

Articles

⌚ Treatment of Parkinson's disease with pergolide and relation to restrictive valvular heart disease

Guy Van Camp, Anja Flamez, Bernard Cosyns, Caroline Weytjens, Luc Muyltermans, Michel Van Zandijcke, Johan De Sutter, Patrick Santens, Pierre Decoodt, Christian Moerman, Danny Schoors

Summary

Background Restrictive valvular heart disease has been reported in patients with Parkinson's disease treated with pergolide. However, few data are available on frequency, severity, dose dependency, and reversibility of pergolide-induced disease, nor on the pulmonary pressures of these patients. We aimed to clarify these characteristics in a large group of patients.

Methods 78 patients with Parkinson's disease treated with pergolide and 18 never treated with an ergot-derived dopamine agonist (controls) were evaluated by echocardiography. A valvular scoring system was used, ranging from 1 (proven ergot-like restrictive valvular heart disease) to 4 (no disease). For the mitral valve, tenting areas and tenting distances were measured. Systolic pulmonary artery pressures were derived from the tricuspid regurgitant jet.

Findings Restrictive valvular heart disease of any type was present in 26 (33%) patients in the pergolide group and none in controls ($p=0.0025$). Important disease (score 1 or 2) was present in 15 (19%) patients in the pergolide group and none in controls ($p=0.066$). Mean tenting distances and tenting areas of the mitral valve were 1.08 cm (range 0.55–2.66) and 2.39 cm² (0.88–4.59) in the restrictive mitral valve group versus 0.63 cm (0.22–1.20) and 1.39 cm² (0.39–3.23) in the non-restrictive group ($p=0.003$ and $p<0.0001$, respectively). Significant correlation was noted between cumulative doses of pergolide and tenting areas of the mitral valves ($r=0.412$, $p=0.017$). Mean systolic pulmonary artery pressures were 39.3 mm Hg (range 25–71) in the high-dose group versus 38.5 mm Hg (20–65) in the low-dose group ($p=0.76$) and 31 mm Hg (25–40) in controls ($p=0.02$ vs all patients given pergolide). In six patients, pergolide treatment was stopped because of restrictive valvular heart disease, in two of whom regression of disease was shown.

Interpretation Restrictive valvular heart disease is not a rare finding in patients treated with pergolide. Clinicians should consider changing to a non-ergot drug if this disease is diagnosed.

Lancet 2004; **363**: 1179–83

Department of Cardiology (G Van Camp MD, B Cosyns MD, C Weytjens MD, D Schoors MD) and **Neurology** (A Flamez MD), **AZ VUB, Brussels, Belgium; Department of Cardiology** (L Muyltermans MD) and **Neurology** (M Van Zandijcke MD), **AZ St Jan, Brugge, Belgium; Department of Cardiology** (J De Sutter MD) and **Neurology** (P Santens MD), **UZ Gent, Gent, Belgium; and Department of Cardiology** (P Decoodt MD) and **Neurology** (C Moerman MD), **CHU Brugmann, Brussels, Belgium**

Correspondence to: Dr G Van Camp, Department of Cardiology, Free University Brussels (AZ VUB), Laarbeeklaan 101, 1090 Brussels, Belgium (e-mail: guy.vancamp@az.vub.ac.be)

Introduction

Pergolide—an ergot-derived dopamine receptor agonist used to treat Parkinson's disease and restless legs syndrome—has been associated with retroperitoneal, pleural, and pericardial fibrosis;^{1–4} drug-induced restrictive valvular heart disease has also been described.^{5–8} Histological analysis has shown findings similar to those seen in carcinoid syndrome or related to use of ergot-derivatives (eg, methysergide, ergotamine) or anorectic drugs (eg, fenfluramine, dexfenfluramine).^{5,8} A serotonin 5-HT_{2B} receptor has been detected that could account for the common pathway through which these drugs induce fibrotic valvular heart disease.^{9–11} In view of this evidence, there can be little doubt of the potential role of pergolide in induction of restrictive valvular heart disease.

The initial estimate of the frequency of valvular heart disease in patients taking pergolide was very low (one in 20 000),¹² although researchers later suggested a higher value.^{5–8} However, few data are available on the exact frequency, severity, possible dose dependency, and reversibility of pergolide-induced restrictive valvular heart disease, nor on the pulmonary pressures of patients taking this drug. We aimed to clarify these characteristics in a large group of patients and to identify ergot-like induced valvular diseases.

Patients and methods

Patients

From December, 2002, to January, 2004, we asked all patients with Parkinson's disease who presented at the neurology ambulatory department of four hospitals (AZ St Jan, Brugge; AZ VUB and CHU Brugmann, Brussels; and UZ Gent, Gent) to participate in our study. We excluded those with a history of coronary heart disease or valvular heart disease (rheumatic heart disease or other) or who had used Chinese herbs, anorectic drugs, or other ergot-derived drugs. Four patients in the pergolide group took—for a very short period (weeks)—low doses of bromocriptine before actual study inclusion (1, 3, 5, and 12 years). They were not excluded since the role of bromocriptine in inducing restrictive valvular heart disease in these patients was very unlikely.

The study was approved by the ethics committee of AZ VUB. Written informed consent was not deemed necessary by the ethics committee since patients only underwent echocardiography. Oral informed consent was received for every patient after complete explanation about the goal of the study.

