Terazosin for Parkinson’s?

A recent article in Journal of Clinical Investigation included a comprehensive assessment of the potential for Terazosin (TZ) as a neuroprotective drug in PD, by exploring its effects across a range of in vivo and in vitro models and exploring epidemiological associations in prospective PD databases. TZ is licensed for the treatment of Benign Prostatic Hyperplasia (BPH) and for hypertension. Its beneficial actions in these conditions are mediated through its blockade of alpha 1 adrenergic receptors. This article follows an earlier study which identified that, in addition to alpha 1 receptor blockade, TZ has an action on phosphoglycerate kinase 1 (PGK1) activity, thus increasing the product of glycolysis, i.e. pyruvate. This has downstream consequences at increasing oxidative phosphorylation, mitochondrial activity levels and ATP levels all of which may have direct implications for the pathophysiological processes of PD.

More specifically, the article describes strongly positive effects of TZ in the MPTP mouse model, the 6-hydroxy dopamine (6OH-DA) rat model, fly models with Pink1 mutations or LRRK2 mutations, as well as in inducible pluripotent stem cells taken from a PD patient with a LRRK2 G2019S mutation. The authors demonstrated rescue of dopaminergic cells and phenotype even when TZ was administered 7 days after MPTP in mice, or 2-5 weeks after 6OH-DA in rats.

To add weight to the putative mechanism of action, they showed in a rotenone fly model of PD that TZ protected flies, enhanced ATP levels and that these protective effects depended upon intact PGK1 activity. By also showing the relevance of this mechanism for flies with Pink1 mutations, LRRK2 mutations and flies over-expressing alpha synuclein, the authors have shown the potential applicability of PGK1 activation to a broad range of pathophysiological processes that all present as PD, both clinically and pathologically. In the model which most accurately represents the human condition, they took iPS cells from PD patients with the LRRK2 G2019S mutation, and differentiated them into dopaminergic cells, finding that TZ reduced the rate of alpha synuclein accumulation in these cells.

The PPMI cohort includes detailed prospectively collected information from patients with early stages of PD. Within this cohort, 7 people used TZ. Their rate of progression was 0.01 UPDRS points per year in comparison to 0.54 points per year in a comparable control sample of 269 individuals. Patients treated with tamsulosin, an alpha blocker that lacks any effect on PGK1 had no significant advantage in terms of their rate of disease progression. Inclusion of patients treated with other alpha 1 antagonists, Doxazosin (DZ) and Alfuzosin (AZ), (which, unlike Tamsulosin, have the same crystal structure that might enhance PGK1 activity) revealed the rate of PD progression was also only 0.02 points per year in this group.

In a separate database, they looked at problems and complication rates that occurred among people with PD finding that overall, there were fewer hospital visits, nonmotor symptoms, admissions and motor complications among those patients taking TZ/AZ/DZ compared with PD patients using Tamsulosin. Furthermore, among patients without a diagnosis of PD taking TZ/AZ/DZ, 0.15% of them developed PD over a 9-month period compared with 0.25% of individuals taking Tamsulosin. Inevitably, the breadth of these data and the consequent
publicity surrounding the publication has an immediate impact on people currently desperately seeking an intervention to slow down their PD.

*Can I have a prescription for TZ please?*

With the current state of knowledge, TZ should not yet be recommended for use in PD for the following reasons. Firstly, there are a large number of agents that have previously been effective in the animal models of PD but have subsequently failed to translate when tested in the clinic. Furthermore, patients with PD frequently suffer from a degree of autonomic dysfunction which can lead to postural hypotension. There is therefore a potential downside from the hypotensive effects of TZ, which could aggravate falls and cognitive dysfunction in vulnerable PD patients.

It is also worth pausing for a moment to consider alternative explanations for the epidemiological data. The relative safety and tolerability of Tamsulosin verses TZ may influence how many individuals continue use of these drugs and in turn (consciously or unconsciously) the prescribing habits of clinicians. For example, if TZ has an increased side effect profile, then only the more robust patients will continue on it. Indeed, in a systematic review Tamsulosin was found to be better tolerated in terms of dizziness, hypotension and dry mouth than TZ3. Therefore, it has to be acknowledged that there is potential for a bias in prescribing habits that may contribute to the epidemiological associations reported.

*Where to from here?*

It should be easy for independent teams to investigate whether the reported effects of TZ on the glycolytic pathway are reproducible and to compare the relative efficacy and brain penetration of TZ, DZ and AZ. There are also a large number of other well studied cohorts that could be usefully explored, (in a similar fashion to the studies published following the suggestion that the Beta 2 agonists might potentially have neuroprotective properties)4-6 Beyond this, it is pleasing to note that the authors of this article have already set up a safety and tolerability trial of 20 people to take 5mg of TZ or placebo in University of Iowa. (ClinicalTrials.gov Identifier: NCT03905811).

Assuming that this 12-week trial confirms that the drug has acceptable tolerability in PD, the next step will be planning an efficacy trial. The authors speculate that the putative increase in ATP associated with TZ may push the equilibrium of aggregated vs soluble alpha synuclein in a beneficial direction or may have an anti-apoptotic effect. If so, then this intervention may have relevance for the broader population of PD patients rather than just the “mitochondrial” subgroup of patients. In summary, TZ has certainly suddenly leapt into a growing pool of drugs that have a repurposed role in PD, such as Exenatide, Salbutamol, UDCA, Nilotinib, Deferiprone and Ambroxol7. Clever approaches to multi-arm neuroprotective trials may increase the efficiency with which we can detect useful verses futile agents. This is at the core of the Linked Clinical Trials Initiative in PD8.

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