Crossover Studies in Monkeys Suggest that the New Ultra-Short Acting Nondepolarizer, CW 1759-50, in Contrast with Gantacurium, has Direct Circulatory Mechanisms and Elicits no Histaminoid Phenomena

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Introduction:

The Weill Cornell NMB Development Program has sought to reduce the side-effect profile of Gantacurium (GW 280430A, AV 430A) with respect to histaminoid phenomena. CW 1759-50 has been chosen as a candidate compound.

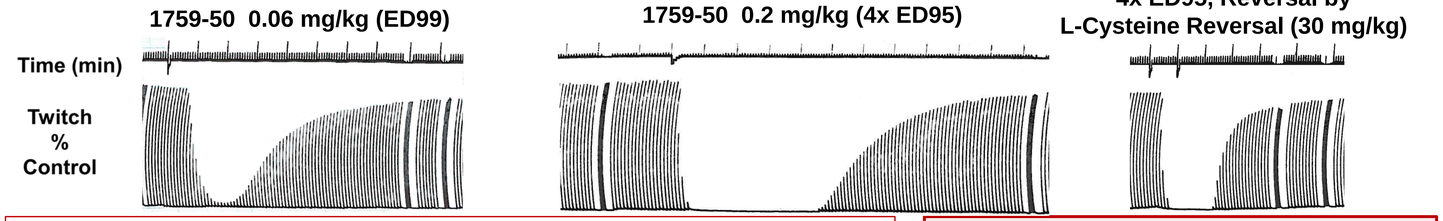
Methods:

With IACUC approval, seven animals weighing 9-18 kg, known to show increasing dose-related histaminoid phenomena to gantacurium were selected for a crossover comparison with CW 1759-50 under isoflurane (1.2-2.0%) and N_2O/O_2 (70:30). Ventilation was controlled at 20 BPM. SpO2 and T were maintained between 96-100% and 99-101.5ºF. Twitch, TOF, BP and HR were recorded continuously. Gantacurium or CW 1759-50 (2.0 to 4.0 mg/kg, or 30 to 80x ED95) were given as the "first dose of the day". One data point per day therefore was obtained from each experiment. Animals were studied at 4-6 week intervals.

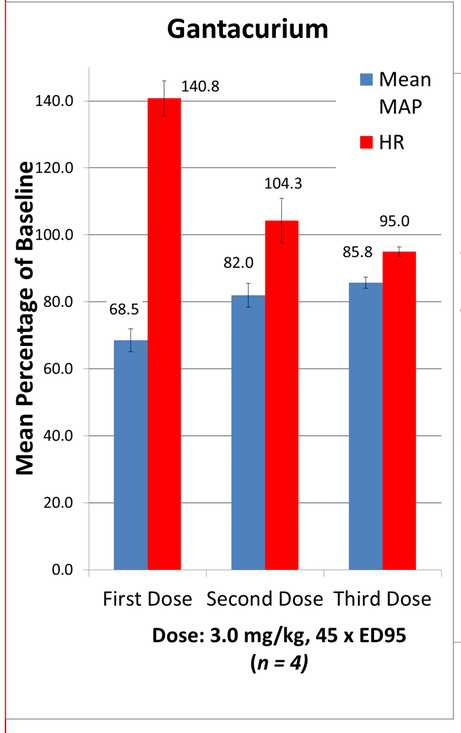
Dose-response curves for MAP and HR were constructed. Facial flushing was evaluated.

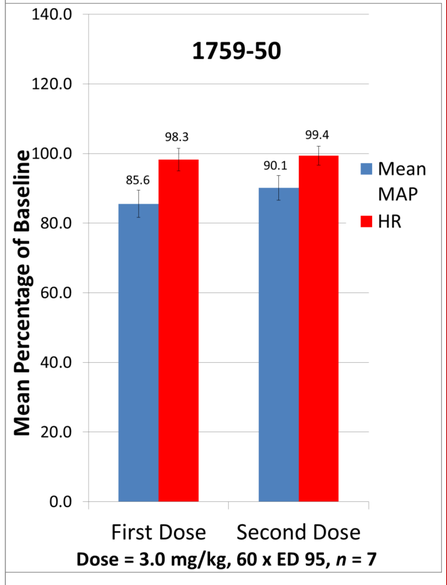
Tachyphylaxis: Two (1759-50) or three (gantacurium) doses of 3.0 mg/kg of each compound were given at 15 minute intervals to ascertain whether MAP, HR, and skin changes decreased during sequential dosing.

H_1 + H_2 prophylaxis: Diphenhydramine 5 mg/kg and ranitidine, 5 mg/kg were given 30 min prior to dosing with the NMBS. Changes in MAP and HR and presence of facial flushing following doses of 3.0 mg/kg of each NMB were compared with data from experiments where prophylaxis was not given.



Tachyphylaxis to Circulatory Changes





Results:

Gantacurium caused increasing tachycardia, hypotension, and facial flushing as dosage increased from 2.0 to 4.0 mg/kg. Three successive doses of gantacurium 3.0 mg/kg resulted in marked tachyphylaxis to MAP decrease and HR increase . MAP decrease, HR increase and facial flushing were abolished by H1 + H2 prophylaxis.

CW 1759-50 caused gradual reductions of both MAP and HR over the dose range 2.0-4.0 mg/kg . MAP reduction developed slowly, peaking in 3-5 min, in contrast with gantacurium, where MAP decrease was sudden and followed by a sudden increase in HR. Tachyphylaxis did not occur. Repetitive dosing caused HR and MAP changes which were qualitatively similar, and the peak changes did not differ significantly. Antihistamine prophylaxis had no effect on circulatory changes. Facial flushing did not occur. There was no relation of HR change to dose of 1759-50.

Conclusion:

Development of tachyphylaxis and the effectiveness of antihistamine prophylaxis suggest an indirect mechanism, i.e. histamine release, for gantacurium. CW 1759-50 has lesser circulatory effects than gantacurium in the monkey. Lack of tachyphylaxis and failure of H_1 + H_2 prophylaxis suggest that CW 1759 50 does not cause histaminoid side effects at dosage up to 80 x ED 95 (4.0 mg/kg) in the monkey. Additional unpublished data [1,2] suggest that direct autonomic mechanisms, such as blockade of autonomic ganglia, may cause moderate decreases of blood pressure after 80xED95 of 1759-50.

Antihistamine Prophylaxis Prevents Gantacurium effects on MAP and HR But Does not affect 1759-50