Procedures

We divided patients into those treated with pergolide as the only ergot-derived drug and those never treated with an ergot-derived dopamine agonist. We defined high-dose pergolide as 5 mg or more daily and low-dose as less than 5 mg per day. When the neurologist and cardiologist agreed to stop pergolide in patients with restrictive valvular heart disease, these individuals were re-evaluated after

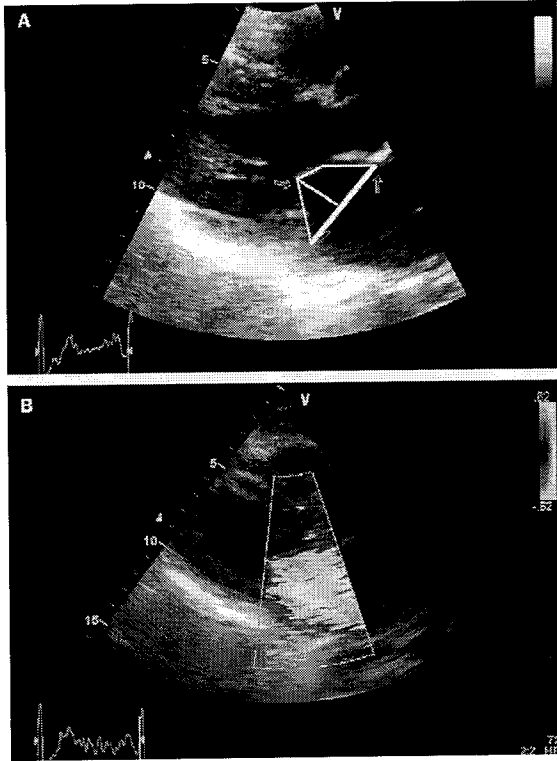


Figure 1: Restrictive mitral valve with tenting
 (A) Transthoracic echocardiography parasternal long axis view. Green arrows indicate markers to define tenting area and distance, tracing the contours of the anterior and posterior leaflet at end-systole and using the annular plane. (B) Corresponding mitral regurgitant jet with colour doppler.

6 months. The decision to stop pergolide was based on the favourable effects of the drug on Parkinson's disease symptoms, the possibility to switch to another treatment, and severity of restrictive valvular heart disease.

All patients underwent a complete transthoracic echocardiographic examination, with special attention towards valvular status, which was done by the same sonographer in every centre with the same GE VIVID 7 machine (GE Medical Systems, Milwaukee, WI, USA). Mitral, aortic, and tricuspid valves were recorded from all possible views with the zoom function. We recorded all semiquantitative and quantitative measurements for quantification of regurgitant valvular diseases from the continuous wave, pulsed wave, and colour doppler examinations. We saved examinations digitally in one centre (AZ VUB) and on videotape in the others. One independent sonographer (BC)—who was masked to patient's treatment—read all examinations.

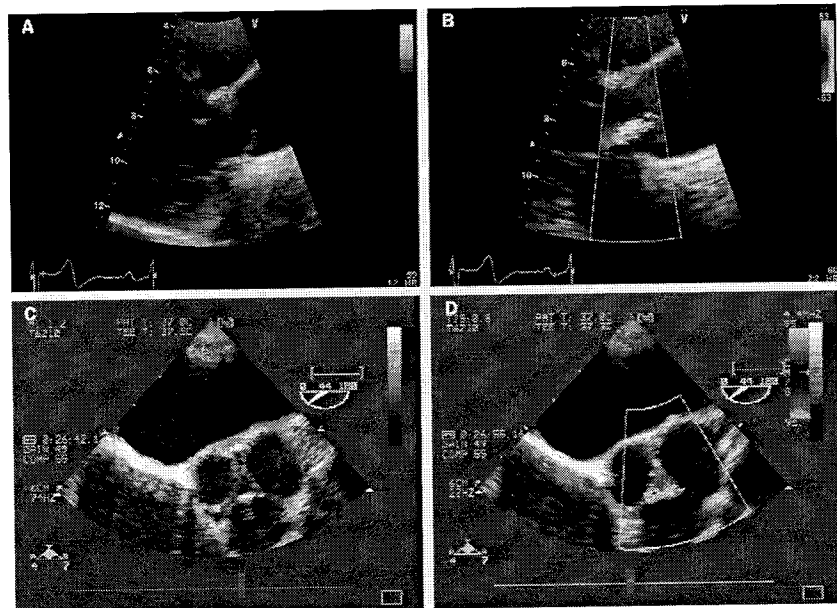


Figure 2: Typical systolic doming of thickened aortic non coronary cusp and incomplete coaptation of three leaflets at end-diastole
 (A) Transthoracic echocardiography parasternal long axis view. (B) Corresponding aortic regurgitant jet with colour doppler. (C) Transoesophageal echocardiography transverse view at the level of the aortic valve. (D) Corresponding aortic regurgitant jet with colour doppler.

We deemed non-pergolide induced valvular diseases to be calcified valves, regurgitant valvular diseases associated with annular dilatation or excessive leaflet motion, and mitral regurgitant jets in patients with left ventricular wall motion abnormalities or left ventricular dilatation. Mitral and tricuspid valves were regarded as restrictive if leaflets were stiffer than normal and if retraction of leaflets or subvalvular apparatus towards the apex existed (figure 1). For the mitral valve, we measured tenting distance and tenting areas (from digitally recorded studies only) and used this information as quantitative data for apical displacement of the leaflet coaptation, just as it is used in mitral regurgitation in ischaemic heart disease (figure 1).¹³ We judged aortic valves restrictive when the valve opened or closed with evident doming of leaflets (figure 2). We quantified regurgitant lesions by integration of all semiquantitative and quantitative measurements, and a final score was given from 1/4 to 4/4.

For restrictive valvular heart disease, we used a valvular scoring system from one to four, giving restrictive tricuspid valve motion more power for defining ergot-like abnormalities compared with mitral and aortic restrictive function: 1, proven restrictive valvular heart disease (pathology, regression after interruption of pergolide treatment, or both); 2, important valvular disease (regurgitant jet $\geq 2/4$) suggestive for restrictive valvular heart disease or restrictive tricuspid disease even if less than 2/4; 3, mild to moderate (regurgitant jet $< 2/4$) restrictive valvular disease; and 4, no restrictive valvular dysfunction.

