Oxidative polymorphism of debrisoquine in Parkinson's disease


Abstract

Oxidative phenotype and metabolic ratio (MR) of debrisoquine (DBQ) have been determined in 87 patients with Parkinson's disease and in 556 healthy control subjects. Three patients (3-45%) and 34 control subjects (6-12%), having an MR > 12-6, were classified as poor metabolisers (PM) of DBQ (ns). The distribution of MR values in the 84 Parkinsonian patients classified as extensive metabolisers (EM) showed a less efficient oxidative rate when compared with controls of the same phenotype (p < 0-001). This difference may be due to enzymatic inhibition caused by drug treatment in 40 of these patients. As in patients not taking any drug known to inhibit the oxidation of DBQ, distribution of MR values was not different from that in controls. A negative correlation (r = -0-36, p < 0-02) was found between MR of DBQ and age at onset of disease in patients free of drugs known to interact with DBQ metabolism. A higher rate of DBQ oxidation could be a genetic factor that delays the clinical onset of Parkinson's disease in predisposed people.

Debrisoquine (DBQ), an adrenergic-blocking drug, is oxidised in the liver to 4-hydroxydebrisoquine (4-OH DBQ) following a polymorphic reaction that depends on the isozyme db1 of the microsomal cytochrome P-450 system (P-450 II D1). The rate of activity of this isozyme shows a genetic polymorphism: homozygotes for the recessive allele are almost completely unable to 4-hydroxylate DBQ and are designated poor metabolisers (PM) of DBQ, whereas homo and heterozygotes for the dominant allele hydroxylate DBQ efficiently and are classified as extensive metabolisers (EM). The biochemical defect in PM might be due either to the synthesis of an abnormal molecule of the isozyme or, more probably, to the absence of isozyme. Two mutant alleles associated with this deficiency have been identified, and the gene controlling the synthesis of this isozyme has been traced to the long arm of chromosome 22. Drugs that share the oxidative pathway of DBQ are competitive inhibitors of its metabolism, in addition there are other drugs that, although not following this route, may interfere with it. On the other hand, the activity of the isozyme P-450 db1 is hardly modifiable by some known inducers of the oxidative microsomal system, and seems not to be influenced by age, sex or tobacco and alcohol consumption.

The cause of Parkinson's disease is unknown. However, genetic predisposition, ageing, and neurotoxicity by chemicals, may all play a role. Barbeau et al determined the oxidative polymorphism of DBQ in a group of Parkinsonian patients and stated that "poor metabolisers among PD patients tended to have an earlier age at onset of the disease". Afterwards, the same group attributed much of that lower oxidative rate to enzymatic blocking caused by the concurrent administration of the antihistamine drugs diphenhydramine or orphenadrine, but concluded that "the observation that non-(poor) metabolisers of debrisoquine tend to have an earlier age of onset and an early severe course of PD still holds true". Comella et al and Tanner et al detected a non-significant excess of slow metabolisers of DBQ in their patients aged under 40 years at clinical onset.

In this study we have aimed to elucidate the possible relationship between Parkinson's disease and oxidative polymorphism of DBQ, taking particular care to eliminate bias produced by the concomitant use of drugs capable of interfering with its enzymatic activity.

Patients and methods

The study involved 87 patients (46 male, 41 female, mean age 65-1 years, SD 9-9) with a diagnosis of Parkinson's disease. Informed consent was a prerequisite for inclusion in the study, as indeed was normal gut, liver and kidney function. Data on age at clinical onset of the disease, tobacco and alcohol use and current drug treatment were collected in every case. The clinical staging of the disease was established according to Hoehn and Yahr.

Forty five patients not receiving drugs or only levodopa-carbidopa and/or bromocriptine formed the subgroup A ("untreated"). The remaining 42 patients (subgroup B, "treated"), were receiving one or more of the following drugs known to affect DBQ metabolism: neuroleptics, anticholinergics, tricyclic antidepressants, and beta blocker agents. No patient had received any antihistamine drug, either anti-H1 or anti-H2, in the previous three weeks.

The control group comprised 556 healthy subjects (272 male, 284 female, mean age 25 years, SD 7-3), who were not taking any drug.

The oxidative ratio of DBQ was determined by giving a 10 mg Declinax tablet at 22.00 hours, (two hours after a light dinner) and
collecting all the urine in the following eight hours. The volume was measured and aliquots were stored at −20°C until analysis.

Measurement of DBQ and of its main metabolite, 4-OH DBQ, in urine was performed using the flame-ionisation gas-chromatographic method described by Lennard et al.21 Metabolic ratio was calculated according to the formula:

\[ MR = \frac{\% \text{ Dose excreted as unchanged DBQ}}{\% \text{ Dose excreted as 4-hydroxy DBQ}} \]

The limit between poor and extensive metabolisers was established at a value for MR of 12.6 (log 1.1), proposed by Price-Evans et al.21

The statistical analysis was performed using the Chi-squared test with Yates’ correction, the nonparametrical Kolmogorov-Smirnov test and the calculation of linear correlation coefficients when appropriate.23 The null hypothesis was rejected when \( p < 0.05 \).

