The Physical Compatibility of Glycopyrrolate and Rocuronium

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Objective: Scientific evidence has rarely, if at all, been reported in the literature demonstrating analytical confirmation of the physical compatibility and stability of glycopyrrolate and rocuronium combined. The purpose of this experiment was to determine if glycopyrrolate and rocuronium are physically compatible.
Methods: Glycopyrrolate and rocuronium were combined in various containers, observed over a 60-minute period, and compared against positive and negative controls. Measured metrics included color change, precipitate formation, Tyndall beam test, turbidity, and pH. Statistical analyses were used to assess significance of data trends.
Results: The combination of glycopyrrolate and rocuronium did not result in any color change, precipitate formation, a positive Tyndall beam test, or a significantly positive turbidity and did not result in any significant change in pH, regardless of container.
Conclusion: Per the protocol used in this study, glycopyrrolate and rocuronium were determined to be physically compatible.

Key Words: Glycopyrrolate; Rocuronium; Intravenous administration; Drug interactions; Drug compatibility.

Intravenous (IV) administration of incompatible drugs can go unrecognized and may lead to adverse outcomes, as medications are often administered simultaneously through the same IV line. Notably, not all medications can be mixed due to incompatibility, resulting in negative consequences and even death in some extreme cases when administered concurrently.[1] There are 3 types of incompatibilities associated with IV administration: physical, chemical, and therapeutic.[2] An example of physical incompatibility occurs when thiopental and rocuronium are combined, resulting in the formation of a precipitate due to discordant differences in pH.[3]

Glycopyrrolate, an anticholinergic agent, and rocuronium, a nondepolarizing neuromuscular blocking agent, are 2 drugs commonly used during general anesthesia although usually not concurrently as glycopyrrolate is used during reversal of rocuronium-induced paralysis. However, coadministration may occur if the anticholinergic effects of glycopyrrolate are indicated independent of rocuronium administration. If the patient's physiologic state (eg, excessive salivation, bradycardia) independently warrants an anticholinergic like IV glycopyrrolate at the time rocuronium is administered, unintended mixture may occur. Although coadministration is possible, the current literature is devoid of any discussion regarding the compatibility and stability of glycopyrrolate and rocuronium combined.

The objective of this study was to determine if glycopyrrolate and rocuronium are physically compatible when combined for up to 60 minutes. While these drugs are not usually mixed in the same syringe, residual drug present in the IV tubing could be incompatible with another drug delivered into the same tubing.[2] If incompatibility is noted, future research should be performed to determine whether there are circumstances under which glycopyrrolate and rocuronium can be administered without concern for incompatibility (eg, flushing the IV tubing between drug administrations). If

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physical compatibility is determined, coadministration can be performed with greater confidence.

The impact of this study will result in an increased availability of pharmacologic information useful for patient care. If incompatibility of these 2 drugs is suspected, avoidance of coadministration is warranted until further research determines what effects may come from coadministration. Anesthesia providers will benefit by having increased awareness of drug compatibility, which in turn improves patient safety. This research also provides examples of basic evaluations clinical providers can use to help determine drug compatibility in various settings.

METHODS AND MATERIALS

Conditions for compatibility were simulated and solutions were assessed over a 60-minute observation period in the 3 visual metrics of color change, precipitate formation, and a Tyndall beam test, the optical metric of turbidity, and the chemical metric of pH. Tyndall beam observes the scattering of a light source through a liquid medium. The Tyndall beam test was performed using a laser from a laser pointer directed through the solution to assess colloid formation. Turbidity measures the relative clarity or "haziness" of a liquid. The turbidity meter was calibrated using 0 nephelometric turbidity units (NTU) and 100 NTU calibration solutions. The pH meter was calibrated using a 7.0 pH buffer. Physical incompatibility was defined a priori as color change, precipitate formation, a positive Tyndall test, a significant difference in turbidity from the negative control, or a significant change in pH at any time during the 60-minute observation period (times 0, 15, 30, 45, and 60 minutes). Furthermore, incompatibility for pH was defined as a significant difference in pH attributed to a different container.

Four samples of glycopyrrolate and rocuronium were tested individually in test tubes to determine baseline values for the 5 metrics. Rocuronium is known to be physically compatible with lidocaine, and 3 specimens of this combination in a test tube served as the negative control. Rocuronium is known to be physically incompatible with ketorolac, so 3 specimens of this combination in a test tube served as the positive control.[4] Compatibility testing of the combination of glycopyrrolate and rocuronium in test tubes, syringes, and IV tubing was performed 5 times each.