We derived systolic pulmonary artery pressures from the tricuspid regurgitant jet, adding 10 mm Hg to the maximum gradient of the tricuspid regurgitant jet or 5 mm Hg if the vena cava inferior diameter was less than 10 mm with complete respiratory collapse and 15 mm Hg if the vena cava inferior was greater than 20 mm without respiratory variation.

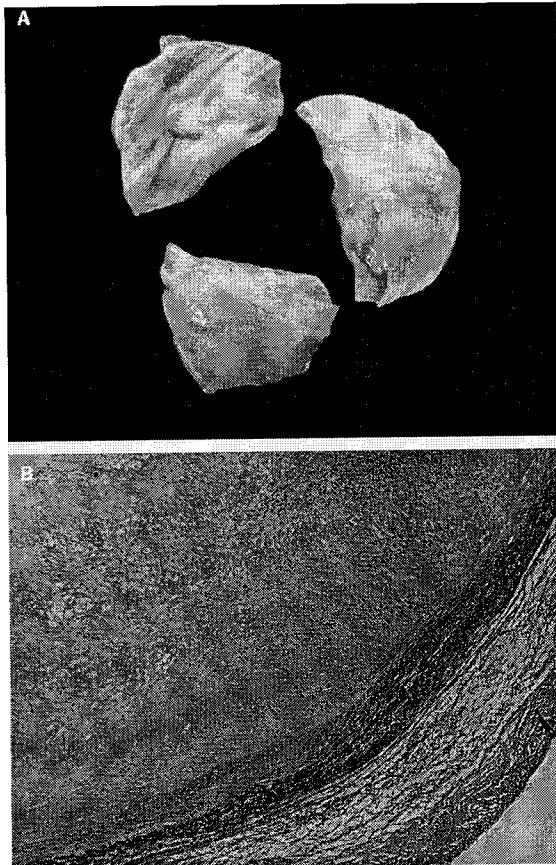


Figure 3: Macroscopic examination (A) and histology (B) of the aortic valve

(A) Reprinted from *Eur Heart J* 2003; 24: front cover, with permission of the European Society of Cardiology. (B) From upper to lower layer: plaque; ventricularis; spongiosa; fibrosa.

Statistical analysis

Values are given as mean (range). We measured differences in age between groups with the unpaired *t* test and differences in sex ratio with the Mann-Whitney *U* and Fisher's exact tests. We compared restrictive valvular heart disease score between patients treated with high-dose and low-dose pergolide and controls with the Mann-Whitney *U* and Kruskal-Wallis tests. We used the unpaired *t* test to compare tenting distances and areas in patients taking pergolide with and without restrictive mitral valves and in controls. We assessed the correlation between cumulative doses of pergolide and tenting distances and areas by linear regression. To estimate the interobserver variability of our scoring system, we compared—with κ statistics—the initial score by the researcher who did the examinations with that given by the masked reader.

Results

We enrolled 78 patients treated with pergolide as the only ergot-derived drug and 18 who had never been treated with an ergot-derived dopamine agonist. Mean age of patients taking pergolide was 70.9 years (range 51–87) and that of controls was 72.8 years (60–80; $p=0.332$). Mean age of individuals taking high-dose and low-dose pergolide was 68.7 years (53–83) and 72 years (51–87), respectively ($p=0.077$). The man/woman ratio was 45/33 in the pergolide group versus 9/9 in controls ($p=0.604$)

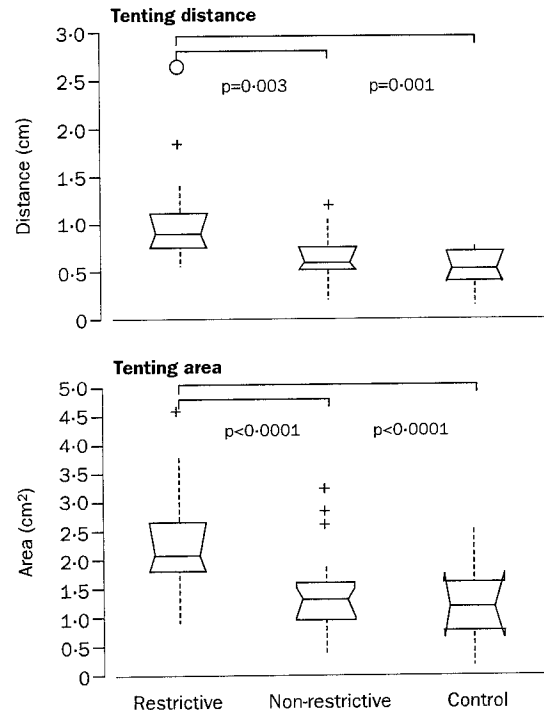


Figure 4: Box-plot of tenting distances and areas of restrictive and non-restrictive mitral valves

Horizontal bars show the median and 95% CI. Interrupted lines show individual values. Cross marks and circles show outliers.

and 13/13 in the high-dose versus 32/20 in the low-dose group ($p=0.34$). Mean cumulative dose of pergolide was 3003 g (51–10950) and mean duration 18.2 months (4–57). In the high-dose group versus the low-dose group, these respective values were 4403 g (769–10980) versus 2220 g (51–6637; $p=0.0047$) and 15.5 months (4–41) versus 20.9 months (6–57; $p=0.31$).

Any restrictive valvular heart disease (score 1–3) was recorded in 26 (33%) patients in the pergolide group versus none in controls ($p=0.0025$). Important disease (score 1 or 2) was present in 15 (19%) people in the pergolide group (five [19%] high dose *vs* ten [19%] low dose; $p=1.00$) and none in controls ($p=0.066$). In patients with restrictive valvular heart disease, mitral, aortic, and tricuspid disease was reported in 20 (26%), seven (9%), and six (8%) individuals, respectively.

