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ZEBRAFISH PROVIDES A PREDICTIVE MODEL FOR IDENTIFICATION OF DRUGS PROVIDING NEUROPROTECTION IN HUMAN SEVERE ACUTE ORGANOPHOSPHORUS POISONING

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Acute organophosphorus poisoning (OPP) has become a worldwide clinical and public health problem, with an estimation of around 3 million cases and 300,000 deaths annually. Along with acetilcholinesterase (AChE) inhibition, neurodegeneration and brain damage is one of the hallmarks of severe OPP. Recently, we have generated a zebrafish severe model for human OPP using the prototypic organophosphorus (OP) compound, chlorpyrifos-oxon (CPO). This model was characterized by a compacted head, with areas of opacification indicating necrosis of the brain. Further investigation revealed mechanistic similarities in the pathophysiological processes behind human severe OPP as in AChE inhibition, activation of the NMDA-receptor, inflammatory and immune responses and calcium dysregulation. The purpose of this study was to assess the suitability of the developed chemical zebrafish model for severe OPP to be used in the identification of new molecules providing neuroprotection in human severe OPP. Considering this, we tested prophylactic and treatment properties of standard human OPP treatment drugs (atropine and pralidoxime), reversible AChE inhibitors (huperzine-A, galantamine, physiostigmine and pyridostigmine) and molecules modulating pathways involved in human OPP, such as NMDA-receptor antagonists (MK-801, memantine), dual-functional NMDA-receptor and acetylcholine receptor (AChR) antagonists (caramiphen, benactyzine) and anti-inflammatory drugs (dexamethasone, ibuprofen). The effect on the 24 h survival and the prevalence of “abnormal” heads was determined for all the compounds. Moreover, effectiveness of the countermeasures was further confirmed by histopathological analysis and by the quantification of gene expression levels of four selected genes (*opn1mw1*, *il-12*, *hspb11*, *pth1a*) potentially involved in the severe OPP pathogenesis. Our results demonstrate that the zebrafish model for severe OPP provides reasonable accurate evaluations of the neuroprotective effect offered by these drugs that are well characterized in mammalian models.

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