Dopaminergics & Cardiac Valvulopathy: Where Next?

Robert D Murray
Consultant Endocrinologist & Honorary Senior Lecturer
Leeds Teaching Hospitals NHS Trust
Leeds, UK

A.

Dopaminergic agonists are the mainstay of therapy of both tumoral and non-tumoral hyperprolactinaemia.

Dopaminergics in Endocrinology.

Usage – Control of hyperprolactinaemia

Regression of tumour volume in prolactinomas

Control of GH hypersecretion

Low doses & limited duration of use in many individuals

Cabergoline & BC: D2R-specific ergot-derived dopamine agonist

Quinagolide: D2R-specific, non-ergot

Side-effect profile low with cabergoline

Case reports of valvular heart disease with BC (x1), cabergoline, and pergolide used in treatment of Parkinson's dis (2000 onwards)

B.

The start of the story……..

Potent agonists of the 5-hydroxytryptamine 2B ($5\text{-}HT_{2B}$) receptor subtype are associated with cardiac valvopathies.

Rothman R et al 2000, Circulation, 102; 2836.

Serotonergic drugs 'Fenfluramines', Ergotamine, & Methysergide associated with valvular heart disease (VHD).

5HT mitogenic

Safety of other serotonergic drugs?

Drugs associated with VHD vs. drugs not associated with VHD

Serotonin subtype receptor ligand binding & functional assays

Fenfluramine
Ergotamine
Methysergide

} All partial / full agonists at $5HT_{2B}$-R & $5HT_{2C}$-R

The $5HT_{2B}$ Receptor

(1) Located on mitral & aortic valves

(2) Mediates mitogenesis

(3) Norfenfluramines have high affinity & efficacy

(4) Ergotamine and methylergonovine, high affinity partial agonists

(5) Negative control drugs (fluoxetine etc) low affinity & lack of agonist activity

'All clinically available medications with serotonergic activity should be screened for activity at the $5HT_{2B}$ receptor'

Setola V et al 2003, Mol Pharmacol, 63; 1223.

Pergolide (Parkinson's dis)
Dihydroergotamine (Migraine)
MDMA (Ecstacy)

} Agonists at $5HT_{2B}$ receptor

Jahnichen S et al 2005, Eur J Pharmacol, 513; 225.

Pergolide
Cabergoline

} Potent full agonist $5HT_{2B}$ receptor

Bromocriptine — Partial agonist $5HT_{2B}$ receptor

Lisuride
Terguride

} Antagonist $5HT_{2B}$ receptor

C.

Cardiac valvulopathies are increased by ergot-derived dopaminergics use in treatment of Parkinson's disease.

Schade R et al 2007, NEJM, 356(1); 29-38.

Nested cohort study – UK GP research database

11, 417 pts: >2 prescriptions Parkinson's med, 40-80yrs

31 validated new cardiac valve regurgitation

Adjusted incidence ratio - pergolide x 7.1 (excess 33/10,000)

- cabergoline x 4.9 (excess 21/10,000)
- BC, ropinirole, pramipexole n/s

AIR with doses >3mg od - pergolide x 37.1

- cabergoline x 50.3

Valvulopathies – MR x 9, AR x 8, TR x 3

Zanettini R et al 2007, NEJM, 356(1); 39-46.

155 consecutive pt with Parkinson's disease

Rx only one type dopaminergic > 12mths

Echo screening (regurg: absent 0, tr 1, mild 2, mod 3, sev 4)

Hi'er prevalence Gr 2-4 regurg in pergolide & cabergoline grps

No increase with non-ergot dopaminergics

Clin signif regurg (Gr 3/4): 23.4% pergolide, 28.6% cabergoline,

5.6% controls, 0% non-ergots

Valvulopathies RR, Cabergoline: MR x 4.6, AR x 7.3, TR x 5.5

Linear relationship cumulative dose and valve regurg cumulative score (Gr 0-2 dose 2341mg, Gr 3/4 dose 4015mg)

D.

Regulatory body guidance suggests limitation of use of pergolide / cabergoline, and regular echocardiographic monitoring.

Food & Drug Administration.

FDA March 2007

> ‘Manufacturers of pergolide used to treat Parkinson’s disease, will voluntarily remove these drugs from the market because of the risk of serious damage to patients heart valves’

Medicines & Health Regulatory Agency.

MHRA 2007 - Cabergoline

Restriction of use of in Parkinson's disease (PD) to second line therapy (patients intolerant to or fail treatment with a non-ergot compound) as monotherapy, or as adjunctive treatment

Cabergoline to remain first line therapy for hyperprolactinaemia

Contraindicated in patients with a hx of pulmonary, pericardial,or retroperitoneal fibrotic disorders, or in those with anatomic evidence of cardiovalvulopathy.

Monitoring for development of valvular disease or fibrosis is recommended. Echocardiography within 3–6 months, and at least every 6–12 months thereafter

Pfizer, July 2007 - Dostinex.

Contraindicated in pts with a hx of fibrotic disorders / evidence of cardiac valvulopathy on pre-treatment echocardiography.