Distilled water was used to clean the pH meter and turbidimeter sample vial between test runs. Normal saline was used to flush the IV tubing prior to injection of glycopyrrolate and rocuronium at the Y-site.

Drug doses, volumes, and concentrations used during compatibility testing mirrored those frequently utilized in vivo.

- Glycopyrrolate 0.4 mg; 2 mL of 0.2 mg/mL solution
- Rocuronium 50 mg; 5 mL of 10 mg/mL solution
- Lidocaine 50 mg; 5 mL of 10 mg/mL solution
- Ketorolac 30 mg; 1 mL of 30 mg/mL solution

To ideally simulate clinical conditions, 3 types of containers were used: (1) a 17-mL glass test tube, (2) a 10-mL plastic medical syringe, and (3) IV tubing with a 14-mL priming volume previously flushed with normal saline. Glass test tubes provided adequate containers for the testing of all 5 metrics but are not used clinically. Because of the enclosed nature of IV tubing and the medical syringe, pH and turbidity final values were obtained only at the end of the experimental time rather than being assessed at periodic intervals.

Test Tube

The individual or correct pair of drugs was sterilely removed from a previously unopened glass vial using a blunt-tip needle syringe and injected into a clean glass test tube. At time 0 minutes, color change and precipitate formation were evaluated visually, while the Tyndall beam test was performed using a laser pointer. A clean pH meter was inserted into the glass test tube. The solution was then transferred from the test tube into a clean sample vial to assess turbidity. After completing all metric measurements at time 0, the solution was transferred back into the original glass test tube for subsequent testing at each of the following four 15-minute intervals.

Syringe

Rocuronium was sterilely drawn up into a medical syringe from a previously unopened vial. Using the same syringe already containing rocuronium, glycopyrrolate was drawn up from a previously unopened vial to create a combined solution. Color change, precipitate formation, and the Tyndall beam test were performed at time 0 and repeated at the four 15-minute intervals. At time 60 minutes, the solution was transferred to a glass test tube for pH measurement and then to a clean sample vial for turbidity measurement.

IV Tubing

Rocuronium was sterilely drawn up from a previously unopened vial and injected into the IV tubing injection

Table. Results at 60 Minutes.

Drug(s)	*Container*	*Study metrics*			
		Color change†	*Precipitate formation‡*	*Tyndall beam test†*	*Turbidity (mean NTU)*
Glycopyrrolate, n = 4	Test tube	No	No	–	1.65
Rocuronium, n = 4		No	No	–	0.06
Rocuronium/lidocaine, n = 3		No	No	–	0.03
Rocuronium/ketorolac, n = 3		Yes (white)[a]	No	+†	719.33§
Glycopyrrolate/rocuronium, n = 5		No	No	–	0.40
Glycopyrrolate/rocuronium, n = 5	IV tubing	No	No	–	0.06
Glycopyrrolate/rocuronium, n = 5	Syringe	No	No	–	0.45

† $P = .001$ (Fisher exact test).
‡ Responses were not tested for significance, as no differences were found.
§ $P < .001$ (Tukey-Kramer test).

port previously flushed and filled with normal saline. Glycopyrrolate was sterilely drawn up and injected into the same port. The total volume of the medications injected (~10 mL) did not exceed the volume of the length of tubing found after the injection port. At time 0 minutes, color change and precipitate formation were evaluated visually. Subsequent repeat testing was performed at times 15, 30, 45, and 60 minutes from time 0. At 60 minutes from time 0, the solution was transferred to a glass test tube for Tyndall beam testing and pH measurement and then transferred to a clean sample vial for turbidity measurement.

Statistical Analysis

Separately, the results of color change, precipitate formation, and Tyndall beam test at 60 minutes were analyzed using Fisher exact test, followed by pairwise comparisons of the positive control (rocuronium/ketorolac) to each of the 3 glycopyrrolate and rocuronium combination test groups and the negative control (rocuronium/lidocaine). Turbidity values at 60 minutes were analyzed using a 1-way analysis of variance (ANOVA) over each of the test groups, with pairwise comparisons tested using the Tukey-Kramer method. The entire pH data set was first analyzed by a repeated-measures ANOVA with time as the within-subject factor. Then the mean pH of the test groups with the glycopyrrolate and rocuronium combination were compared for significant differences between all times and between all containers.

