

# The effect of cold-chain re-introduction on the molecular integrity of Rocuronium Bromide

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## Introduction:

This study aimed to examine the effect of breakages and re-introduction into the cold chain on the rocuronium bromide compound. Rocuronium bromide is frequently used in routine theatre lists and plays a vital role in modified rapid sequence induction and intubation for emergency patients who have contraindications to the primarily used muscle relaxant, succinylcholine.

With the current practice of removing the drug from, and then reintroducing it into the cold chain, unpredictable clinical effects, including delayed onset of action and shortened duration of action have been observed. This may pose a significant risk to the patient.

## Methods:

Rocuronium bromide was subjected to different clinically applicable storage and temperature scenarios, after which the compound was analysed for integrity and quantities of the active compound, including detection of possible degradation products, by means of ultra-purity liquid chromatography quadrupole time-of-flight mass spectrometry, and compared to cold chain control samples.

Analysis was done on a total of 6 limbs. The control groups comprised of cold chain intact and room temperature groups which were analysed on weeks one, six and twelve. The experimental groups were first divided into 18° Celsius and 24° Celsius limbs, and further subsequently subdivided into single breakage exposure and double breakage exposures groups, yielding four experimental groups.

Dilution analysis was done on 10ppm (10µg/ml) preparations with a quantification ion of 529.4002 m/z ([M]<sup>+</sup> salt counterion).

## Results:

There were no significant differences between any of the temperature exposure groups or between the single or double exposures at these temperatures. No statistically significant difference could be demonstrated between the two control groups with testing done at weeks one and six. However, week twelve analysis revealed a statistically significant result which translated to a 26µg/ml difference, which is not clinically significant.

Substantial results were obtained with a secondary exposure to air, which lead to a 20% decrease in the rocuronium concentration (p=0.02).

## Conclusion:

Practice should be adapted by keeping careful documentation as to when the cold chain was broken, and when the recommended 12-week period will lapse. Vial sharing as a standard is not recommended. If small quantities are repeatedly withdrawn from the vial during a prolonged case, the unused contents should be discarded after eight hours.

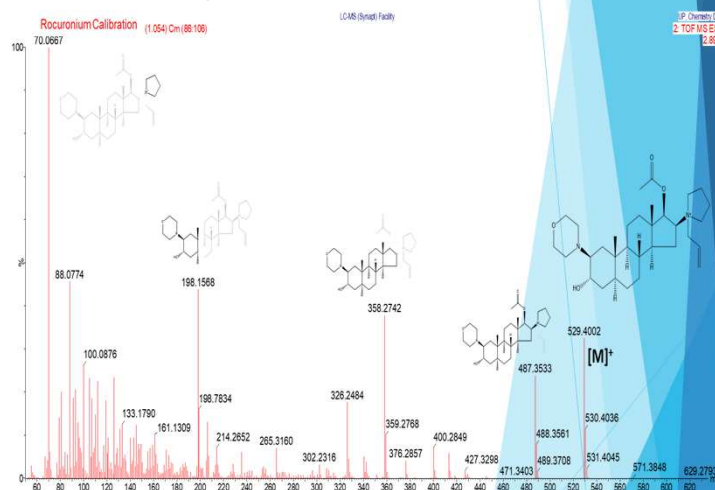
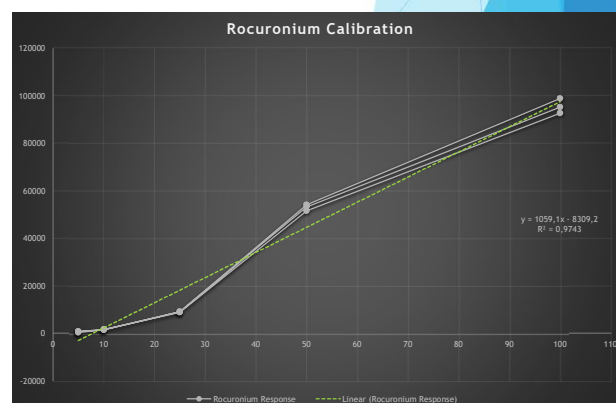


Figure 1: High energy mass spectrum of rocuronium (529.4002 m/z) ([M]<sup>+</sup> salt counterion) giving the MS/MS fragmentation pattern of the compound for qualitative confirmation

Table 1: Data analysis from all groups

		Before Exposure ppm	After Exposure ppm	p-Value	Air Mod ppm	p-Value
18 Degrees Single Exposure	Batch A	8,21	8,31	8,32	8,31	
18 Degrees Single Exposure	Batch B	8,56	8,66	8,39	8,36	0,273
24 Degrees Single Exposure	Batch A	8,47	8,52	8,62	8,61	0,067
24 Degrees Single Exposure	Batch B	8,39	8,43	8,52	8,50	
18 Degrees Double Exposure	Batch A	10,86	10,31	8,76	8,81	0,465
18 Degrees Double Exposure	Batch B	9,65	9,36	9,67	9,69	0,02
24 Degrees Double Exposure	Batch A	9,44	9,23	9,86	9,90	0,068
24 Degrees Double Exposure	Batch B	8,74	8,55	11,01	11,06	0,043

		Week 1	Week 6	Week 12	Week 1 vs Week 12			
Control Group 1	Batch A	8,41	8,45	7,87	7,89	8,11	8,33	
Control Group 1	Batch B	8,61	8,63	7,87	7,89	8,22	8,40	p-Value 0,068
Control Group 2	Batch A	8,46	8,45	7,89	7,91	8,40	8,56	
Control Group 2	Batch B	8,40	8,37	7,89	7,90	8,53	8,62	p-Value 0,144
		p-Value 0,149	p-Value 0,248	p-Value 0,043				
Global p-Value Experimental Groups vs Control Group 1 Week 1: 0,395								



Graph 1: Rocuronium Bromide Calibration