Eli Lilly. In a trial of 60 patients, a combination of pemetrexed and gemcitabine produced a median survival of 11.3 months and a median time to progression of 4.9 months. In addition, 50 per cent of patients had disease stabilisation and 44 per cent were alive one year after enrollment.

Data were presented at the 27th European Society for Medical Oncology Congress in Nice last month.

## Long-acting form of filgrastim improves chemotherapy-induced neutropenia

PEGFILGRASTIM (Neulasta), a long-acting form of filgrastim (Neupogen), has the potential to improve the management of neutropenia in cancer patients with non-myeloid malignancies receiving myelosuppressive chemotherapy, new data show.

Pegfilgrastim, which is being developed by Amgen and is expected to be launched in the United Kingdom next year, is administered once per chemotherapy cycle, unlike filgrastim which is given by daily injections.

A combined analysis of two phase III trials of patients with breast cancer showed

that 11 per cent of patients given a single injection of pegfilgrastim (n=226) experienced febrile neutropenia compared with 19 per cent of patients given daily injections of filgrastim (n=222).

A single dose of pegfilgrastim provided protection from infection associated with chemotherapy-induced neutropenia comparable to a median of 11 daily injections of filgrastim.

Data were presented at the 27th European Society for Medical Oncology in Nice last month.

### BRIEFLY

#### Alternative to penicillin for erysipelas

Pristinamycin, an antimicrobial active against *Streptococcus pyogenes*, could be an alternative to a regimen of intravenous and then oral penicillin for the treatment of erysipelas, an acute superficial cellulitis, researchers report.

After 14 days of treatment, the cure rate was 81 per cent with pristinamycin (n=102) and 67 per cent with penicillin (n=102) (*BMJ* 2002;325:864).

# 5HT<sub>4</sub> agonist is effective IBS treatment

TEGASEROD (Zelmac), a 5HT<sub>4</sub> partial agonist, is effective for the treatment of irritable bowel syndrome (IBS) without diarrhoea, according to new data presented at the 10th annual United European Gastroenterology Week congress in Geneva last week.

In a trial of Asian-Pacific patients, researchers randomly assigned, after a base-line period of two weeks, 259 patients to receive tegaserod 12mg daily and 261 patients to receive placebo for 12 weeks, followed by a four-week treatment-free withdrawal period.

The overall discontinuation rate was 16 per cent in the tegaserod group and 12 per cent for the placebo group, with discontinuation due to adverse events occurring in 7.7 per cent of patients in the tegaserod group and 3.1 per cent of patients taking placebo. Diarrhoea was the most common adverse event. Discontinuation due to diarrhoea occurred in 2.3 per cent of patients taking tegaserod and none of those taking placebo.

As a result, the researchers say that tegaserod is a safe, effective and well tolerated treatment for non-diarrhoea IBS in an Asian-Pacific population, with a sustained effect over 12 weeks.

In another, phase III, study, published in *Alimentary Pharmacology and Therapeutics* recently (2002;16:1877), new data show that tegaserod provides rapid relief from abdominal pain, discomfort, bloating and constipation associated with IBS in women. Researchers randomly assigned 1,519 women, from 131 centres in the United States, to receive tegaserod 6mg twice daily or placebo for 12 weeks. Treatment was preceded by a four-week base-line period without treatment and followed by a four-week open withdrawal period.

The researchers say that patients treated with tegaserod experienced less bloating, more bowel movements with a softer consistency and less need to strain. IBS symptoms returned rapidly after cessation of treatment, but did not return to base-line within the four-week withdrawal period. They conclude that "the efficacy of tegaserod in IBS patients persists for at least 12 weeks of treatment".

Marketing approval has now been gained in the US following a request by the US Food and Drug Administration for more data about the drug (*P7*, 23 June 2001, p845). Novartis, the company developing

tegaserod, plans to submit an application for a licence for the product to the European Agency for the Evaluation of Medicinal Products. However, it is not known when tegaserod is expected to receive a licence in the United Kingdom.

## Enzyme inhibitor that targets cancer cells spares healthy cells

A NEW enzyme inhibitor, bortezomib, may be an effective way of targeting cancer cells while sparing healthy ones, according to Millennium Pharmaceuticals, the company developing the drug.

The company explains that bortezomib inhibits proteasome, an enzyme complex in the cell responsible for breaking down a variety of proteins, including many that regulate cell division. Inhibiting proteasome with bortezomib disrupts regulation of cancer cell regulatory processes, inducing programmed cell death.

Data from a phase II trial presented at the European Society of Medical Oncology in Nice last month show that myeloma protein, a marker of myeloma tumour burden,

was stabilised or reduced in 77 per cent of the 70 patients with multiple myeloma treated with bortezomib for up to 24 weeks.

A total of 14 patients had a greater than 90 per cent reduction in myeloma protein levels and 33 had at least a 25 per cent reduction. Overall, the median time to progressive disease had not been reached after 6.2 months of follow-up.

Side effects of bortezomib included nausea, fatigue, diarrhoea, headache, decreased platelets and peripheral neuropathy.

The company says that bortezomib is being investigated in clinical studies for solid tumours, including colon, lung, breast, prostate and pancreatic cancers.

## Synthetic molecule provides potential alternative to HRT for osteoporosis

A SYNTHETIC compound that could be used as an alternative to hormone replacement therapy (HRT) for osteoporosis has been identified by researchers in the United States.

Comparing the effects of the compound, 4-estren-3 $\alpha$ ,17 $\beta$ -diol (estren) to those of 17 $\beta$ -estradiol (E<sub>2</sub>) and dihydrotestosterone (DHT) on bone and reproductive tissues in mice, the researchers found that although estren was at least as effective as estradiol in preserving global and spinal bone mineral density in females, it had, in contrast to E<sub>2</sub>

and DHT, no effect on reproductive tissues. They say that irrespective of the sex of the mouse, a replacement dose of either E<sub>2</sub> or DHT or administration of estren to female or male mice, prevented gonadectomy-induced programmed cell death in osteoblasts in the lumbar vertebrae.

The researchers conclude that the favourable effects of estren on bone and its lack of effect on reproductive tissues indicate that mechanism-specific ligands may offer advantages over oestrogens for the prevention of osteoporosis.

### BRIEFLY

#### Cancer cells selectively targeted

A new drug that selectively targets breast cancer cells is expected to enter clinical trials early next year.

The drug, "phortress", may be effective in up to a quarter of breast cancers and does not rely on the presence of the oestrogen receptor. It may be possible to test tumours for their susceptibility to the drug, Nottingham University report at the Cancer Research UK annual conference in Warwickshire, this week.

#### DNA-repair process disabled

A new class of drugs that disable the DNA-repair process after radiotherapy has been developed by researchers at the Cancer Research UK unit, Newcastle University.

The researchers explain that the drugs inhibit poly (ADP-ribose) polymerases, thus blocking the action of DNA repair and sensitising cancer cells to radiotherapy. The research was presented at the Cancer Research UK annual conference in Warwickshire this week.

#### Thalidomide analogues

Two classes of second generation thalidomide analogues have shown anti-angiogenic activity independently of immunomodulatory effects.

Researchers say that the study provides further evidence of the clinical potential of these compounds as antitumour drugs (*British Journal of Cancer* 2002;87:1166).