Toxicological evaluation of new tacrine analogues from 4-Amino-1*H*-pyrrole-3-carbonitrile

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Tacrine is a reversible inhibitor of cholinesterase activity prescribed for symptomatic treatment of Alzheimer's disease. Therapy with tacrine requires dose escalation and liver test monitoring[1] since it can induce a reversible liver toxicity, limiting their therapeutic use. Tacrine hepatotoxicity was also demonstrated in rat liver, reinforcing the belief that it is a direct toxicity rather than immunoallergy [2]. Despite the liver toxicity associated with treatment with tacrine, new compounds have been synthesized based on the tacrine, with the objective of obtaining more selective molecules and therefore less cytotoxic.

The present work was aimed at studying the effect of two new tacrine analogues, acethylcholinesterase inhibitors synthesized from 4-amino-1H-pyrrole-3-carbonitrile, in comparison with tacrine, to evaluate the in vivo effect on liver and mitochondrial functionality of Wistar rats. We have previously showed the molecular mechanism underlying the impact on brain activity of tacrine and of these two novel tacrine analogues [3]. The evaluation of liver and kidney biomarkers shows that, contrarily to tacrine, the novel compounds (T1 and T2) were not toxic. Mitochondrial bioenergetics was significantly affected by tacrine, but T1 and T2 compounds did not induce any negative effect when used at the same concentration as tacrine. Using the comet assay we found that tacrine induce significant DNA damage in rat hepatocytes. Comet assay with cells digested in the presence of FPG enzyme shows that the DNA strand breaks were due oxidative processes. Tacrine significantly decrease calcium load capacity of mitochondria but T1 and T2 compounds does not show any significant effect on mitochondrial calcium load capacity. Our results clearly demonstrate that the two novel tacrine analogues were much less hepatotoxic and nephrotoxic than tacrine. The negative effect promoted by tacrine in mitochondrial bioenergetics was not observed with these two new compounds. From our results we can conclude that the novel compounds show no toxicological problems like tacrine, and therefore their pharmacological use could have benefits over tacrine.

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References

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