classified 8.6 more slides in these categories per 1000 women screened than did conventional cytology. However, it is estimated that about half of these abnormalities will regress to normal.⁷ The increased detection of low grade cytological lesions by the imager might result in higher rates of further testing. On the other hand, together with our finding of improved detection of histological cervical intraepithelial neoplasia grade 2, it does raise the possibility that the increased detection of squamous abnormality by the Imager might allow longer screening intervals.

Although more glandular abnormalities were reported with conventional cytology than with the Imager, the two were equivalent in detecting reference standard positive cases at a referral threshold of atypia. The decreased detection of cytological glandular lesions by the ThinPrep Imager in our study was not at the cost of reduced detection of histological glandular disease, although this result is limited by the small number of cases.

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Commentary: Liquid automation refreshes Dr Papanicolaou

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That the Papanicolaou test has been modified so little during the greater part of its existence is surely a tribute to the insight and inventiveness of the physician scientist from whom it takes its name. When change began to be mooted in the 1980s it was because new levels of computing power were making it realistic to think of automating the microscopic examination of cells from the cervix. But to do so reliably depended on first improving the quality of the smears. This prompted the development of liquid based cytology—and with it a need for realistic comparative assessments: of the performance of the new technique as against conventional methods,¹ and of automated as against manual microscopy for examining cervical cell preparations.²

Various liquid based cytology systems are now commercially available. In methods and equipment their details differ from one manufacturer to another, but all dispense with a core feature of the conventional cervical smear test. Instead of smearing the cervical material on to a microscope slide, the tester rinses the brush-like sample collection device in a small pot of preservative fluid. At the cytology lab the floating cells are dispersed and variously

centrifuged or filtered to remove blood, mucus, and other debris, and then allowed to form a monolayer on a microscope slide.

In principle this approach confers several advantages. Virtually all the cells collected from the cervix should be present in the suspension, allowing the final sample to be more representative of the original population. The cells themselves, besides being more evenly distributed across the slide, should also be better preserved. Consequently, the proportion of specimens rejected as unsuitable for examination should fall, allowing the productivity of cytology labs to rise. Laboratory staff taking part in a UK Department of Health evaluation study generally approved the system.³

Moving on to automation, here too one of the goals is an increase in productivity—coupled, it has been hoped, with improved accuracy. The ThinPrep imaging system used by Davey et al² is intended not to replace human judgment, but to facilitate it by drawing the attention of the microscopist to the cells of most relevance.⁴ It uses a stain that gives an appearance similar to that used in the conventional smear test, but in which the intensity of colouration is closely

correlated with the DNA content of the nucleus. The underpinning biological principle is that “abnormal cells have abnormal DNA content.”⁵

The automatic analyser works its way through a cartridge of slides, scanning each for the largest and darkest cells. It records the locations of 20 that are likely to be of interest to the cytologist. It also identifies two more locations based on the cells’ clustering characteristics. When the operator comes to examine the slide, the motorised stage of the microscope moves these sites successively into the field of view. If the operator judges any cells to be abnormal, the entire slide is then scanned. The location of suspicious cells can be electronically marked before the slide is passed to the cytologist for further examination. The system aims to focus human attention and expertise where it is most needed.

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BMJ updates

Yearly infusion of zoledronic acid helps prevent fractures in postmenopausal women with osteoporosis

Research question

Is once yearly intravenous zoledronic acid an effective treatment for postmenopausal osteoporosis?

Answer

Yes. Yearly treatment prevents fractures and increases bone mineral density compared with a placebo.

Why did the authors do the study?

Oral bisphosphonates help prevent fractures in postmenopausal women, but they can be inconvenient to take and many women stop their treatment. These authors wanted to test whether a more convenient yearly infusion of intravenous zoledronic acid would also reduce the risk of fractures.

What did they do?

7765 postmenopausal women with osteoporosis took part in a randomised, double blind trial, sponsored by the manufacturers of zoledronic acid. Participants were given three infusions of zoledronic acid (5 mg) or a placebo at yearly intervals. They were followed up for 12 months after their last infusion. The authors looked for vertebral fractures in yearly spinal radiographs. Other fractures, including hip, were reported by participants and confirmed by radiographs. The authors monitored participants’ bone mineral density using dual energy x ray absorptiometry and used serum markers to monitor bone turnover. An adjudication committee reviewed serious adverse events. The authors compared treatment and placebo groups using intention to treat analysis, but confined their analysis of vertebral fractures to women not taking any other treatments for osteoporosis at baseline.

What did they find?

3.3% (92/2822) of the women given zoledronic acid had a vertebral fracture, a reduction of 70% compared with the 10.9% (310/2853) of those given placebo (relative risk 0.30 (95% CI 0.24 to 0.38)). Zoledronic acid also significantly reduced the risk of hip fracture (1.4% v 2.5%, hazard ratio 0.59 (0.42 to 0.83)), all non-vertebral fractures, all clinical fractures, and clinical vertebral fractures. It also significantly increased women’s bone mineral density at the hip, lumbar spine, and femoral neck compared with placebo (by 6%, 6.7%, and 5.1%) and reduced bone turnover.

Infusion of zoledronic acid was associated with a higher incidence of fever, myalgia, flu-like symptoms, headache, and arthralgia. It was also associated with a higher risk of serious atrial fibrillation (5% v 1.3%, $P<0.001$), but no long term renal toxicity. One woman in each group developed osteonecrosis of the jaw, a rare side effect of intravenous bisphosphonates given in high doses to patients with cancer.

What does it mean?

A single yearly infusion of 5 mg zoledronic acid helped prevent important osteoporotic fractures in this vulnerable population of postmenopausal women. It seems reasonably safe, although the excess of atrial fibrillation is a worry and needs further investigation. Some women might find a yearly infusion easier and more convenient than regular oral drugs, and it’s possible the two routes are equally effective. But we won’t know for certain until researchers do a large, head to head trial.

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