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Non-linear dose-response of aluminium hydroxide adjuvant particles: Selective low dose neurotoxicity

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Abstract

Aluminium (Al) oxyhydroxide (Alhydrogel®), the main adjuvant licensed for human and animal vaccines, consists of primary nanoparticles that spontaneously agglomerate. Concerns about its safety emerged following recognition of its unexpectedly long-lasting biopersistence within immune cells in some individuals, and reports of chronic fatigue syndrome, cognitive dysfunction, myalgia, dysautonomia and autoimmune/inflammatory features temporally linked to multiple Al-containing vaccine administrations. Mouse experiments have documented its capture and slow transportation by monocyte-lineage cells from the injected muscle to lymphoid organs and eventually the brain. The present study aimed at evaluating mouse brain function and Al concentration 180days after injection of various doses of Alhydrogel® (200, 400 and 800μg Al/kg of body weight) in the tibialis anterior muscle in adult female CD1 mice. Cognitive and motor performances were assessed by 8 validated tests, microglial activation by Iba-1 immunohistochemistry, and Al level by graphite furnace atomic absorption spectroscopy. An unusual neuro-toxicological pattern limited to a low dose of Alhydrogel® was observed. Neurobehavioural changes, including decreased activity levels and altered anxiety-like behaviour, were observed compared to controls in animals exposed to 200μg Al/kg but not at 400 and 800μg Al/kg. Consistently, microglial number appeared increased in the ventral forebrain of the 200μg Al/kg group. Cerebral Al levels were selectively increased in animals exposed to the lowest dose, while muscle granulomas had almost completely disappeared at 6 months in these animals. We conclude that Alhydrogel® injected at low dose in mouse muscle may selectively induce long-term Al cerebral accumulation and neurotoxic effects. To explain this unexpected result, an avenue that could be explored in the future relates to the adjuvant size since the injected suspensions corresponding to the lowest dose, but not to the highest doses, exclusively contained small agglomerates in the bacteria-size range known to favour capture and, presumably, transportation by monocyte-lineage cells. In any event, the view that Alhydrogel® neurotoxicity obeys "the dose makes the poison" rule of classical chemical toxicity appears overly simplistic.

Keywords: Adjuvant; Aluminium oxyhydroxide; Macrophagic myofasciitis; Neurotoxicity; Non-monotonous dose response; Particle.