Results
Three patients (3.45%), one (age of disease onset 24 years) in subgroup A and two (age of disease onset 55 and 78 years respectively) in subgroup B, and 34 control subjects (6.12%) with MR values > 12.6, were classified as poor metabolisers of DBQ (Chi squared = 0.99, not significant).

A separate analysis has been performed in extensive metabolisers (EM) of both patients and control groups. The distribution of MR values of DBQ showed higher values in patients (\( p < 0.001 \)), reflecting a lower oxidative rate in the whole group of EM patients than in EM controls subjects. This difference persisted at the same level of significance when EM patients of subgroup B ("untreated") were compared with controls, but disappeared when EM patients of subgroup A ("untreated") were compared (fig, table).

In the subgroup A ("untreated"), at age onset of the disease and MR values were inversely and significantly related (\( r = -0.36, \ p < 0.02 \)). The only PM patient in the subgroup A was a male whose age of disease onset was 24 years. In the other patient in subgroup A with young onset (<40 years) symptoms began at age 33. In contrast, no correlation with age was found when analysing either subgroup B ("treated") or the whole series.

Clinical stage of the disease was not related to MR values in either the whole series or in subgroups A and B considered separately.

Discussion
The distribution of the oxidative polymorphism of DBQ in our patients with Parkinson’s disease did not differ from that found in the control group. Nevertheless, when analysing separately the distribution of MR of DBQ just in extensive metabolisers, we found a lower oxidative rate in EM patients than in EM controls.

Although mean age is lower in the control group than in patients, ageing does not reduce the oxidative rate of DBQ.14 Subgroup A ("untreated") includes both genuinely untreated patients and patients on treatment only with levodopa and/or bromocriptine, which do not interfere with the metabolism of DBQ.16 The distribution of MR values in EM patients of subgroup A is not different from that noticed in EM subjects of the control group (fig). However, when comparing the distribution of MR values between EM subjects of the group of patients treated with drugs capable of interfering with DBQ metabolism, a higher oxidative rate of DBQ was detected in patients. This reduction in the oxidative rate of DBQ in these “treated” Parkinsonian patients with the EM phenotype is probably due to the inhibitory effect that some drugs exert on the cytochrome P-450 db1.8,12 This finding agrees.
with those of Poirier et al.,\(^7\) that antihistamine drugs affected DBQ metabolism in their patients.

After excluding, as far as possible, confounding drug interactions, the main conclusion of our study is that oxidative rate of DBQ and age at onset of Parkinson's disease are inversely correlated. This result supports the theory that a high oxidative rate of DBQ might exert a protective effect against development of disease in predisposed people, by possibly providing a better means of inactivating some chemical(s), endogenous and/or exogenous, hypothetically involved in the neuronal damage that causes the disease.

MPTP (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a contaminant of "synthetic" heroin, can cause a clinical picture very similar to idiopathic Parkinson's disease and has been used to induce diverse experimental models of the illness. Its neurotoxic effect seems to be mediated by its metabolite MPP\(^+\),\(^24,25\) which is formed in situ in the brain by the action of the mitochondrial MAO.\(^26,27\) MPTP is also oxidised in the liver by the P-450 dlb isoform.\(^28\) In addition, the existence of P-450 cytochromes of families C and D in the rat brain has recently been shown.\(^29\) The fraction of MPTP that follows the P-450 cytochrome pathway escapes transformation to MPP\(^+\) and, assuming that the alternative metabolites are not neurotoxic, this enzymatic route should protect against the neurotoxic effects of MPTP. Cytochrome P-450 dlb shows polymorphic activity so that the degree of protection that it might provide should vary as a function of its genetic endowment.

In the environment there are substances structurally related to MPTP that might be involved in the cause of Parkinson's disease, such as some pesticides and herbicides.\(^30-32\) N-methyl derivatives of β-carbolines form a group of endogenous substances with some resemblance to MPTP and hypothetically related to the origin of Parkinson's disease.\(^33-37\) They also follow the P-450 dbl pathway.\(^10\)

The isozyme P-450 dlb represents only a small part of the whole oxidative capacity of the cytochrome P-450 system. Many other isozymes intervene in the metabolism of endo- and xenobiotics, and the rate of activity of some of these is also genetically determined. Data on the activity of these other isozymes in Parkinson's disease\(^38\) and in other neurological conditions with genetic and environmental causes\(^39\) are scanty. Nevertheless, their relative importance in the origin of many of such diseases should be fully investigated.

Addendum: Steventon et al.\(^40\) studied 66 patients with untreated idiopathic parkinsonism. They found no differences between cases and controls when comparing either the distribution of hydroxylator phenotype of DBQ or the distribution of MR values for DBQ. They concluded that “detoxification by P-450-dlb . . . appears to be irrelevant to the aetiology of PD”.

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