Other trials: unconvincing results

A Cochrane collaboration review group examined trials published up to November 2002 that evaluated the use of oestrogen for urinary incontinence (8).

A placebo-controlled trial of an oestrogen-progestin combination showed no efficacy (8).

Fifteen trials compared oral oestrogen (without a progestin) with placebo in a total of 216 women with stress incontinence; 43% of women on oestrogen judged themselves to be cured or improved, compared with 27% of women on placebo (significant difference) (8).

Two trials compared local oestrogen therapy with oral oestrogen therapy (in 20 women) and with an oral oestrogen-progestin combination (40 women), but these studies were too small to draw firm conclusions (8).

More recently, a randomised double-blind trial involving 40 women using either an oestrogen implant or placebo showed no difference after 6 months of therapy (9).

In practice

The belief that hormone replacement therapy has a positive impact on female urinary incontinence has persisted for many years (10). But the WHI and HERS trials have clearly shown that hormone replacement therapy offers no protection against urinary incontinence after the menopause. There is no other body of clinical trial evidence that challenges these results. On the contrary, urinary incontinence appears to be an adverse effect of oestrogen-progestin-based hormone replacement therapy.

Selected references from Prescrire's literature search.

1- Prescrire Editorial Staff "Postmenopausal hormone therapy: cardiovascular risks" *Prescrire Int* 2003; **12** (64): 65-69.

2- Prescrire Rédaction "Ménopause: arrêt de l'essai WHI estrogène versus placebo" *Rev Prescrire* 2004; **24** (249): 273.

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4- Hendrix SL et al. "Effects of oestrogen with and without progestin on urinary incontinence" *JAMA* 2005; **293** (8): 935-948.

5- Grady D et al. "Postmenopausal hormones and incontinence: the Heart and Estrogen/progestin replacement study" *Obstet Gynecol* 2001; **97**: 116-120.

6- Prescrire Rédaction "Traitement hormonal de la ménopause et risque cardiovasculaire" *Rev Prescrire* 1999; **19** (191): 57-58.

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9- Rufford J et al. "A double-blind placebo-controlled trial on the effects of 25 mg estradiol implants on the urge syndrome in postmenopausal women" *Int Urogynecol J Pelvic Floor Dysfunct* 2003; **14** (2): 78-83.

10- Dubeau CE "Estrogen treatment for urinary incontinence. Never, now, or in the future?" *JAMA* 2005; **293** (8): 998-1001.

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METHYLPHENIDATE: CARDIAC RISKS

Methylphenidate is an amphetamine psychostimulant marketed in France for attention deficit-hyperactivity disorders in children over 6 years of age. It is known to increase both blood pressure and heart rate (1-3).

In February 2006 an *ad hoc* FDA committee examined 160 reports of deaths of patients taking methylphenidate in the US pharmacovigilance database (3). There were 8 sudden deaths (occurring immediately or within 24 hours after collapse), reported between January 1999 and December 2003, involving patients not exposed to other potentially hazardous substances (4). The victims were a 42-year old woman and 7 children aged 9 to 14 who had been treated with methylphenidate for 2 months to 10 years. Three children had a history of cardiovascular disorders (congenital cardiopathy, dilated cardiomyopathy, syncope).

Ten sudden deaths in patients taking methylphenidate, including 7 children, were reported before 1999. Cardiac abnormalities were found in 2 of these patients at autopsy (5). No new cases were reported between January 2004 and February 2005. Eight severe but non fatal cardiovascular events were reported between 1999 and 2003 in children with an average age of 11.5: 1 stroke, 1 syncope, and 6 cases of cardiac arrhythmias. Another 11 reports involved adults.

This risk of life-threatening cardiac effects is a further reason to reserve prescribing of methylphenidate to the specific subset of patients who really need it.

1- "Methylphenidate hydrochloride". In: "Martindale The complete drug reference" 34th ed, The Pharmaceutical Press, London 2005: 1590-1591.

2- Prescrire Editorial Staff "Methylphenidate" *Prescrire Int* 2004; **13** (74): 203-206.

3- U.S. Food and Drug Administration "Drug safety and risk management advisory committee Volume I transcript Thursday February 9, 2006" 9 February 2006. Website http://www.fda.gov accessed 10 March 2006.

4- U.S. Food and Drug Administration "Memorandum: Review of AERS data for marketed safety experience during stimulant therapy: death, sudden death, cardiovascular SAEs (including stroke)" 27 April 2004. Website http://www.fda.gov accessed 10 March 2006.

5- U.S. Food and Drug Administration "Safety review: follow up review of AERS search identifying cases of sudden death occurring with drug used for the treatment of attention deficit hyperactivity disorder (ADHD)" 28 February 2006. Website http://www.fda.gov accessed 27 March 2006.

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FREE ACCESS TO PHARMACOVIGILANCE DATA

Two national pharmacovigilance agencies have decided to make part of the adverse drug reaction reports they receive freely accessible on the Internet.

The UK regulatory agency (www.mhra.gov.uk) has posted reports received up to June 2005, in alphabetical order of the international non proprietary names (INN) of the drugs involved (1).

The Dutch Lareb centre provides access to reports, also in INN alphabetical order, at www.lareb.nl, in both English and Dutch (2).

The reports can be searched by key words denoting adverse effects (classified by organ or organ group) and lists of adverse effects can be downloaded. It is crucial to bear in mind that these are reports of suspected adverse effects, and that attribution to the drugs is not proven. No data on population exposure to each drug are included. It is therefore impossible to estimate the frequency of adverse effects.

Despite these limitations, online publication of these reports is a welcome sign of transparency and should be encouraged. The French Agency should follow suit.

1- "Drug analysis prints: data on suspected adverse drug reactions". Website www.mhra.gov.uk accessed 24 February 2004.

2- "Search adverse drug database" Website www.lareb.nl accessed 24 February 2004.