Tolcapone

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Summary

• Tolcapone is an orally active specific inhibitor of peripheral catechol-O-methyltransferase (COMT), which has therapeutic potential as an adjunct to levodopa in the treatment of patients with Parkinson’s disease.

• Accumulation of 3-O-methyldopa, the inactive metabolite of levodopa formed by COMT, has been associated with reduced transport of levodopa into the brain and also with the ‘wearing-off’ phenomenon.

• Plasma levodopa concentrations are increased, and 3-O-methyldopa concentrations are decreased, when tolcapone is coadministered with levodopa/carbidopa, levodopa/benserazide or levodopa alone.

• Coadministration of tolcapone and levodopa (in most instances plus benserazide or carbidopa) increased the duration of ‘on’ time in patients with Parkinson’s disease.

• Tolcapone allowed the dose and frequency of administration of levodopa (alone or with carbidopa) to be reduced.

• Preclinical studies indicate that tolcapone may have antidepressant activity.

• Tolcapone was generally well tolerated, with few reported adverse events.
The dopamine precursor levodopa is the usual symptomatic treatment for patients with Parkinson's disease. Levodopa is predominantly metabolised in the periphery by aromatic L-amino acid decarboxylase (AADC) to dopamine, which can cause such adverse effects as emesis, orthostatic hypotension and cardiac arrhythmia. Therefore, levodopa is usually administered with a peripheral AADC inhibitor (carbidopa or benserazide). When given with such inhibitors, only a small proportion of an oral dose of levodopa reaches the brain unchanged, very little dopamine is formed in the periphery and much of the drug undergoes \( \text{O}- \) methylation. \( \text{3-O-methyldopa} \) has a long half-life (about 15 hours compared with about 1 hour for levodopa) so this metabolite can accumulate during long term levodopa therapy.

The long term use of levodopa is complicated by the development of the "wearing-off" phenomenon (motor fluctuations during levodopa therapy). Accumulation of \( \text{3-O-methyldopa} \) has been implicated in the development of the "wearing-off" phenomenon. In addition, \( \text{3-O-methyldopa} \) may compete with levodopa for transport across the blood-brain barrier, as both agents use the same saturable carrier system. This may explain how \( \text{3-O-methyldopa} \) attenuates the effects of levodopa.

Catechol-\( \text{O}- \)methyltransferase (COMT) is one of the main enzymes responsible for the central and peripheral metabolism of catecholamines (e.g. dopamine, noradrenaline and adrenaline) and levodopa. Agents which inhibit this enzyme, usually in the gastrointestinal mucosa, reduce the degradation of levodopa to \( \text{3-O-methyldopa} \). However, the metabolic capacity of COMT in peripheral tissue is high, so only minor general COMT inhibition can be achieved, reducing the likelihood of adverse events with COMT inhibitors.

1. Pharmacodynamic Profile

- Tolcapone, and its oxidated metabolites RO 471868 and RO 471669, had a strong inhibitory effect on COMT from rat liver \textit{in vitro} [concentrations producing 50% inhibition of activity (IC\textsubscript{50}) were 36, 77 and 39 nmol/L, respectively] and \textit{ex vivo}. In contrast, the metabolite \( \text{3-O-methyl-tolcapone} \) did not have an inhibitory effect on COMT.

- Tolcapone 30 mg/kg did not alter basal dopamine levels in the striatum of rats, but 3,4-dihydroxyphenylacetic acid (DOPAC) levels were significantly increased (by 89%) and homovanillic acid (HVA) levels and 3-methoxytyramine levels were significantly reduced (by \( \geq 89\% \)), indicating central inhibition of COMT. Striatal levels of \( \text{S-adenosyl-L-methionine} \) (SAM) [a cofactor of the COMT transmethylation process] were also significantly increased by oral tolcapone at doses of 3 or 30 mg/kg.

- Tolcapone 30 mg/kg increased striatal concentrations of levodopa (by \( 51\% \)) and dopamine (by \( 117\% \)), and increased DOPAC (by \( 55\% \)) and decreased HVA (by \( 74\% \)) formation, compared with controls (levodopa only), when administered to rats before a bolus dose of levodopa. Concentrations were measured \textit{in vivo} microdialysis techniques. Similar significant changes in striatal area under the concentration-time curve (AUC) values for these substances, in addition to a \( 73\% \) decrease in the AUC of 3-methoxytyramine and apparent complete blockage of \( \text{3-O-methyldopa} \) formation, compared with controls, were observed when the same dose of tolcapone was given with levodopa/benserazide. Thus, striatal levodopa concentrations were increased because of decreased central and peripheral methylation and possibly decreased competition (from \( \text{3-O-methyldopa} \)) for transport into the brain. Tolcapone 30 mg/kg also attenuated the decrease in SAM induced by levodopa/benserazide alone.

- In contrast with the dose-dependent peripheral and central inhibition of COMT activity seen with tolcapone, entacapone, another COMT inhibitor, acted only peripherally in rats. Tolcapone was