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EFFECT OF THE PHOSPHOLIPASE A2 INHIBITOR VARESPLADIB, AND ITS SYNERGISM WITH CROTALIC ANTIVENOM, ON THE NEUROMUSCULAR BLOCKADE INDUCED BY CROTALUS DURISSUS TERRIFICUS VENOM (WITH AND WITHOUT CROTAMINE) IN MOUSE NEUROMUSCULAR PREPARATIONS 67

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The venom of the South American rattlesnake *Crotalus durissus terrificus* causes an irreversible neuromuscular blockade in isolated preparations due to action of the presynaptically-acting heterodimeric phospholipase A2 (PLA2) crotoxin. Some populations of this subspecies contain, in addition to crotoxin, the toxin crotamine, which acts directly on muscle fibers. In this study we used *C. d. terrificus* venoms with (crot+) or without (crot-) crotamine to test whether Varespladib, a PLA2 inhibitor, is able to abrogate the neuromuscular blockade induced by these venoms comparatively with crotalic antivenom. Mouse phrenic nerve-diaphragm preparations were exposed to venoms previously incubated with two different concentrations of Varespladib or antivenom, or with a mixture of these two agents, before addition to the bath. In another experimental setting, venoms were initially added to the system, followed by the addition of Varespladib or antivenom 10, 30, or 60 min after venom. This study was approved by an institutional Committee for Ethics in Animal Use (CEUA/UNOESTE, Protocol No. 6919/2021). At the highest concentrations tested, Varespladib and antivenom inhibited the action of the venom > 80% and > 70%, respectively. With lower concentrations the inhibition of neuromuscular blockade decreased, but when low doses of the two agents were incubated together with the venom, the inhibitory effect improved, underscoring a synergistic phenomenon. When added after venom, Varespladib was able to halt the progression of the neuromuscular blockade even when added at 60 min. Antivenom, in contrast, exhibited a lower ability to inhibit the toxic effect of the venoms in these conditions. In conclusion, the PLA2 inhibitor Varespladib is highly effective at abrogating the neuromuscular blocking activity of crotamine-positive and crotamine-negative *C. d. terrificus* venoms and seems to act synergistically with antivenom. Órgão de fomento financiador da pesquisa: UNOESTE E UNISO Protocolo CEUA: 6919.