Urology

Prostate specific alpha blockers increase risk of falls

The newer prostate-specific alpha blockers produce a small but significant increase in the risk of falls in older men with lower urinary tract symptoms (LUTS), a study from Canada has shown.

The investigators looked at the incidence of falls and fractures in men commencing tamsulosin, alfuzosin or silodosin for LUTS, using community datasets, in a matched cohort study.

The alpha blocker cohort consisted of 147,084 men aged 66 years and over, starting a selective alpha blocker (84% tamsulosin). An equal cohort of matched men, not taking alpha blockers was created on a 1:1 basis.

The primary outcome measures were falls and fractures 90 days after initiation of therapy. Secondary outcomes were major osteoporotic fractures, hip fractures, hypotension and head trauma.

Risk of falling was higher in men taking alpha blockers compared with the unexposed cohort:

- Odds ratio (OR) 1.14 (95% CI: 1.07-1.21)
- Absolute increased risk 0.17%

Likewise, risk of fractures was increased:

- OR 1.16 (95% CI: 1.04-1.29)
- Absolute increased risk 0.06%

The two outcomes appeared to be inter-related as 80% of those who sustained a fracture also had a fall.

Secondary outcomes were also significantly increased in the alpha blocker group:

- Hypotension OR 1.80 (95% CI: 1.59-2.03)
- Head trauma OR 1.15 (95% CI: 1.04-1.27)

The authors conclude that alpha blockers are associated with a »

*In the 52-week trials, SPIOLTO® administered once daily in the morning provided clear improvement in lung function within 5 minutes after the first dose compared to tiotropium 5 µg (mean increase in FEV_1 of 0.137 L for SPIOLTO® vs. 0.058 L for tiotropium 5 µg [p<0.0001]).[1] †SPIOLTO® resulted in statistically significant improvements in SGRQ total scores and responder rates vs. both monotherapies (p<0.05) after 24 weeks. Response defined as a ≥4 change in SGRQ score. Pooled analysis of the pivotal phase III TONADO™ 1 and 2 studies.[1] ‡After 24 weeks, SPIOLTO® Respimat® significantly improved mean TDI focal score compared to tiotropium 5 µg. More patients treated with SPIOLTO® Respimat® had a clinically meaningful improvement in TDI focal score (MCID, defined as a value of at least 1 unit) compared to tiotropium 5 µg (54.9% vs. 50.6%, p=0.0546).[1]

References:

1. SPIOLTO® Respimat® Summary of Product Characteristics. **2.** Beeh K-M *et al. Pulm Pharmacol Ther* 2015;32:53–59. **3.** Buhl R *et al. Eur Resp J* 2015;45:969–979. **4.** Boehringer Ingelheim. Data on file TOL15 02(c). **5.** Spiriva® Respimat® Summary of Product Characteristics. **6.** Spiriva® HandiHaler® Summary of Product Characteristics. **7.** Dalby R, Spallek M, Voshaar T. *Int J Pharm* 2004;283:1–9. **8.** Pitcairn G *et al. J Aerosol Med* 2005;18:264–272. **9.** Hochrainer D *et al. J Aerosol Med* 2005;18:273–282.

