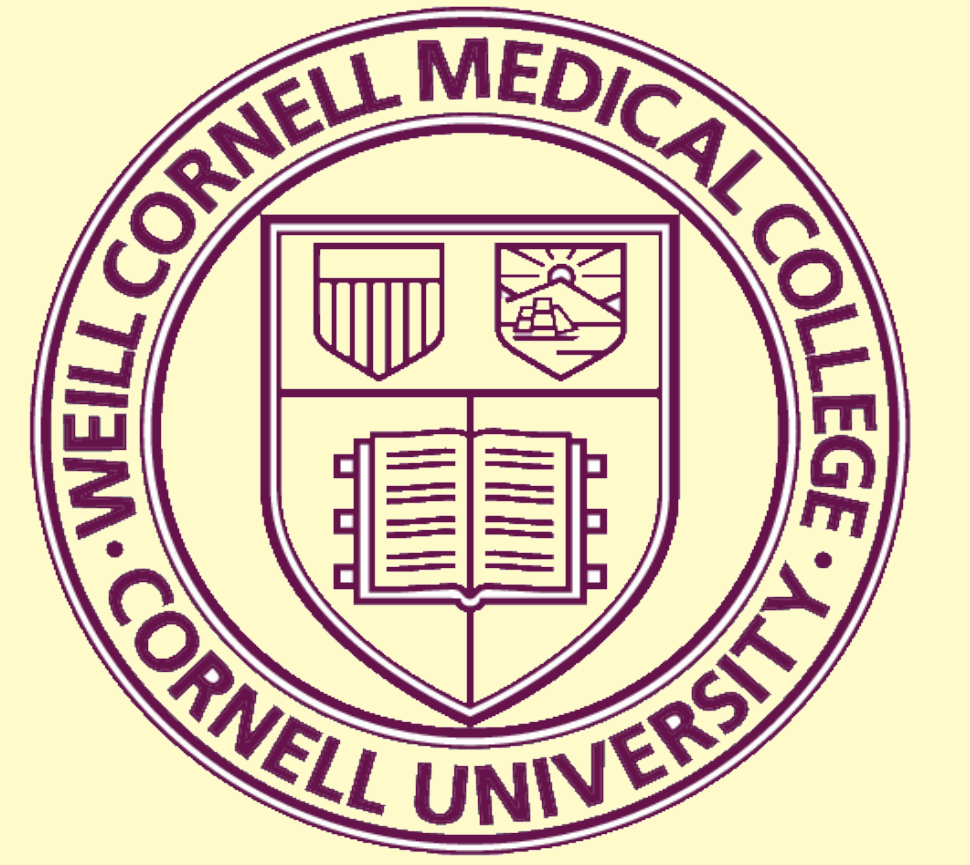


# CW 1759-50 An ultra-short acting nondepolarizer immediately antagonized at any time by L-cysteine



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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phenomena/NMB ED95] is approximately four to seven times greater in monkeys and dogs versus that of gantacurium (unpublished data).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/N<sub>2</sub>O/O<sub>2</sub> anesthesia (1.5-2.0%); twitch, TOF, blood pressure and heart rate were recorded continuously. Controlled ventilation was maintained and temperature, ETCO<sub>2</sub>, and SpO<sub>2</sub> 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 from 5-95% twitch height. Intervals [5-95% 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).

## Reversal of CW 1759-50 by L-Cysteine vs. Spontaneous Recovery in Monkeys following Bolus Dosage and Infusions

| Key Points    | Dose mg/kg                       | ED                  | n  | Total Duration (min)* (Spontaneous Recovery) | 5-95% Interval (Spontaneous Recovery) | n  | 5-95% Interval with L-Cysteine** | n  |
|---------------|----------------------------------|---------------------|----|----------------------------------------------|---------------------------------------|----|----------------------------------|----|
|               | 0.05 - 0.06                      | ED <sub>99</sub>    | 28 | 7.9 ± 1.6                                    | 5.1 ± 0.3                             | 28 | NA                               | NA |
| Point "A"**** | 0.2                              | 4x ED <sub>95</sub> | 55 | 11.9 ± 0.3                                   | 6.2 ± 0.2                             | 45 | 1.9 ± 0.2 <sup>A</sup>           | 9  |
| Point "B"**** | Continuous Infusions 30-120 mins |                     | 20 | NA                                           | 5.3 ± 0.4                             | 10 | 2.1 ± 0.2 <sup>ab</sup>          | 10 |