One patient taking high-dose pergolide needed mitral and aortic valve replacement and tricuspid valve repair. Histopathological data in this individual were consistent with ergot-like valvular lesions (figure 3). One other patient with important restrictive valvular heart disease died suddenly, and necropsy was not done.

Mean tenting distances and areas were 1.08 mm (0.55–2.66) and 2.39 mm² (0.88–4.59) in patients with restrictive mitral valves and 0.63 mm (0.22–1.20) and 1.39 mm² (0.39–3.23) in those with non-restrictive mitral valves ($p=0.003$ and $p<0.0001$, respectively). In controls, these values were even lower, with a mean tenting distance of 0.54 mm (0.12–0.78) and area of 1.27 mm² (0.14–2.59; $p=0.001$ and $p<0.0001$, respectively, *vs* restrictive group; figure 4). Interobserver variability of our scoring system had a κ of 0.88.

Restrictive valvular heart disease was present in 11 (42%) patients given high-dose pergolide versus 15 (29%) on low-dose drug ($p=0.31$); no controls had this

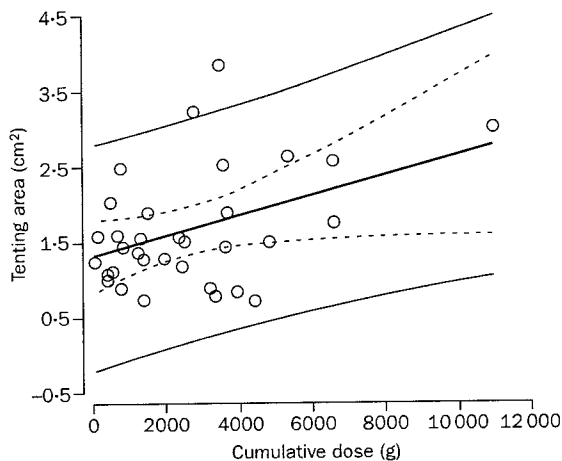


Figure 5: Correlation between cumulative doses of pergolide and tenting area of the mitral valve

Thick solid line=fitted regression line. Dotted lines=95% CI. Thin solid lines=95% predicted interval.

disease ($p=0.0025$ vs all patients given pergolide). A significant correlation was recorded between cumulative doses of pergolide and tenting areas of the mitral valves ($r=0.412$, $p=0.017$; figure 5). (The value and significance of this relation is affected by one large value; however, evidence of the relation still exists.) Cumulative dose did not differ significantly between restrictive valvular heart disease scores 1 and 2 and scores 3 and 4 (mean 3367 g [51–10 990] vs 2938 g [126–10 800]; $p=0.65$).

Pergolide treatment was stopped in six patients, two of whom had important regression of restrictive mitral valve disease at the first re-evaluation visit 6 months later. In these two patients, cumulative doses were 769 and 1500 g and duration of pergolide treatment was 4 and 12 months, and in the four without regression these values were 1200, 10 950, 1301, and 3492 g and 7, 20, 16, and 18 months. Mitral regurgitant jets diminished from 2/4 and 3/4 towards 1/4 in the two patients with regression. Tenting distances regressed from 1.12 and 1 cm to 0.74 and 0.60 cm, and tenting areas from 2.51 and 2.67 cm² to 1.81 and 1.3 cm².

Mean systolic pulmonary artery pressures were 39.3 mm Hg (25–71) in patients given high-dose pergolide, 38.5 mm Hg (20–65) in those given low-dose

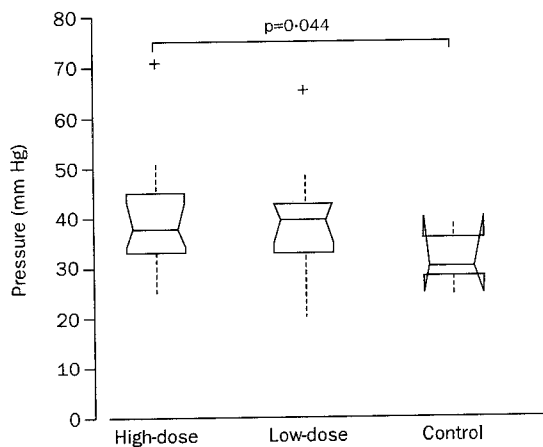


Figure 6: Box-plot of systolic pulmonary artery pressures
Horizontal bars show the median and 95% CI. Interrupted lines show individual values. Cross marks show outliers.

drug ($p=0.76$) and 31 mm Hg (25–40) in controls ($p=0.02$ vs all patients given pergolide and $p=0.044$ for high-dose pergolide vs control; figure 6). When patients with mitral regurgitation greater than 2/4 were excluded, these mean systolic pulmonary artery pressures were 37.6 mm Hg (25–52), 37.8 mm Hg (20–49; $p=0.94$), and 31 mm Hg (25–40; $p=0.016$), respectively.

Discussion

We have shown a higher frequency of pergolide-induced restrictive valvular heart disease than previously reported. The initial low frequency of restrictive valvular heart disease in patients with Parkinson's disease taking pergolide¹² could be accounted for by the high rate of degenerative valve lesions that have some degree of valvular regurgitation in this older population. However, accurate identification of restrictive valvular heart disease in these individuals is difficult. To define pergolide-induced disease, presence of a regurgitant jet by colour doppler is inaccurate, which also means that US Food and Drug Administration (FDA) criteria for appetite suppressant-induced valve disease cannot be applied.¹⁴

Ergot-like drugs induce fibrotic changes in leaflets and subvalvular apparatus of valves. They become stiffer, resulting in incomplete closure of leaflets above the annular plane. This stiffening leads to typical apical displacement of the incomplete leaflet coaptation in mitral and tricuspid valves and in the doming motion of the valves—diastolic for mitral and tricuspid valves and systolic for the aortic valve. This restrictive motion was the most important criterion of our scoring system, and we gave more diagnostic power to the presence of a restrictive tricuspid motion. In this older population with Parkinson's disease, tricuspid involvement is even more diagnostic for restrictive valvular heart disease since degenerative and calcified valvular disease affects the tricuspid valve less frequently than the mitral and aortic valve.

