A single injection of botulinum toxin decreases the margin of safety of neurotransmission at local and distant sites.

Abstract: We tested the hypothesis that a single injection of botulinum toxin not only has local, but also distant effects on muscle function, biochemistry, and pharmacodynamics of atracurium. Botulinum toxin (2.5 U) was injected into the tibialis muscle of anesthetized rats (n = 26). The contralateral side with no injection served to study distant effects. Control animals (n = 25) received a saline injection. Neuromuscular function, pharmacology, and expression of acetylcholine receptors (nAChRs) were evaluated in the tibialis at 0, 4, and 16 days after injection and in comparison with saline-injected controls. On day 4, botulinum toxin caused complete paralysis of the tibialis, while its contralateral side showed a decrease in absolute twitch tension (1.8 N [1.6; 1.9] vs 3.0 N [2.8; 3.1], Newton, P< 0.05). On day 16, muscle weakness was only present on the toxin-injected side where absolute twitch tension was decreased (0.6 N [0.6, 0.7] vs 3.4 N [3.1, 3.7], P< 0.05). Tibialis mass was decreased on the toxin-injected side at day 4 (1.46 mg/g [1.43, 1.48] vs 1.74 mg/g [1.72; 1.75], P< 0.05) and on day 16 (0.78 mg/g [0.76, 0.79] vs 1.73 mg/g [1.69; 1.77], P< 0.05). Effects distant from the site of injection were seen on day 16, when muscle atrophy was also present in the adjacent gastrocnemius and soleus muscles. Normalized to tibialis mass, specific twitch tension (tension/g muscle) was reduced on the contralateral side at day 4 and on
the toxin-injected side at day 16 in relation to saline controls. At day 16, an increased sensitivity to atracurium was seen on the toxin-injected side, evidenced as a decreased ED(50) (0.23 mg/kg [0.13, 0.33] vs 0.72 mg/kg [0.63, 0.82], P< 0.05) and a lower infusion rate (38 ?L/kg/min [32, 43] vs135 ?L/kg/min [126, 144], P< 0.05), together with a reduced plasma concentration requirement of atracurium (0.5 ?g/mL [0.4, 0.7] vs 4.5 ?g/mL [3.8, 5.2], P< 0.05) to achieve a steady state 50% reduction in baseline (absolute) twitch tension. ED(50) of atracurium was also decreased on the contralateral side at day 16 in relation to saline controls. The nAChRs in the tibialis were increased on the toxin-injected side to 123 fmol/mg [115, 131] vs 28 fmol/mg [25, 29] (P< 0.05) in time-matched saline-injected controls at day 4 and to 378 [341, 413] vs 27 fmol/mg [25, 29] (P< 0.05) at day 16. Botulinum toxin has local and distant effects on muscle. The decrease in specific twitch tension indicates that the muscle atrophy alone cannot explain the functional changes; neuromuscular transmission is also impaired. An increased sensitivity to atracurium on the toxin-injected side, despite up-regulation of nAChRs, seems unique to botulinum toxin.

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