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Drug interactions with selegiline versus rasagiline

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ABSTRACT

In patients with Parkinson's disease (PD), long-term, successful use of a medication is not only determined by its efficacy, but also by its therapeutic safety and tolerability. This is especially relevant when two effective medications from the same class of active substances are available, in our case two monoamine oxidase B inhibitors (MAO-BI): Rasagiline and selegiline. The monitoring, collection, analysis and reporting of information for drug safety ("pharmacovigilance") are receiving increasing attention. Ever increasing demands are placed on the establishment of faster lines of communication between physicians, the pharmaceutical industry and the supervising authorities for reporting and investigating adverse events. Neglect or delay in the communication of serious side effects can also – even after introduction onto the market – entail immediate sanctions, extending to authorisation restrictions or revocation of the authorisation. Hence the broad application of budipine was considerably restricted due to its possible prolongation effect on the QT interval, cisapride was removed from the market and cabergoline and pergolide may only now be used as second-line dopamine agonists. It is not generally known to the physicians that adverse effects of a medication are frequently caused by interactions with other drugs. As a chronic progressive neurodegenerative illness, PD necessitates lifelong continual treatment with a highly complex combination of active substances. Adding to this are concomitant diseases requiring treatment and the generally advanced age of the patients. The main focus of the present work is to demonstrate possible drug interactions described in the literature when using rasagiline and selegiline, which could lead either to limitation in efficacy or to potential harm to the patient through an unforeseen alteration of efficacy. In addition, differences in the interaction potential of both MAO inhibitors are addressed.

Introduction

Since 2005, rasagiline, in addition to selegiline, is available as a further irreversible, selective inhibitor of monoamine oxidase B for therapy of Parkinson's disease (PD). The most important pharmacological difference between the two substances relate to their metabolism, which, in the case of oral selegiline but not in the case of rasagiline leads to the formation of amphetamine and metamphetamine. The principal metabolite of rasagiline is aminoindane, which – similar to rasagiline itself – shows neuroprotective effects in various experimental studies.

Monoamine oxidases (MAO) are mitochondrial enzymes that break down monoamines through oxidative deamination to the corresponding aldehydes, ammonia and hydrogen peroxide. They are localised in the outer mitochondrial membrane. Two MAO isoforms are distinguished according to their substrate preference and localization. MAO-A is found at high concentrations in the wall of the small intestine, in the liver as well as generally in peripheral catecholaminergic neurons. In the brain MAO-A is involved in the breakdown of dopamine, noradrenaline and serotonin. The dominant isoform in the brain with over 80%, is MAO-B, preferentially located in the basal ganglia and in the thalamus, followed by the cortex and cerebellum. Most of the MAO in platelets is also present as the MAO-B isoenzyme [1].

In the brain MAO-B is principally responsible for the breakdown of dopamine to 3,4-dihydroxyphenylacetic acid (DOPAC) as well as for the deamination of ß-phenylethylamine, a probable modulator of dopaminergic transmission [2]. Selective inhibition of MAO-B

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leads to an improvement in the Parkinson symptoms via an increase in the dopamine concentration in the synaptic cleft.

Selegiline

Pharmacodynamic properties of selegiline

Selegiline is an irreversible and, at low concentrations, selective inhibitor of monoamine oxidase B (MAO-B). At higher concentrations selegiline loses its selectivity. The approved dose of 10 mg per day should therefore not be exceeded. Selegiline increases the central bioavailability of dopamine via two mechanisms. First by inhibition of MAO-B, second by inhibiting presynaptic reuptake, although this effect is much less relevant. Selectivity for MAO-B leaves MAO-A functional and, in contrast to non-selective MAO inhibitors (A + B), no critical rise in blood pressure can occur after consuming food containing tyramine (''cheese effect''). Due to the irreversible enzyme binding there is no correlation between selegiline plasma levels and clinical efficacy. Complete attenuation of the selegiline effect depends on re-synthesis of the enzyme and takes several weeks [3]. Demethyl selegiline, L-amphetamine and L-metamphetamine are formed as the principal effective metabolites. Demethyl selegiline likewise irreversibly inhibits MAO-B, but with almost 60-fold less affinity. As, however, the plasma levels of demethyl selegiline are markedly higher after taking selegiline than those of the parent substance, an involvement of demethyl selegiline cannot be excluded in the inhibition of MAO-B activity through orally administered selegiline [4,5]. The remaining two metabolites (L-amphetamine and L-metamphetamine) are CNS stimulants that possibly contribute to the side-effect profile of selegiline [6].