Taking into account only patients with major suspicion of restrictive valvular heart disease (score 1 and 2), 19% of those taking pergolide presented some degree of disease. This frequency is higher than the early reported frequency of pergolide-induced restrictive valvular heart disease.⁶ However, that study used data of the registry of the FDA, and the methodology used could account for any differences: first, rare pathology must be recognised; and second, doctors must take time and effort to fill in the necessary documents. Compared to appetite-suppressant drugs, the frequency of score 1 or 2 restrictive valvular heart disease is very similar.^{15,16}

A very comprehensive and easy method to quantify restrictive mitral pathology by echocardiography is to measure tenting distance and area. This method is used regularly in ischaemic left ventricle pathology, even during exercise.¹³ In ischaemic heart disease, mitral regurgitation results from tethering of the valve because of left ventricular remodelling. Although the mechanism can be different in pergolide-induced valvular disease, the result is the same, namely apical displacement of the mitral leaflet coaptation. With these criteria, we reported high tenting distances and areas in mitral valves that were visually estimated as restrictive. Less important values were noted in non-restrictive valves, and the lowest values were recorded in controls.

We noted a higher frequency of proven and important restrictive valvular heart disease in patients taking high-doses of pergolide than in those taking lower doses. We recorded a significant correlation between the cumulative dose of the drug and the tenting area of the mitral valve. We did not note a significant difference in cumulative

dose between score 1–2 and 3–4. One explanation could be the difficulties to obtain exact cumulative doses in a retrospective study because to get exact timings is difficult. The daily dose at the time of the echocardiographic examination is more accurate.

Our study group was not large enough to assess the effect of reversibility of restrictive valvular heart disease in patients taking pergolide. We could have had more data if the drug was stopped in all patients. The patient, neurologist, and cardiologist all had to agree before pergolide was stopped. In most cases the drug was not stopped because patient and neurologist preferred the beneficial neurological effects of pergolide rather than the cardiac side-effects. However, reversibility was clearly shown in two of six patients in whom the drug was stopped. This finding accords with data on appetite-suppressant drugs, in which reversibility has also been described.¹⁵

Appetite-suppressant drugs have also been implicated in the development of pulmonary hypertension.^{16,17} We recorded higher pulmonary pressures in pergolide-treated patients than in controls. These higher pressures can be accounted for by the higher frequency of mitral valve disease. But if patients with relevant mitral valve regurgitation (jet >2/4) were excluded, pulmonary pressures still differed significantly between treated patients and controls.

Increasing evidence suggests that appetite-suppressant drugs induce heart disease by interaction with the serotonin 5-HT_{2B} receptor,^{9–11} and data show that pergolide interacts with this receptor.¹¹ This serotonin receptor might therefore be the missing link in the understanding of drug-induced valvular diseases and pulmonary hypertension.¹⁸

Our study has some limitations. First, it was not prospective. Patients were already taking pergolide at inclusion and we did not have echocardiographic data before treatment was started. Second, the definition of restrictive valvular heart disease in this older population could be criticised. However, we believe that our scoring system was as accurate as possible. Scoring was done by a skilled echocardiographer who was masked to patient's treatment, and it combined structural characteristics of restrictive valve disease with functional abnormalities identified by regurgitation, as shown by doppler examination. The scoring system was reproducible as shown by the good interobserver variability. Finally, even if we tried to exclude patients treated with other drugs inducing restrictive valvular heart disease, we cannot exclude the possibility that a few patients in the past took any of these drugs for a short period. However, this possibility holds true for the control group.

Although pergolide remains a good treatment for the symptoms of Parkinson's disease, our findings underline the necessity to inform patients of the possible risk of inducing restrictive valvular heart disease and pulmonary hypertension. Clinicians must be aware of this possible side-effect, and close clinical and echocardiographic follow-up is mandatory. Changing drugs to a non-ergot alternative should be considered whenever restrictive valvular heart disease has been diagnosed. When a new murmur appears and echocardiography confirms this disease, endocarditis prophylactic treatment should be advised.

Contributors

G Van Camp, B Cosyns, C Weytjens, and D Schoors were cardiologists, and A Flamez the neurologist, from the central hospital of this study (AZ VUB), and they developed the idea for and designed the study,

recruited patients, analysed echocardiograms, and wrote the report. L Muyldermans and M Van Zandijcke, J De Sutter and P Santens, and P Decoodt and C Moerman are, respectively, the cardiologist and neurologist of the other participating centres (AZ St Jan Brugge, UZ Gent, and CHU Brugmann), and they recruited and did echocardiography of the patients of their centre, participated in discussion of study design, and corrected the manuscript.

Conflict of interest statement

None declared.

Acknowledgments

We thank S Droogmans (AZ VUB) and Prof L Kaufman (VUB, Brussels, Belgium) who acted as statistical advisers. No sponsorship was received for this study.

