Clin Auton Res (2010) 20:205–207
DOI 10.1007/s10286-009-0049-7

RESEARCH LETTER

DBH deficiency in an elderly patient: efficacy and safety of chronic droxidopa

Fabien Despas · A. Pathak · M. Berry · R. Cagnac · P. Massabuau · E. Liozon · M. Galinier · J. M. Senard

Received: 2 July 2009 / Accepted: 22 December 2009 / Published online: 9 January 2010

Abstract We describe the effects of chronic droxidopa in a patient with Dopamine beta-hydroxylase deficiency diagnosed at the age of 73. Investigations were performed to assess sympathetic activity (MIBG scintigraphy, catecholamines) and cardiovascular droxidopa safety.

Keywords Dopamine beta-hydroxylase · Droxidopa · Orthostatic hypotension · Elderly

F. Despas · A. Pathak · J. M. Senard
INSERM U858 équipe 8, 31432 Toulouse, France

F. Despas · A. Pathak · J. M. Senard
Institut de Médecine Moléculaire de Rangueil,
Université de Toulouse,
UPS, 31432 Toulouse, France

F. Despas · A. Pathak · J. M. Senard
Department of Clinical Pharmacology,
CHU de Toulouse, 31432 Toulouse, France

M. Berry · P. Massabuau · M. Galinier
Department of Cardiology, CHU de Toulouse,
31432 Toulouse, France

R. Cagnac
Department of Nuclear Medicine,
CHU de Toulouse, 31432 Toulouse, France

E. Liozon
Department of Internal Medicine,
CHU Dupuytren, 87000 Limoges, France

F. Despas (✉)
Laboratoire de Pharmacologie clinique, Faculté de médecine,
37 Allées J. Guesde, 31000 Toulouse Cedex, France
e-mail: fabien.despas@yahoo.fr

Introduction

Dopamine beta-hydroxylase (DBH) deficiency is a very rare form of primary autonomic failure characterised by a complete absence of norepinephrine and epinephrine in plasma together with increased dopamine plasma levels. DBH, which results from heterogeneous molecular alterations of DBH gene [1], is clinically marked by cardiovascular disorders and severe orthostatic hypotension sensitive to restoration of plasma norepinephrine by droxidopa, a synthetic norepinephrine precursor [2]. Most DBH deficiency cases reported today have been described in childhood or early adulthood and little is known about life expectancy and long-term effects of droxidopa.

Methods

A 73-year-old male patient was referred to the autonomic unit of the Toulouse University Hospital in 2006 for a long lasting and never explored symptomatic orthostatic hypotension (OH) known since childhood. At the age of 65 years, OH worsened with increased frequency and intensity of postural symptoms which turned refractory to medications (midodrine, fludrocortisone) and elastic legs socking. Anamnesis indicated the absence of familial history of autonomic disorders. Patient had two healthy children currently aged of 45 and 48 years. The physical examination was normal at entry without neurological features suggesting neurological degenerative disease or peripheral neuropathy. Autonomic functions (sweating, thermoregulation, gastro-intestinal motricity, vesical and sexual functions) were reported as normal. Pupils reacted normally to light and accommodation and autonomic testing revealed isolated neurogenic OH without abnormal responses to deep breathing,

30/15 ratio and handgrip. Routine biology indicated the absence of diabetes mellitus, renal failure or vitamin B12 deficiency. Despite midodrine (10 mg t.i.d.), the patient remained symptomatic and was unable to continue his normal physical activity.

Catecholamine determination in plasma led to diagnosis of DBH deficiency in front of undetectable norepinephrine and epinephrine and elevated dopamine (67 nmol/l). Biochemical determinations were achieved using HPLC and repeated three times with identical results. Enzymatic DBH activity was absent. Thus, patient was placed on droxidopa at increasing doses until control of OH was considered satisfactory (200 mg t.i.d.). 8 months later, patient was re-hospitalised for the assessment of droxidopa efficacy (plasma catecholamine) and cardiovascular safety (24-h EKG, blood pressure monitoring and transthoracic echocardiography). Moreover, MIBG cardiac scintigraphy [3] was performed before and after 48-h droxidopa withdrawal. Patient was then seen every 6 months by a neurologist.

