CW 1759-50 An ultra-short acting nondepolarizer immediately antagonized at any time by L-cysteine

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Introduction: CW 1759-50 has been developed to reduce histamoid phenomena in an ultra-short acting nondepolarizer; when compared with gantacurium (GW 280430A) its safety ratio [ED for histamoid circulatory, pulmonary and cutaneous phenomena/NMB ED95] is approximately four to seven times greater in monkeys and dogs versus that of gantacurium (unpublished data). CW 1759-50 is ultra-short acting because the molecule is inactivated by bodily L-cysteine in a chemical reaction. In this study, we tested spontaneous recovery and antagonism of 1759-50 blockade by exogenous L-cysteine at two key points: one minute following a bolus dose of 4x ED95 (0.20 mg/kg) (point A) and one minute following discontinuation of continuous infusions (point b).

Methods: With IACUC approval, male Rhesus monkeys weighing 9-18 kg were studied under isoflurane/N₂O/O₂ anesthesia (1.5-2.0%); twitch, TOF, blood pressure and heart rate were recorded continuously. Controlled ventilation was maintained and temperature, ETCO₂, and SpO₂ were kept within normal limits under continuous monitoring. ED95 for NMB was calculated.

Neuromuscular function was measured mechanomyographically. Total duration (injection to 95% twitch recovery) following ED98-99 and 4x ED95 dosage was determined. Continuous infusions of CW 1759-50 were given to monkeys for durations of 30-120 min, where 99-99.5% block was maintained. Rate of spontaneous recovery following infusion was measured as the interval of twitch recovery following ED95, 4x ED95 and infusions were compared.

Reversal of neuromuscular blockade by L-cysteine was measured at two key points: (a) at +1 min after injection of 4x ED95 (0.20 mg/kg); (B) at 100% twitch inhibition 1 min after cessation of continuous infusion. The [5-95% interval] following L-cysteine reversal was compared with spontaneous recoveries following bolus dosage and infusion.

Results: Rate of spontaneous recovery [5-95%] interval following bolus dosage (1x - 4x ED95) and infusion do not differ. Rate of accelerated recovery (reversal) by L-cysteine also did not differ (Table).

Conclusions: The data indicate that recovery from 1759-50 blockade, whether spontaneous or L-cysteine accelerated (reversal) is unaffected by bolus dosage or infusion. Dosage for immediate reversal by L-cysteine is identical at all points tested. The neuromuscular properties of 1759-50, together with its reduced association with histamoid phenomena (vis-a-vis gantacurium) suggest that CW 1759-50 may present an improved profile in human subjects.