References

- Shanak S, Wilkins A, Pilling JB, Dick DJ. Pericardial, retroperitoneal, and pleural fibrosis induced by pergolide. *J Neurol Neurosurg Psychiatry* 1999; **66**: 79–81.
- Jimenez-Jimenez FJ, Lopez-Alvarez J, Sanchez-Chapado M, et al. Retroperitoneal fibrosis in a patient with Parkinson's disease treated with pergolide. *Clin Neuropharmacol* 1995; **18**: 277–79.
- Mondal BK, Suri S. Pergolide-induced retroperitoneal fibrosis. *Int J Clin Pract* 2000; **54**: 403.
- Danoff SK, Grasso ME, Terry PB, Flynn JA. Pleuropulmonary disease due to pergolide use for restless legs syndrome. *Chest* 2001; **120**: 313–16.
- Pritchett AM, Morrison JF, Edwards WD, Schaff HV, Connolly HM, Espinosa RE. Valvular heart disease in patients taking pergolide. *Mayo Clin Proc* 2002; **77**: 1280–86.
- Flowers CM, Racoosin JA, Lu SL, Beitz JG. The US food and drug administration's registry of patients with Parkinson's disease associated valvular heart disease. *Mayo Clin Proc* 2003; **78**: 730–31.
- Rahimtoola S. Drug-related valvular heart disease: here we go again: will we do better this time. *Mayo Clin Proc* 2002; **77**: 1275–77.
- Van Camp G, Flamez A, Cosyns B, Goldstein J, Perdaens C, Schoors D. Valvular heart disease in patients with Parkinson's disease treated with high-dose pergolide. *Neurology* 2003; **61**: 859–61.
- Fitzgerald LW, Burn TC, Brown BS, et al. Possible role of valvular serotonin 5-HT_{2B} receptors in the cardiopathy associated with fenfluramine. *Mol Pharm* 2000; **57**: 75–81.
- Rothman RB, Bauman MH, Savage JE, et al. Evidence for possible involvement of 5-HT_{2B} receptors in the cardiac valvulopathy associated with fenfluramine and other serotonergic medications. *Circulation* 2000; **102**: 2836–41.
- Setola V, Hufeisen SJ, Grande-Allen KJ, et al. 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") induces fenfluramine-like proliferative actions on human cardiac valvular interstitial cells in vitro. *Mol Pharm* 2003; **63**: 1223–29.
- FDA. 2003 Safety Alert—Permax (pergolide mesylate). <http://www.fda.gov/medwatch/SAFETY/2003/permax.htm> (accessed Feb 27, 2004).
- Lancellotti P, Lebrun F, Pierard LA. Determinants of exercise-induced changes in mitral regurgitation in patients with coronary artery disease and left ventricular dysfunction. *J Am Coll Cardiol* 2003; **42**: 1921–28.
- US Food and Drug Administration Center for Drug Evaluation and Research, and Center for Disease Control and Prevention. Cardiac valvulopathy associated with exposure to fenfluramine or dexfenfluramine. *MMWR Morb Mortal Wkly Rep* 1997; **46**: 1061–66.
- Shively BK, Roldan CA, Gill EA, Najarian T, Loar SB. Prevalence and determinants of valvulopathy in patients treated with dexfenfluramine. *Circulation* 1999; **100**: 2161–69.
- Abenhaim L, Moride F, Brenot et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. *N Engl J Med* 1996; **335**: 609–16.
- Delcroix M, Kurz X, Walckiers D et al. High incidence of primary pulmonary hypertension associated with appetite suppressants in Belgium. *Eur Respir J* 1998; **12**: 271–76.
- Blanpain C, Le Poul E, Parma J et al. Serotonin 5-HT_{2B} receptor loss of function mutation in a patient with fenfluramine-associated primary pulmonary hypertension. *Cardiovasc Res* 2003; **60**: 518–28.

rabies by use of spiked baits. Such recombinant vaccines would not be suitable for widespread use in human beings because of the hazards associated with vaccinia virus as a smallpox vaccine, and especially because of the risk of dissemination in HIV-infected individuals. Attenuated strains of vaccinia virus—eg, modified vaccinia Ankara (MVA)—and avian strains of poxviruses such as fowlpox virus and canarypox virus do not replicate in humans and are safe.² Recombinants of the latter two viruses that express rabies glycoprotein have been shown to be immunogenic^{3,4} but have never been commercially marketed. There is no risk of contamination with live rabies virus if these recombinant poxvirus vaccines are used.

Recombinant poxviruses can readily be engineered to express many foreign proteins simultaneously, so there is potential to create combined vaccines against several diseases for the cost of the engineering and manufacture of a single recombinant. Recombinant MVA is under separate development as a vaccine for malaria, HIV infection, and tuberculosis. Such vaccines will find wide application if successful, and a rabies vaccine could be incorporated into this scheme at low additional cost. The main problem with this approach is that the antibody responses to these recombinants in DNA prime MVA boost regimens are poor,⁵ although such responses have not been directly explored for rabies glycoprotein.

I own a small number of shares in Oxxon Therapeutics, who own the DNA prime MVA boost CTL patent, as a consequence of being a named inventor. I have no other role in the company.

Tom Blanchard

Liverpool School of Tropical Medicine, Pembroke Place, Liverpool L3 5QA, UK
 (e-mail: tblanch@liv.ac.uk)

- 1 Warrell MJ, Warrell DA. Rabies and other lyssavirus diseases. *Lancet* 2004; **363**: 959–69.
- 2 Blanchard TJ, Alcamí A, Andrea P, Smith GL. Modified vaccinia virus Ankara undergoes limited replication in human cells and lacks several immunomodulatory proteins: implications for use as a human vaccine. *J Gen Virol* 1998; **79**: 1159–67.
- 3 Taylor J, Weinberg R, Languet B, Desmettre P, Paoletti E. Recombinant fowlpox virus inducing protective immunity in non-avian species. *Vaccine* 1988; **6**: 497–503.
- 4 Taylor J, Trimarchi C, Weinberg R, et al. Efficacy studies on a canarypox-rabies recombinant virus. *Vaccine* 1991; **9**: 190–93.
- 5 McConkey SJ, Reece WH, Moorthy VS, et al. Enhanced T-cell immunogenicity of plasmid DNA vaccines boosted by recombinant modified vaccinia virus Ankara in humans. *Nat Med* 2003; **9**: 729–35.