Pharmacokinetics of selegiline

After oral administration selegiline is rapidly and almost completely absorbed. It is very lipophilic and therefore penetrates quickly tissues and the blood–brain-barrier. Therefore high concentrations are reached in the brain parenchyma. Maximum plasma concentrations are found after 30–50 min. Metabolism mainly occurs in the liver via the cytochrome-P-450 system (CYP), especially via the isoenzyme CYP2D6. Because of a high first-pass effect, bioavailability after oral application is less than 10%. Selegiline is excreted unmodified only in very small quantities via the kidneys. Elimination via the urine predominantly occurs after metabolisation in the form of its three principal metabolites, mentioned above, each with a half-life for elimination of about 15 h. As shown by positron emission tomography the half-life of cerebral MAO-B inhibition is about 40 days [3]. Inhibition of MAO-B in platelets is also irreversible but lasts only 10 days, due to the shorter half-life of platelets. Selegiline must not be used in patients with impaired liver or kidney function [7].

Rasagiline

Pharmacodynamics

Rasagiline mesilate is the R-enantiomer of N-propargyl-1-aminoindan [8] and a potent and highly selective inhibitor of MAO-B. Through selective inhibition of MAO-B rasagiline also increases extracellular dopamine levels [9]. In contrast to selegiline, rasagiline is not metabolised to amphetamine derivatives. The main metabolite is aminoindan. Amphetamine-associated side effects or interactions are therefore not expected under rasagiline.

Pharmacokinetics

Rasagiline is rapidly absorbed and reaches its maximum plasma concentration (C_{max}) approx. 30 min following oral administration. It passes the blood–brain-barrier. Absolute bioavailability is higher than with selegiline and amounts to about 36%. This likewise points towards first-pass metabolism, however, to a lesser extent compared to selegiline. As with selegiline, rasagiline is metabolised in the liver primarily via cytochrome-P-450-mediated processes. The isoenzyme primarily involved is CYP1A2.

Excretion of metabolites occurs to 63% via the urine and to 22% in the faeces; less than 1% of oral rasagiline are eliminated unchanged via the kidneys. The terminal half-life of rasagiline in the plasma equals 0.6–2 h, of aminoindan approx. 11 h. The half-life period for inhibition of the cerebral enzymes is around 40 days [10]. Due to the irreversible inhibition of MAO-B there however exists no correlation between the pharmacokinetic and pharmacodynamic half-life. Administration of rasagiline is contraindicated in patients with severe hepatic and renal insufficiency. Therapy should be interrupted if mild hepatic insufficiency progresses to a moderate form, as breakdown is severely delayed under these conditions. Mild or moderate renal function disorders do not significantly influence the pharmacokinetics of rasagiline. Dose adaptation of rasagiline is, in contrast to selegiline, not necessary in these patients.

Comparison of rasagiline and selegiline

The comparative pharmacokinetic properties of rasagiline and selegiline are listed in Table 1.

Pharmacokinetic interactions

Absorption and bioavailability

When given simultaneously, food constituents can reduce or completely inhibit absorption of drugs. Hence polyvalent cations can lead to restricted absorption of levodopa, carbidopa or COMT-inhibitors, which, as catechol structures, chelate e.g. iron [12]. There are no such limitations for selegiline or rasagiline. Concerning simultaneous intake with food, increased bioavailability is described for selegiline and consumption during or after a meal is recommended. In contrast to this, rasagiline can be taken at or irrespective of mealtimes [11].

Metabolisation via the cytochrome P450 enzyme

Both selegiline and rasagiline are metabolised via the cytochrome P450 enzyme (CYP) and consequently both drugs are subject to potential pharmacokinetic interactions through enzyme inhibitors or inducers.

The isoenzyme mainly involved in the metabolism of rasagiline is CYP1A2. CYP 1A2-inhibitors (fluvoxamine, ciprofloxacin) increase the area under the curve for rasagiline [13]. The dose of rasagiline should be adapted during treatment with ciprofloxacin. For this reason, co-medication with fluvoxamine should absolutely be avoided and is considered contraindicated. Omeprazole and smoking are strong inducers of CYP 1A2. Among other aspects they lead to a reduction in the plasma levels of rasagiline [14]. Heavy smokers should therefore not be treated with rasagiline, if PPI therapy is necessary, pantoprazole should be selected.

Selegiline is a substrate of CYP 2D6. Through combination with a strong 2D6 inhibitor there exists the risk of undesired elevations in plasma levels. Important 2D6 inhibitors are fluoxetine, paroxetine, quinidine, sertraline and haloperidol. Genetic differences for