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More about the birds! Avian influenza was discussed in the September *Therapeutics Today* newsletter (TT 2005; No 9 www.nmic.ie). Since then, the Health Protection Surveillance Centre (HPSC) has provided a further update via its November EPI-Insight bulletin (www.hpsc.ie). Avian influenza viruses are highly species-specific and rarely cross the species barrier to infect humans. There are 2 main types – low pathogenic forms which cause mild symptoms in poultry (such as a drop in egg production) and highly pathogenic forms which are highly infectious and rapidly fatal in poultry (up to 100% mortality, often within 48 hours). The current outbreaks of avian influenza involving the highly pathogenic H5N1 strain started in South East Asia in 2003 and have affected many countries in the area since then, as well as Turkey and Romania in recent weeks. Although the mechanism is not fully understood, it is likely that migratory birds are involved in directly spreading the H5N1 virus. To date, 121 cases of human infection with this H5N1 strain (62 deaths) have been reported.

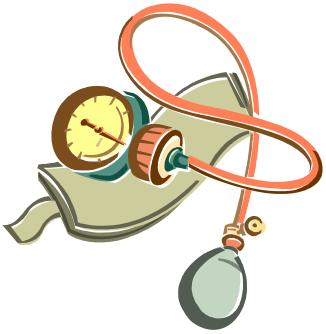
An **influenza pandemic** with any influenza virus requires 1) the emergence of a new virus subtype, 2) the ability to infect humans, causing serious illness and 3) ability to spread easily and sustainably among humans. To date, there has been no evidence that this new avian strain has developed the ability to transmit easily from person to person. Nevertheless, the WHO has published recommended strategic actions for responding to the avian influenza pandemic threat (www.who.int/csr/resources/publications/influenza). The HPSC has prepared a series of guidelines for Ireland, which cover, among others, protection of persons involved in avian influenza control and eradication, advice for travellers going to and returning from affected areas (including an algorithm for the management of returning travellers with febrile respiratory illness) and guidance on reporting and investigation of suspected cases of avian influenza. All of these are available at: www.hpsc.ie/A-Z/Respiratory/AvianInfluenza/Guidance [Editor's note: Readers will find further sources of information on avian influenza at www.le.ac.uk/li/khn5/birdflu.html; BMJ 2005; 331: 1066-9].

Long acting reversible contraception and bone mineral density Progestogen-only injectable contraception is an alternative method of effective contraception for those women in whom oestrogen is contraindicated. However, concern has been expressed about the potential effects of progestogen-only injectable contraceptives on bone mineral density (BMD) particularly in adolescents and older women (NMIC bulletin "Update on hormonal contraception" 2005: Vol 11: 2 www.nmic.ie). The National Institute for Clinical Excellence (NICE) recently issued a guideline on the effective and appropriate use of all long-acting contraception (www.nice.org.uk). The report noted that the studies available for the evaluation of the effects of depot medroxyprogesterone acetate (DMPA) on BMD were heterogeneous and produced conflicting evidence about the potential effects of DMPA on BMD. The report's recommendations are similar to the previously issued advice from the IMB/MHRA on the use of DMPA and include the following:

a) women should be informed that DMPA is associated with a small loss of BMD, which is recovered when DMPA is discontinued
b) there is no evidence that DMPA use increases the risk of fracture
c) women who wish to use DMPA for > 2 years should be re-evaluated
d) care should be taken in recommending DMPA to adolescents; however it may be used once other methods are considered unsuitable or unacceptable
e) care should be taken when recommending DMPA to women over 40 years; however in general, the benefits of DMPA outweigh the risks in this age group and it may be given if other methods are unsuitable or not acceptable.

The NICE review concludes that further research is required in this area.

Information on another long-acting progestogen-only contraceptive (subdermal implant etonogestrel - Implanon®) has shown no evidence of a similar effect on BMD to date.



Amlodipine + perindopril a good bet for hypertension? Hypertension is a major cause of premature death in developed countries. Recent publications have suggested that newer antihypertensive agents might offer more protection from coronary heart disease (CHD) over diuretics and ß blockers. The **ASCOT-BPLA** study was a randomised controlled trial undertaken in hypertensive patients, aged 40-79 years who had either untreated hypertension (approximately 160/100 mmHg) or treated hypertension (approximately 140/90 mmHg) and with at least 3 defined cardiovascular (CVS) risk factors ***(Lancet 2005; 366: 895-906)***. Patients were randomised to receive either amlodipine 5-10mg plus perindopril 4-8mg as required (n=9639) or atenolol 50-100mg plus bendroflumethiazide 1.25-2.5mg as required (n=9618). The study was discontinued prematurely after a median of 5.5 years' treatment. By the end of the trial period, 78% were taking combination therapy, 15% amlodipine alone and 9% atenolol alone. Results showed that overall blood pressure (BP) control was better for the amlodipine regimen compared with the atenolol regimen (average reductions from baseline of 27.5/17.7 mmHg vs. 25.7/15.6 mmHg). Fewer patients in the amlodipine group had an episode of AMI or fatal CHD compared with the atenolol group (429 vs. 474 episodes), but the differences did not reach statistical significance. Secondary outcome results were more favourable for the amlodipine group, including fatal and non-fatal stroke (327 vs. 422 p=0.0003), total CVS events and procedures (1362 vs. 1602 p<0.0001) and all cause mortality (738 vs. 820 p=0.025). The authors suggest that the use of amlodipine (a calcium-channel blocker) with perindopril (an ACE inhibitor) added in as required, is effective in lowering BP and may be more effective in preventing most major CVS events associated with hypertension as compared with the commonly used ß blocker and diuretic combination.

What does this mean for the use of atenolol / ß blockers in the management of hypertension? Two recent meta-analyses have also reviewed the effect of (1) atenolol and (2) ß blockers in general on CVS morbidity or mortality in patients with primary hypertension ***(Lancet 2004; 364: 1684-9; Lancet 2005; 366: 1545-155)***. Based on the results from these analyses the authors also suggest that ß blockers (and atenolol in particular) may have a less than optimum cardiovascular effect compared with other BP regimens.

Are there limitations to the data? In the ASCOT study, the two treatment groups achieved different reductions in blood pressure, which could have had an impact on the clinical outcomes reported. The trials in the meta-analyses were run over two decades, during which time patient profiles and management of BP may have changed. Furthermore, when doing the comparisons, the authors were not able to correlate each clinical outcome to the dosing regimens used or to the level of BP control, which could have had an impact on the results.

What happens now? The British Hypertension Society and the National Institute for Clinical Excellence (www.nice.org.uk) are currently reviewing their hypertension guidelines as a result of the recent trial findings and the NMIC will keep prescribers informed of any changes made to current guidance on the use of atenolol and /or ß blockers in the management of hypertension.

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. References are available on request. This newsletter is produced by the National Medicines Information Centre and the Trinity College Department of Therapeutics, Trinity Centre, St. James's Hospital, Dublin 8. Tel:Direct Line (01) 473 0589 or 1850 727 727 Fax: (01) 473 0596 Email: nmic@stjames.ie