Prolonged administration of pyridostigmine impairs neuromuscular function with and without down-regulation of acetylcholine receptors.

Abstract:

The acetylcholinesterase inhibitor, pyridostigmine, is prophylactically administered to mitigate the toxic effects of nerve gas poisoning. The authors tested the hypothesis that prolonged pyridostigmine administration can lead to neuromuscular dysfunction and even down-regulation of acetylcholine receptors. Pyridostigmine (5 or 25 mg·kg·day) or saline was continuously administered via osmotic pumps to rats, and infused for either 14 or 28 days until the day of neuromuscular assessment (at day 14 or 28), or discontinued 24 h before neuromuscular assessment. Neurotransmission and muscle function were examined by single-twitch, train-of-four stimulation and 100-Hz tetanic stimulation. Sensitivity to atracurium and acetylcholine receptor number (quantitated by I-?-bungarotoxin) provided additional measures of neuromuscular integrity. Specific tetanic tensions (Newton [N]/muscle weight [g]) were significantly (P< 0.05) decreased at 14 (10.3 N/g) and 28 (11.1 N/g) days of 25 mg·kg·day pyridostigmine compared with controls (13.1-13.6 N/g). Decreased effective dose (0.81-1.05 vs. 0.16-0.45 mg/kg; P< 0.05) and decreased plasma concentration (3.02-3.27 vs. 0.45-1.37 ?g/ml; P< 0.05) of atracurium for 50% paralysis (controls vs. 25 mg·kg·day pyridostigmine, respectively).
irrespective of discontinuation of pyridostigmine, confirmed the pyridostigmine-induced altered neurotransmission. Pyridostigmine (25 mg·kg·day) down-regulated acetylcholine receptors at 28 days. Prolonged administration of pyridostigmine (25 mg·kg·day) leads to neuromuscular impairment, which can persist even when pyridostigmine is discontinued 24 h before assessment of neuromuscular function. Pyridostigmine has the potential to down-regulate acetylcholine receptors, but induces neuromuscular dysfunction even in the absence of receptor changes.