Mandatory echocardiography before treatment and regularly during treatment and clinical monitoring of other fibrotic events

Undesirable effects to include cardiac valvulopathy and related disorders (pericarditis and pericardial effusion) as ***very common side effects***

The recommended initial dose remains 0.5 mg per week in one or two doses / wk and titrated to prolactin levels. The therapeutic dose is usually 1 mg per week.

Pregnancy should be excluded before administration of Dostinex. Dostinex should be discontinued at least one month before intended conception.

E.

To date the limited data available are reassuring that cabergoline is not associated with a major increase in VHD, when used in treatment of endocrine conditions.

Cabergoline & Endocrinology.

Lower weekly doses than used in Parkinson's disease

Younger age at onset

Greater female preponderance

Potentially longer duration of therapy

Lancellotti P et al 2008, EJE, 159; 1-5.

102 pt Rx cabergoline >12 mths for hyperprolactinaemia

- Duration Rx 12-228 (median 79) mths
- Cumulative dose 18-1718 (median 204) mg

51 controls (age, sex, co-morbidiy matched)

2 pts mod MR

Valve regurg equally prevalent in each grp; no diff sPAP

No control with valve leaflet restriction

Localised (n=4), and diffuse (n=2) MV thickening; 5/6 mild MR

Mitral tenting area > in pts vs. controls

No relationships with cumulative dose

Wakil A et al 2008, EJE, 159; R11-R14.

44 pt Rx cabergoline >6 mths for hyperprolactinaemia

Duration Rx 44.8 (median 33) mths

Cumulative dose 311(median 86) mg

566 controls referred with palpitations from database

- No mod/sev valvular regurgitation in either grp
- No evidence of abnormal valve morphology in cabergoline grp
- Lt Hrt – OR mild MR 0.4 (P=0.5)

  OR mild AR 1.7 (P=0.2)
- Rt Hrt - OR mild TR 3.1 (P = 0.04)

  OR mild PR 7.8 (P < 0.0001)

Kars M et al 2008 JCEM; 93: 3348-3356.

78 pt Rx dopaminergics >12 mths for prolactinoma

47 cabergoline, 31 BC/quinagolide/terguride

Duration Rx 1-10.3 (mean 5.2) yrs

Cumulative dose 363 (24 - 1768) mg

78 controls referred for echo (palp, syncope, CP)

- Increase mild/mod/sev TR, 51% vs. 28% controls (p=0.01)
- Calcification of MV (38% vs. 21%, p=0.03)
- Calcification of AV (40% vs. 18%, p=0.003)
- TV thickening (6% vs. 0%, p=0.024)
- 8/9 pts with signif valve regurg were Rx with cabergoline

Coloa A et al 2008 JCEM; 93: 3777-3784.

50 pt Rx cabergoline >6 mths for prolactinoma

Duration Rx 74 mths

Cumulative dose 280mg (32 - 1938mg)

50 controls & 20 de-novo pts

- No difference in freq mild regurgitation
- Increase mod TR (Gr 3), 54% vs. 18% controls vs. 0% de novo
- Onset of TR ~10 yrs earlier in treated pts
- Greater prevalence of mod TR in those receiving higher doses
- No morphological valve alterations

Herring N et al 2009, Clin Endo, 70; 104-108.

50 pt Rx cabergoline >12 mths for prolactinoma

Duration Rx 6.6 (1 - 13) yrs

Cumulative dose 443 (52-1872) mg

50 controls referred with palpitations during same time period

- No mod/sev valvular regurgitation in either grp
- No evidence of valve thickening
- Mild regurg (Gr 2) in 8/50 Prl-oma and 13/50 controls
- MV tenting n/s diff to controls, and no α to cumulative dose

Vallette S et al 2009, Pituitary, (e-pub).
Bogazzi F et al 2008, Int J Clin Practice, 62; 1864

Further 178 pts

Duration of Rx; 51 & 67 mths resp

Cumulative dosage; 180 (25-1248)mg & 279 (15-1327)mg

No positive findings

Cabergoline & Hyperprolactinaemia Studies (1).

7 cross-sectional studies, 463 pts Rx 45-79 mths

Cumulative doses 180 – 443 mg

One study signif increase in mod TR; two studies mild TR

Cabergoline also assoc with increased freq

- Valve thickening
- Calcifications
- Increased mitral tenting area

No signif increase in clinically significant valve disease (Gr 3-4)

except Colao et al 54% Gr 3 TR

Cabergoline & Hyperprolactinaemia Studies (2).

Numbers of pts & controls remains small

Methodological differences (mod TR controls 0 to 18%)

Assuming 21 additional cases / 10,000 person yrs (Schade 2007) & ignoring dose effect

Current studies = 2300 person yrs

Warrants larger prospective study with longer follow-up

Ideally, studies of newer non-ergot dopaminergics (ropinirole) in hyperprolactinaemia

F.

Until data are available from long-term echocardiographic prospective studies, we will need to undertake regular screening of pts on cabergoline.

The Present.

Soc. For Endocrinology Statement….

In agreement with MHRA

Options

(1) Continue current therapy with cabergoline and perform annual echocardiograms.

(2) Try to wean cabergoline early (3yrs) in pts who may achieve remission

(3) Use quinagolide as an alternative dopaminergic agonist

Questions???

robert.murray@leedsth.nhs.uk