SPIOLTO® RESPIMAT® (tiotropium/olodaterol)
Inhalation solution containing 2.5 microgram tiotropium (as bromide monohydrate) and 2.5 microgram olodaterol (as hydrochloride) per puff. **Action:** Inhalation solution containing a long acting muscarinic receptor antagonist, tiotropium, and a long acting beta2-adrenergic agonist, olodaterol. **Indication:** Maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). **Dose and Administration:** Adults only aged 18 years or over: 5 microgram tiotropium and 5 microgram of olodaterol given as two puffs from the Respimat inhaler once daily, at the same time of the day. **Contraindications:** Hypersensitivity to tiotropium or olodaterol or any of the excipients; benzalkonium chloride, disodium edetate, purified water, 1M hydrochloric acid (for pH adjustment); atropine or its derivatives e.g. ipratropium or oxitropium. **Warnings and Precautions:** Not for use in asthma or for the treatment of acute episodes of bronchospasm, i.e. as rescue therapy. Inhaled medicines may cause inhalation-induced paradoxical bronchospasm. Caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction. Patients should be cautioned to avoid getting the spray into their eyes. They should be advised that this may result in precipitation or worsening of narrow-angle glaucoma, eye pain or discomfort, temporary blurring of vision, visual halos or coloured images in association with red eyes from conjunctival congestion and corneal oedema. Should any combination of these eye symptoms develop, patients should stop using Spiolto Respimat and consult a specialist immediately. In patients with moderate to severe renal impairment (creatinine clearance ≤ 50ml/min) use only if the expected benefit outweighs the potential risk. Caution in patients with a history of myocardial infarction during the previous year, unstable or life-threatening cardiac arrhythmia, hospitalised for heart failure during the previous year or with a diagnosis of paroxysmal tachycardia (> 100 beats per minute) as these patients were excluded from the clinical trials. In some patients, like other beta-adrenergic agonists, olodaterol may produce a clinically significant cardiovascular effect as measured by increases in pulse rate, blood pressure and/or symptoms. Caution in patients with: cardiovascular disorders, especially ischaemic heart disease, severe cardiac decompensation, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy, hypertension, and aneurysm; convulsive disorders or thyrotoxicosis; known or suspected prolongation of the QT interval (e.g. QT>0.44 s); patients unusually responsive to sympathomimetic amines; in some patients beta2-agonists may produce significant hypokalaemia; increases in plasma glucose after inhalation of high doses. Caution in planned operations with halogenated hydrocarbon anaesthetics due to increased susceptibility of adverse cardiac effects. Should not be used in conjunction with any other long-acting $beta_2$-adrenergic agonists. Immediate hypersensitivity reactions may occur after administration. Should not be used more frequently than once daily. **Interactions:** Although no formal drug interaction studies have been performed, inhaled Spiolto Respimat has been used concomitantly with other COPD medicinal products, including short acting sympathomimetic bronchodilators and inhaled corticosteroids without clinical evidence of drug interactions. The co-administration of the component tiotropium with other anticholinergic containing drugs has not been studied and therefore is not recommended. Concomitant administration of other adrenergic agents (alone or as part of combination therapy) may potentiate the undesirable effects of Spiolto Respimat. Concomitant treatment with xanthine derivatives, steroids, or non-potassium sparing diuretics may potentiate any hypokalaemic effect of adrenergic agonists. Beta-adrenergic blockers may weaken or antagonise the effect of olodaterol. Cardioselective beta-blockers could be considered, although they should be administered with caution. MAO inhibitors, tricyclic antidepressants or other drugs known to prolong the QTc interval may potentiate the action of Spiolto Respimat on the cardiovascular system. **Fertility, pregnancy and lactation:** There is a very limited amount of data from the use of tiotropium in pregnant women. For olodaterol no clinical data on exposed pregnancies are available. As a precautionary measure, avoid the use of Spiolto Respimat during pregnancy. Like other $beta_2$-adrenergic agonists, olodaterol may inhibit labour due to a relaxant effect on uterine smooth muscle. It is not known whether tiotropium and/or olodaterol pass into human breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Spiolto Respimat should be made taking into account the benefit of breast-feeding to the child and the benefit of therapy for the woman. Clinical data on fertility are not available for tiotropium or olodaterol or the combination of both components. **Effects on ability to drive and use machines:** No studies have been performed. The occurrence of dizziness or blurred vision may influence the ability to drive and use machinery. **Undesirable effects:** Common (≥ 1/100 to < 1/10): Dry mouth. Uncommon (≥ 1/1,000 to <1/100): Dizziness, insomnia, headache, atrial fibrillation, palpitations, tachycardia, hypertension, cough, constipation. Serious undesirable effects include anaphylactic reaction and consistent with anticholinergic effects: glaucoma, constipation, intestinal obstruction including ileus paralytic and urinary retention. An increase in anticholinergic effects may occur with increasing age. The occurrence of undesirable effects related to beta-adrenergic agonist class should be taken into consideration such as, arrhythmia, myocardial ischaemia, angina pectoris, hypotension, tremor, nervousness, muscle spasms, fatigue, malaise, hypokalaemia, hyperglycaemia and metabolic acidosis. Prescribers should consult the Summary of Product Characteristics for further information on side effects. **Pack sizes and NHS price:** Single pack: 1 Respimat inhaler and 1 cartridge providing 60 puffs (30 medicinal doses) £32.50 **Legal category:** POM **MA numbers:** PL 14598/0101 **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, D-55216 Ingelheim am Rhein, Germany. Prescribers should consult the Summary of Product Characteristics for full prescribing information. **Prepared in** June 2015

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard Adverse events should also be reported to Boehringer Ingelheim Drug Safety on 0800 328 1627 (freephone). (UK only)

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small but significant increase in the risk of falls and an increase in the risk of fractures of 16% in the first 90 days of use.

