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Tolcapone-Related Liver Dysfunction
Implications for Use in Parkinson's Disease Therapy

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Contents

Abstract

Levodopa is the cornerstone of idiopathic Parkinson's disease (PD) treatment. However, after long-term use of levodopa, a significant percentage of patients experience motor fluctuations, which worsen their quality of life. Catechol-*O*-methyltransferase (COMT) inhibitors reduce levodopa metabolism and enhance the respective plasma levels, resulting in improvements in symptoms and overall quality of life.

Tolcapone was the first drug of this class to be marketed, but was withdrawn in the European Union due to its implication in the deaths of three PD patients due to hepatic failure. Three deaths from fulminant hepatic failure in 40 000 patient-years is a number that is 10–100 times higher than the expected incidence in the general population and, according to the manufacturer's own information, the number is probably underestimated due to under-reporting of cases.

In the US, tolcapone was not withdrawn, but restrictive liver enzyme monitoring measures were issued by authorities, which severely limited its use. No further deaths from hepatic failure were reported since these measures were implemented.

The mechanisms by which tolcapone may induce liver toxicity are still under debate. It was thought that mitochondrial uncoupling of oxidative phosphorylation by tolcapone, and consequent impairment of energy production by hepatocytes, could be responsible for the observed effects.

Some experts consider that the restrictive guidelines issued in the US regarding tolcapone use may be loosened with no consequential reductions in safety. It was suggested that ongoing clinical information about safety should be considered and periodical revisions of the restrictions made accordingly. The identification of the molecular and biochemical basis of tolcapone hepatotoxicity, when completed, should also provide important indications for the clinical use of this drug.

In conclusion, appropriate monitoring of liver function can ensure adequate safety in PD patients receiving tolcapone, who can therefore benefit from the symptomatic improvements obtained with this drug.

Idiopathic Parkinson's disease (PD) is an age-related disorder characterised by a progressive neurodegeneration, resulting in significant motor impairment. Levodopa is the main treatment for the symptoms, resulting in improvements in both the quality and duration of life. Nevertheless, long-term use of levodopa may cause motor complications. This problem, which results in a significant degradation of a patient's quality of life, has received a lot of attention by several research groups, resulting in the research and development of new mechanisms by which to treat PD, such as the inhibition of catechol-*O*-methyltransferase (COMT) activity. Research regarding this mechanism has resulted in the development and introduction to the market of two COMT inhibitors, tolcapone first and then entacapone.[1]

Tolcapone is a potent, selective, reversible and tight-binding inhibitor of COMT.[2-4] The rationale for the use of COMT inhibitors in the adjunctive treatment of PD is based on the fact that by inhibiting levodopa *O*-methylation, its half-life will be increased and the formation of the respective metabolite, 3-*O*-methyldopa will be reduced. This metabolite is the main product of levodopa biotransformation when aromatic-L-aminoacid decarboxylase (AADC) is inhibited, as it is often the case in PD patients. 3-*O*-Methyldopa has a half-life that is far longer (15 hours) than that of levodopa (1 hour).[5] This characteristic, together with the competition between levodopa and 3-*O*-methyldopa for the blood-brain barrier saturable carrier,[6,7] is thought to lead to fluctuations in clinical response, known as the wearing-off phenomenon.[8]

Tolcapone administration in PD patients who were taking the usual dose of levodopa/AADC inhibitor resulted in improvements in clinical parameters, such as increases in the duration of 'on' time, decreases in the duration of 'off' time, reductions of levodopa dose and improvements in patients' overall quality of life.[9-12] Despite such improvements, tolcapone has been associated with hepatotoxicity.[13]

This review addresses the hepatotoxicity problems encountered with the clinical use of tolcapone, and the implications for its use in PD. Literature searches were made electronically via the Internet, using Medline, Current Contents and Ingenta databases (keywords: tolcapone, Parkinson's disease, COMT, hepatotoxicity, mitochondria uncoupling).

1. Tolcapone-Induced Liver Toxicity

Toxicity problems with tolcapone became apparent soon after its introduction to the market.[14] Indeed, three patients taking tolcapone died of hepatic failure, which was attributed to the use of the drug[15,16] and resulted in the suspension of tolcapone in the EU[17] and a black box warning in the US. Three deaths from fulminant hepatic failure in 40 000 patient-years is a number that is 10–100 times higher than the expected incidence in the general population and, according to the manufacturer's own information,[18] the number is probably underestimated due to under-reporting of cases.

In preclinical testing conducted prior to the registration of tolcapone, there was no evidence of liver toxicity with tolcapone. However, phase III clinical trials showed that increases in serum alanine aminotransferase (ALT) were three times higher than the upper limit of normal (ULN) in 1% of patients taking 100mg three times daily and 3% in patients taking 200mg three times daily (compared with placebo).[13] ALT is considered as a marker of the turnover of liver cells. Therefore, a high plasma ALT level indicates an increased rate of hepatocyte death, an index of hepatocellular toxicity (see review by Watkins[13]). According to Watkins,[13] the 3-fold increase above the ULN compared with placebo represents the point where such an increase should be considered clinically significant. For this reason, and taking into account that in the same clinical trials some patients reached serum ALT levels that were eight times above the ULN, it was recommended that routine ALT monitoring (every 4 weeks in the first 3 months of treatment and every 6 weeks during the next 3 months; see section 3) should be performed for patients taking tolcapone.[19]