Authors' reply

Sir—We vigorously deny Henry Wilde and colleagues' assertion that our Seminar creates "another source of

confusion about optimum post-exposure rabies treatment". The essential role of rabies immune globulin (RIG) in post-exposure treatment is undisputed. This we have made clear in our Seminar and elsewhere. Primary vaccine treatment alone cannot be expected to prevent disease in all cases, especially where there are head and face bites, as in the tragic case of the 7-year-old Thai girl.

In the only study comparing the eight-site and the two-site post-exposure intradermal vaccine regimens, titres above the arbitrary threshold of 0.5 IU/mL on day 7 were achieved only with the eight-site regimen, and the geometric mean titre was significantly higher on that day than with the two-site regimen.¹ The authors of that report concluded that the eight-site method gave a more rapid antibody response. It also has a greater margin of safety than other economical intradermal regimens. Less skill is required for injection since if four of the eight injections are not truly intradermal, an adequate immune response is still produced.² The use of an entire ampoule for the first dose removes the need to share ampoules and avoids wastage, and treatment can be started in any clinic. This regimen is recommended by WHO as the most suitable treatment when RIG is not available.³ Human rabies post-exposure prophylaxis in developing countries involves making the best use of the available resources for each patient.

It was not possible to cover all aspects of rabies in our Seminar, and we thank the correspondents for introducing further issues. Ajit Kashyap and colleagues point out that rabies diagnosis by identification of Negri bodies with Seller's stain of brain smears, although superseded by staining with immunofluorescent rabies antibody, is still used. However, interpretation demands great technical skill, false-positive results occur, and it has proved consistently less sensitive than immunofluorescence. It might be useful in the absence of fluorescent microscopy, but WHO now recommends the immunofluorescence method.

We agree with Tom Blanchard that mass pre-exposure rabies prophylaxis would be ideal, and that anyone living in areas where dog rabies is endemic should be immunised. A vaccinated population would need less vaccine and no RIG if subsequently exposed to rabies. Although the addition of rabies vaccine to WHO's Expanded Programme for Immunization would prove effective and feasible,⁴ the cost is prohibitive without the provision of

funds from an international charitable organisation. A canarypox virus rabies recombinant vaccine induced some rabies antibody in humans beings,⁵ but the slow response, typical of these vaccines, would restrict its use to pre-exposure treatment. If pox recombinants were used in mass immunisation schemes in Asia or Africa, the addition of rabies antigens could be of great benefit.

*Mary Warrell, David Warrell

Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Oxford OX3 9DU, UK
 (e-mail: mary.warrell@ndm.ox.ac.uk)

- 1 Madhusudana SN, Anand NP, Shamsundar R. Evaluation of two intradermal vaccination regimens using purified chick embryo cell vaccine for post-exposure prophylaxis of rabies. *Natl Med J India* 2001; **14**: 145–47.
- 2 Suntharasamai P, Warrell MJ, Viravan C, et al. Purified chick embryo cell rabies vaccine: economical multisite intradermal regimen for post-exposure prophylaxis. *Epidemiol Infect* 1987; **9**: 755–65.
- 3 World Health Organization. WHO recommendations on rabies post-exposure treatment and the correct technique of intradermal immunization against rabies. WHO/EMC/ZOO.96.6. <http://www.who.int/emc-documents/rabies/docs/whoemczoo966.pdf> (accessed Jan 6, 2004).
- 4 Lang J, Hoa DQ, Gioi NV, et al. Immunogenicity and safety of low-dose intradermal rabies vaccination given during an Expanded Programme on immunization session in Viet Nam: results of a comparative randomized trial. *Trans R Soc Trop Med Hyg* 1999; **93**: 208–13.
- 5 Cadoz M, Strady A, Meignier B, et al. Immunisation with canarypox virus expressing rabies glycoprotein. *Lancet* 1992; **339**: 1429–32.

Pergolide in Parkinson's disease: time for a change?

Sir—Guy Van Camp and colleagues (Apr 10, p 1179)¹ report that higher than expected rates of restrictive valvular heart disease occur in patients with Parkinson's disease treated with the ergot dopamine agonist, pergolide. Given that 27 of 78 patients were affected, changes were deemed important in 15 of 78, and none of 18 control patients (those receiving other treatments for Parkinson's disease) were affected we are surprised that pergolide was stopped in only six of 78 cases.

Given the availability of two non-ergot dopamine agonists (ropinirole and pramipexole) that are at least as beneficial in disease control as pergolide, we urge the authors to consider a switch from the treatment they have identified as hazardous.

We recently switched 88 of 99 patients from ergot-based dopamine agonists to a non-ergot treatment; 69 of 88 were on pergolide (78%), and retention of the switch dopamine agonist was 82% after 11 months of follow-up.² The switch was undertaken because of potential ergot side-effects in most patients (71 of 88, 81%). We produced an equivalence conversion chart for available dose levels between five dopamine agonists, which guides the clinician in this task.^{2,3}

DG has received honoraria for presentations about Parkinson's therapy from several pharmaceutical companies.

Katherine A Grosset, *Donald G Grosset
Department of Neurology, Institute of Neurological Sciences, Glasgow G51 4TF, UK
(e-mail: d.grosset@clinmed.gla.ac.uk)

- 1 Van Camp G, Flamez A, Cosyns B, et al. Treatment of Parkinson's disease with pergolide and relation to restrictive valvular heart disease. *Lancet* 2004; **363**: 1179–83.
- 2 Grosset KA, Needleman F, Macphee G, Grosset DG. Switching from ergot to non-ergot dopamine agonists in Parkinson's disease: a clinical series and 5 drug dose conversion table. *Mov Dis* (in press).
- 3 Stewart DA, Morgan E, Burn D, et al. Dopamine agonist switching in Parkinson's disease. *Hosp Med* 2004; **65**: 215–19.