\* From injection to 95% twitch height following bolus doses

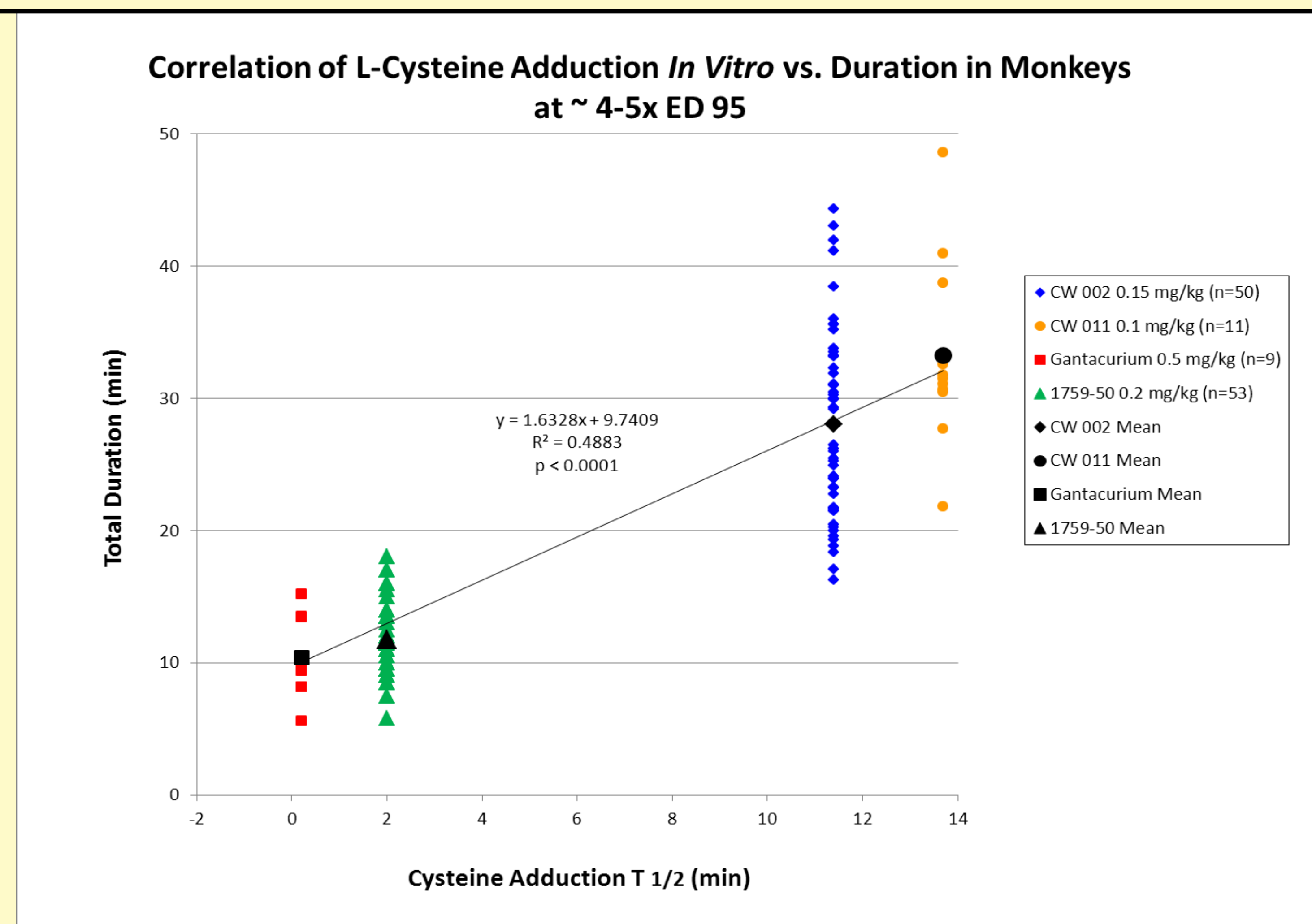
\*\* L-Cysteine dosage 30 mg/kg

\*\*\* Comparative recovery intervals (spontaneous vs. L-cysteine reversal) when L-cysteine is given at +1 min following bolus dosage of 4x ED95 (0.2 mg/kg)

\*\*\*\* Comparative recovery intervals (spontaneous vs. L-cysteine reversal) when L-cysteine is given at +1 min following discontinuation of infusion

a p<0.01 vs. spontaneous recovery

b p>0.05, reversal of 4x ED95 vs. reversal of infusions



**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.