This could seem alarming, but it is important to remember that this is a large study, powered to detect statistically significant differences at a small effect size. The absolute increased risk of falls and fractures is small, and the number needed to harm in the 90 days after initiation of a selective alpha blocker is 588 for falls, and 1,666 for fracture.

Thus, it is important to counsel men that if they experience postural symptoms on an alpha blocker they should have a discussion with the prescribing doctor about reviewing the risk:benefit ratio.

However, we should not overplay the risk of prescribing these medications which for many men with LUTS can transform their quality of life.

DR JONATHAN REES

● **Welk B, McArthur E, Fraser L-A et al. The risk of fall and fracture with the initiation of a prostate-selective alpha antagonist: a population based cohort study. *BMJ* 2015;351:h5398**

Obstetrics and gynaecology

PCOS mothers with twin pregnancies at high risk of preterm birth

In twin pregnancy women with a history of polycystic ovarian syndrome (PCOS) are a high-risk group for preterm birth.

Using the comprehensive Swedish medical birth and national patient registers almost 1.5 million births over a 15-year period, between 1995 and 2009, were identified. Of these, 20,965 were twin births of which 223 (1.1%) were to women who had a diagnosis of PCOS.

Women with PCOS were more likely to have a higher early pregnancy BMI ($P < 0.0001$) and to have used assisted reproductive technology to conceive 31.4% vs 15.0% ($P < 0.001$). They were also on average older ($P = 0.2$) and more likely to be non-smokers ($P = 0.03$).

As can be seen in table 1, below, women with PCOS were more likely to have a preterm birth, adjusted risk ratio (RR) 1.16 (95% CI: 0.99-1.35) particularly a very preterm birth, adjusted RR 1.51 (95% CI: 0.99-2.3), compared with women without PCOS, a significant proportion of which followed spontaneous preterm delivery.

Caesarean section rates did not differ between the groups although birthweight for babies to PCOS women was on average lower. After controlling for preterm delivery this difference disappeared.

There were no significant differences between the groups in pre-eclampsia, low Apgar scores or perinatal mortality.

This study has shown that in twin pregnancy women with a history of PCOS are a high-risk group for preterm birth.

Even after controlling for confounding variables the authors considered that a 'PCOS factor' remained. This may be due to hyperandrogenism, disturbed glucose/insulin metabolism and an inflammatory state: all more commonly seen in women with PCOS. Indeed PCOS is considered by some to be the ovarian manifestation of the metabolic syndrome.

The population incidence of PCOS is estimated to be 5-15%. Because so few women in this study were identified with PCOS (1.1%) the findings presented here may well have underestimated the 'PCOS factor'.

DR CHRIS BARCLAY

● **Løvvik TS, Wikström A-K, Neovius M. Pregnancy and perinatal outcomes in women with polycystic ovary syndrome and twin births: a population-based cohort study. *BJOG* 2015;122:1295-1302**

Table 1

Outcomes in women with and without PCOS giving birth to twins

	PCOS women (%)	Non-PCOS women (%)	*Adjusted risk ratio (95% CI)	P
Preterm birth (< 37 weeks)	51.3	42.8	1.16 (0.99-1.35)	0.054
Very preterm birth (< 32 weeks)	14.4	7.9	1.51 (0.99-2.3)	0.054
Moderately preterm birth (32-36+6 weeks)	43.1	38.0	1.13 (0.94-1.36)	0.18
Iatrogenic preterm birth (< 37 weeks)	14.4	15.0	1.04 (0.73-1.49)	0.82
Spontaneous preterm birth (< 37 weeks)	36.9	27.8	1.27 (1.05-1.53)	0.015

* Adjusted for maternal age, parity, education, smoking, year of delivery and BMI