Risk of cancer from diagnostic X-rays

Sir—Amy Berrington de González and Sarah Darby (Jan 31, p 345)¹ base their estimation of the number of cancers induced by diagnostic X-rays on the hypothesis of a linear non-threshold (LNT) dose-effect relation. Unfortunately, they do not underline the speculative nature of this hypothesis.

Research has shown the complexity and effectiveness of the cell's defences against ionising radiation.^{2,3} Hundreds of enzymes in a mammalian cell are devoted to protection against these effects. Some detect DNA lesions and can distinguish the various types and assess their number. Others activate proteins involved in DNA repair or apoptosis. Moreover, signals coming from the surrounding microenvironment affect the cell's fate. Damaged cells are eliminated or undergo DNA repair. Several repair mechanisms exist, which differ in their speed and the probability of misrepair. There is no single defence mechanism but a variety, taking into account the number and severity of lesions and the number of damaged cells. At low or very low doses of radiation, the system seems to be highly effective, since when the number of damaged cells is

small, they are eliminated by cell death.² An adaptive effect exists and a hormetic effect has even been seen in more than half of experimental studies after low or moderate doses.^{4,5} Extrapolation from high doses to low doses with LNT is unlikely to be able to assess the risks accurately.

For doses within the range of natural irradiation (1–20 mSv per year) the carcinogenic effect, if any, seems to be very small and comparisons between geographic regions have not detected any differences in cancer incidence. Most diagnostic X-ray examinations deliver doses of about the same magnitude. Despite hundreds of epidemiological surveys and thousands of experimental studies, none of them has been able to show a carcinogenic effect of doses below 50 mSv delivered after birth.

LNT is compatible with the excess of solid tumours among atomic bomb survivors exposed to between 200 mSv and 3 Sv. However, other relations are also compatible at about 50 mSv and better fit other data. LNT implies that the contribution to radiocarcinogenesis of an electron track traversing a cell nucleus is identical whether there is only one electron track or hundreds of them. Experimental studies show clearly that the cell reactions vary with their number.

We fear that these calculations might have a detrimental effect by dissuading individuals from doing X-ray examinations for fear of a carcinogenic effect. Only a cost-benefit approach can facilitate decision-making. The potential rise in death associated with a decrease in the number of X-ray examinations should also be estimated.

*M Tubiana, A Aurengo, R Masse, A J Valleron

Centre Antoine Beclere, Centre Universitaire des Saints-Pères, 45 rue des Saints-Pères, 75006 Paris, France
(e-mail: maurice.tubiana@biomedicale.univ-paris5.fr)

- 1 Berrington De González A, Darby S. Risk of cancer from diagnostic X-rays: estimates for the UK and 14 other countries. *Lancet* 2004; **363**: 345–51.
- 2 Rothkamm K, Löbrich M. Evidence for a lack of DNA double-strand break repair in human cells exposed to very low x-ray doses. *Proc Natl Acad Sci U S A* 2003; **100**: 5057–62.
- 3 Tubiana M. The carcinogenic effect of low doses: the validity of the linear no-threshold relationship. *Int J Low Radiation* 2003; **1**: 1–33.
- 4 Dupont P. A data base of cancer induction by low-dose radiation in mammals: overviews and initial observations. *Int J Low Radiation* 2003; **1**: 120–31.
- 5 Calabrese EJ, Baldwin LA. Toxicology rethinks its central belief. *Nature* 2003; **421**: 691–92.

Sir—Amy Berrington de González and Sarah Darby¹ find that, in the UK, about 0.6% of the cumulative risk of cancer to age 75 years can be attributed to diagnostic X-rays. This proportion is equivalent to about 700 cases of cancer per year.

The authors note that the calculations involved several assumptions and so are subject to substantial uncertainty. A sensitivity analysis was done to assess this uncertainty by varying the assumptions in the calculations. The six assumptions listed cover a wide range of possible sources of error, and it was useful to have these detailed explicitly. However, a further possible source of error was not considered but merely hidden in the opening paragraph of the Discussion. The relevant sentences read, "Our estimates are based on the assumption that small doses of radiation can cause cancer. The weight of evidence from experimental and epidemiological data do not suggest a threshold below which radiation exposure does not cause cancer." In this context, the term "small doses of radiation" mostly refers to organ-specific doses of less than 10 mGy, the only exceptions being those arising from barium enema and certain CT investigations.

There is a substantial weight of evidence against this key assumption.² Muirhead and colleagues³ found that, for every 100 radiation workers who might have been expected to have died, only 82 had actually done so. The trend in mortality as a function of dose showed that the observed versus expected ratio from all causes of death and from all malignant neoplasms did not exceed unity for any dose up to 400 mSv (except for one point close to 200 mSv).

If, as Berrington de González and Darby did, we look at the data from the Japanese atomic bomb survivors, it again becomes clear that the assumption of detriment at low doses is open to challenge. For example, Heidenreich and colleagues⁴ maintain that the data from this group do not support the idea of an increased tumour rate at doses below 200 mSv, as do Preston and colleagues.⁵ In the light of this information, perhaps Berrington de González and Darby should have built the uncertainty surrounding the low-dose effects into their analysis.

J A Simmons

74 Whitehall Park, London N19 3YN, UK
(e-mail: simmons74@btinternet.com)

- 1 Berrington de González A, Darby S. Risk of cancer from diagnostic X-rays: estimates