Assessment of neuromuscular dysfunction during poisoning by organophosphorus compounds.

Abstract:
Dysfunction of respiratory muscles is a life-threatening complication in poisoning by organophosphorus compounds (OPs). It is both of central and peripheral origin due to impaired cholinergic signalling upon inhibition of acetylcholinesterase (AChE). The dysfunction at neuromuscular synapses is not amenable to anticholinergics and remains a therapeutic challenge. Thus, a clear understanding of the distinct mechanisms occurring at neuromuscular synapses is decisive for the development and improvement of therapeutic strategies, particularly with nerve agent poisoning, where clinical studies are prevented by ethical considerations. Using red blood cell AChE, the kinetics of OP induced inhibition, aging, and spontaneous and oxime-induced reactivation have been elucidated. In a dynamically working in vitro model with real-time determination of membrane-bound AChE, it was shown that the kinetic constants derived from erythrocyte AChE are comparable to muscle AChE in a given species. To assess, whether kinetic considerations of AChE activity are relevant for the neuromuscular function, organotypic spinal cord-skeletal muscle cocultures have been established. In this model neostigmine and VX affected neuromuscular transmission as anticipated from their known actions on AChE. Also oxime-induced restoration of the neuromuscular transmission was observed. These
findings were confirmed by functional studies on diaphragm muscles of various species with
determination of muscle force generation upon phrenic nerve or indirect electrical field stimulation
techniques. Investigations with human intercostal muscles are in progress to assess the conditions in
human tissue. The results obtained with paraoxon favourably correlate with data from clinical findings
of parathion-poisoned patients where the correlation of neuromuscular transmission with the activity
of erythrocyte AChE could be established. In conclusion, a variety of methods are available to follow
the microscopic reactions occurring at the synaptic level. Due to the lack of clinical data with different
OPs, e.g. nerve agents, well designed animal experiments, reflecting the human situation as close as
possible, are indispensable for the development of new drugs against the deleterious OP effects.