The important issue of the biochemical and physiopathological mechanisms of tolcapone liver toxicity is still under debate. The reports from the first patient who died with tolcapone-related fulminant hepatic failure showed that this patient had alterations of hepatocyte mitochondria, such as mitochondrial swelling, loss of cristae and reduction in the matrix density,[15,20] which are typical of fulminant hepatic failure of any cause. On the other hand, the observed increase in mitochondrial density could not be ascribed to fulminant hepatic failure alone. In an earlier paper by Nissinen and coworkers[21] it was shown that tolcapone was capable of uncoupling oxidative phosphorylation at pharmacologically relevant concentrations in mitochondrial preparations, cell cultures and isolated hearts. It was mentioned that tolcapone showed an uncoupling activity that was five times higher than that of 2,4-dinitrophenol, a compound that was used in the 1930s for weight reduction and was discontinued because of serious adverse effects. These authors also indicated that this characteristic of tolcapone (which was not shared by entacapone) could represent a problem for the normal function of the heart, brain, kidney or gastrointestinal tract, but did not mention any potential for liver toxicity.

A recent experimental toxicological study[22] confirmed the ability of tolcapone to induce rat liver toxicity in doses that yielded a plasma area under the curve (AUC) that was 14 times higher than that observed in humans for the tolcapone 200mg three times daily dose. Entacapone showed no hepatotoxicity for the doses studied (plasma AUC up to 21 times higher than that observed in humans for the 10 × 200 mg/day dose).

The hepatotoxic differences between tolcapone and entacapone are thought to be related to the higher lipid solubility of tolcapone, which facilitates its penetration in mitochondrial inner membrane,[21] and to the higher affinity of entacapone for glucuronidation, the main metabolising pathway in humans.[23] It is not possible, at this point, to determine whether the effects of tolcapone are a class effect or are due to the compound itself.

2. Implications for Use in Parkinson's Disease

As stated in section 1, soon after its introduction to the market, tolcapone was withdrawn from European market. However, in the US the drug is still available, but submitted to very strict regulations issued by the US FDA and the manufacturer, Roche,[18,24] which include:

- the only patients eligible to receive tolcapone are those with motor fluctuations who do not respond to, or are not candidates for, other adjunctive therapies;
- liver enzymes (ALT and aspartate aminotransferase [AST]) must be tested every 2 weeks for the first year, and every 4 weeks for the next 6 months and every 8 weeks thereafter;
- tolcapone therapy should be immediately withdrawn if one of the enzymes' values is above the ULN.

While no further cases of fulminant hepatic failure have been reported since these measures were issued, these regulations have seriously limited the use of tolcapone in PD patients. That is, the number of patients who can receive the drug has been reduced. There is also the possibility that physicians may be deterred from prescribing tolcapone.

A panel of 16 experts, supported by Roche,[25] was formed to assess the problem that the use of tolcapone in PD patients is limited. They concluded, based on literature data, that the above measures are unnecessarily restrictive. It was suggested that an equivalent security level could be obtained with a less demanding enzyme monitoring schedule after the first 6 months, because all deaths occurred within this period, among other reasons. The panel also suggested that the limit of ALT and AST levels should be raised to 2–3 times the ULN, as an indication for the drug to be withdrawn.

As a general practical conclusion, this group of experts recommended that the guidelines should receive periodical reviewing, based on ongoing safety data, and suggested that adequate safety can be obtained with a less demanding blood analysis programme after 6 months of initiating therapy. This

may allow for more patients to benefit from tolcapone, with few adverse effects.

It is noteworthy that none of the three patients who died from hepatic failure associated with tolcapone were regularly monitored (as recommended at the time), and that no cases of hepatic failure were reported in patients submitted to the liver enzyme monitoring scheme recommended in the drug's labelling.[13] Therefore, if tolcapone is available, the proposed liver enzyme monitoring schedule provides adequate safety for PD patients who may benefit from the drug. It is possible in the future that a less restrictive scheme can be adopted, if ongoing clinical safety information provides strong evidence to do so.

The other COMT inhibitor, entacapone, can be an alternative for these patients with fluctuating disease, if available. No reports of hepatic toxicity related to entacapone are found in the literature, the drug has an adequate level of safety and its use does not require liver monitoring.[26] The clinician should bear in mind, though, that the efficacy of entacapone seems to be less than that of tolcapone.[27,28] Indeed, in a comprehensive review[29] of available clinical trials[30,31] the authors concluded that the effect of entacapone therapy (increase in 'on' and decrease in 'off' periods, overall ratings of quality of life and Unified Parkinson's Disease Rating Scale scores) is modest.

The suggested antidepressant activity of tolcapone may, if confirmed, yield additional benefits for a significant percentage (40–50%) of PD patients who also have depression.[11]

The identification of the molecular and biochemical basis of tolcapone hepatotoxicity, when completed, should provide important indications for the clinical use of this drug.

3. Conclusions

The inhibition of COMT by nitrocatechol derivatives provides significant improvements in PD patients, reducing the well-known deleterious effects of long-term levodopa therapy. Introduction of the first compound of this class, tolcapone, was soon followed by safety problems. These problems, which resulted in three patient deaths, were attributed to liver toxicity of the drug. The biochemical mechanisms responsible for this effect are thought to be related to uncoupling of liver mitochondrial oxidative phosphorylation. In the countries where the drug is still available, very strict regulations regarding criteria for admission and liver enzymes monitoring have seriously reduced the number of PD patients treated with tolcapone. It is concluded that a complete understanding of the mechanisms underlying tolcapone hepatotoxicity is necessary in order to establish its validity in PD treatment. In the meantime, some authors, based in current data, suggest a less restrictive blood analysis programme, which will allow more patients to benefit from the symptomatic improvements yielded by tolcapone.

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