Results

Clinical postural symptoms dramatically improved, allowing return to normal activity. No significant adverse event related to droxidopa was noticed. This positive response lasted for at least 30 months and was associated with normalisation of norepinephrine (1.78 nmol/l), epinephrine (<0.5 nmol/l) and dopamine (<0.5 nmol/l) plasma levels.

After 8 months of droxidopa treatment, 24-h blood pressure was normal (110/64 mmHg) and day/night cycle was preserved. No significant rhythm disturbance was noticed on 24-h EKG. Transthoracic cardiac echocardiography was normal without left ventricular hypertrophy. Moreover, systolic and diastolic function and segmental contractility were normal.

[I^{123}]MIBG scintigraphy performed after a 48-h droxidopa withdrawal indicated both elevated early (3.0) and delayed (3.7) H/M ratio (normal laboratory value 1.2). Under stable droxidopa treatment, early and delayed H/M ratio values were, respectively, 4.2 and 5.0. Wash-out rate without droxidopa (45%) was above the normal laboratory range (20–35%) and was normal under droxidopa (35%).

Discussion

Data from this peculiar case report indicate that DBH deficiency can occur in elderly and can be safely treated with droxidopa.

This patient was, during long years, considered as suffering from pure autonomic failure (PAF) in view of chronic-isolated autonomic failure and OH, without associated neurological features. The absence of Askenaze extraction allowed discarding familial dysautonomia and there was no familial history, clinical or electrophysiological evidences for sensory peripheral neuropathy. The clinical and biochemical autonomic profile together with the dramatic improvement with droxidopa permitted to confirm the diagnosis of DBH deficiency despite this condition has never been reported in elderly [1]. In fact, usually, symptoms often start during perinatal period and progressively worsen during late adolescence and early adulthood [1]. We suggest that plasma catecholamine determinations should be realised in all patients with chronic-isolated autonomic failure in order to eliminate DBH deficiency, even if this condition is very rare.

Droxidopa is a synthetic precursor of norepinephrine able to shunt the absence of DBH enzyme and to restore normal catecholamine concentration. This drug has been proposed for OH management in primary autonomic failures and familial amyloidosis [4]. However, data on its cardiovascular safety are scare and this drug potentially can elevate blood pressure and promote cardiac remodelling in autonomic failure patients who are at risk of cardiovascular morbidity/mortality [5]. In this particular patient, specific explorations failed to suggest any negative cardiovascular impact of droxidopa.

From a physiological point of view, MIBG scintigraphy clearly indicates normal cardiac sympathetic nerve density and further discriminates DBH deficiency from PAF. Elevated basal WOR corroborates the elevated sympathetic nerve traffic previously demonstrated in DBH deficiency using microneurography [2]. Moreover, high [^{123}I]MIBG uptake indicated that the heart sympathetic fibres are able to normally uptake and store catecholamines, independently of droxidopa. Our results also suggest that [^{123}I]MIBG cardiac scintigraphy could be used to differentiate PAF from DBH deficiency since this technique is more widely available than microneurography which remains restricted to a reduced number of laboratories.

In conclusion, the main finding from this work is first that DBH deficiency may be compatible with roughly normal life expectancy despite pronounced OH and that this possible diagnosis has to be considered in elderly patient. The second finding is that chronic droxidopa treatment is efficient and safe. Third, MIBG findings confirm that in DBH deficiency sympathetic nerves are intact and functional.

References

1. Senard JM, Rouet P (2006) Dopamine beta-hydroxylase deficiency. Orphanet J Rare Dis 1:7

2. Biaggioni I, Robertson D (1987) Endogenous restoration of noradrenaline by precursor therapy in dopamine-beta-hydroxylase deficiency. Lancet 2(8569):1170–1172
3. Courbon F, Brefel-Courbon C, Thalamas C et al (2003) Cardiac MIBG scintigraphy is a sensitive tool for detecting cardiac sympathetic denervation in Parkinson's disease. Mov Disord 18(8):890–897
4. Kaufmann H, Saadia D, Voustianiouk A et al (2003) Norepinephrine precursor therapy in neurogenic orthostatic hypotension. Circulation 108(6):724–728
5. Fedorowski A, Stavenow L, Hedblad B, Berglund G, Nilsson PM, Melander O (2009) Orthostatic hypotension predicts all-cause mortality and coronary events in middle-aged individuals (The Malmo Preventive Project). Eur Heart J