RESULTS

The positive control (rocuronium/ketorolac) produced a color change from clear to white upon mixing that persisted for all measured time intervals (time 0-60 minutes). However, there was no precipitate noted at any time during the experiment for this combination. A positive Tyndall beam test was also noted at all time intervals. The turbidity measurements for the positive control (mean 719.33 NTU) were significantly different at all time intervals during the experiment when compared with the other drugs and drug combinations ($P < .001$). There was no significant change in pH from time 0 to time 60 minutes within the positive control group (Table).

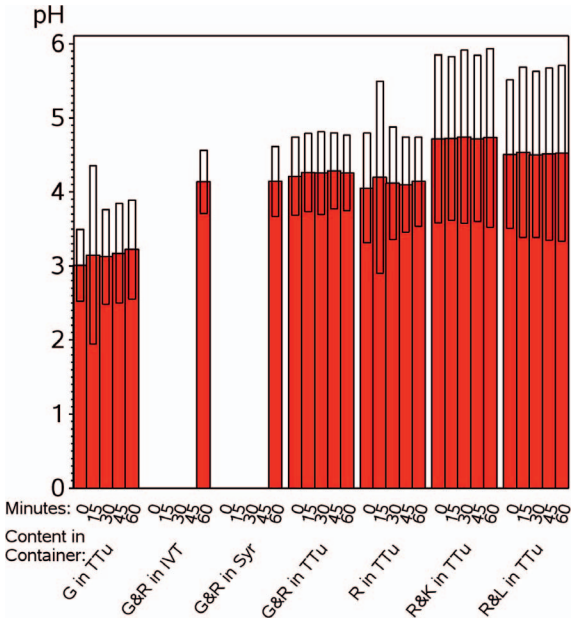
The negative control (rocuronium/lidocaine) produced no color change or precipitate formation, a negative Tyndall beam test, and a mean turbidity of 0.03 NTU that lacked statistical significance. The pH of the negative control did not significantly change throughout the experiment (Table).

The remaining individual drug and drug combinations did not produce color changes or precipitate formation in any of the containers at any time from 0 to 60 minutes. The lack of color changes and negative Tyndall beam test results were all significantly different compared with the positive control ($P < .001$). The mean turbidity measurements for the remaining individual drugs and drug combinations were all <1.66 NTU and found to be statistically significant when compared with the positive control ($P < .001$; Table). No significant pH changes were measured for any individual drug or drug combinations regardless of container type (Figure).

DISCUSSION

Drug incompatibility can be divided into 3 categories: physical, chemical, or therapeutic. Physical incompatibility refers to the metrics used within this study such as color change, turbidity, or precipitate formation.

Figure. pH values over time.



Mean and 95% confidence limits of pH values of each test group over the times tested. G, glycopyrrolate; R, rocuronium; G&R, glycopyrrolate and rocuronium; R&K, rocuronium and ketorolac; R&L, rocuronium and lidocaine; TTu, test tube; IVT, intravenous tubing; Syr, syringe.

Chemical incompatibilities are typically not visible and lead to degradation, formation of harmful by-products, or loss of drug potency.[5] Therapeutic incompatibility refers to a change in a drug's effectiveness as it pertains to its original therapeutic function due to the concurrent use or mixing with another drug.

The combination of rocuronium and glycopyrrolate demonstrated no change in color, positive Tyndall beam test, turbidity, or pH. As expected, there was an obvious color change, positive Tyndall beam test, and increased turbidity for the positive control (rocuronium/ketorolac). The negative control (rocuronium/lidocaine) produced no color change, no precipitate, a negative Tyndall beam test, and negligible turbidity. However, because of the sample size, there was no statistically significant difference detected between the positive and negative controls when pairwise comparisons were made. While no statistical difference was detected, the negative Tyndall beam test and lack of color change results that came from combining rocuronium and glycopyrrolate in the test tube were the same as the negative control, suggesting their physical compatibility.

The greatest pH change observed throughout the study was a change of 0.40 in a test tube sample. This fell beneath Hanifah's described change in pH of 0.5 required for incompatibility.[6] Furthermore, no significant pH changes were observed in any of the experimental groups with glycopyrrolate and rocuronium over the 60-minute period regardless of container, demonstrating the stability of glycopyrrolate and rocuronium.

The combination of rocuronium and ketorolac produced an extremely cloudy solution, resulting in a mean turbidity measurement >600 NTU. No other drug or drug combination produced a mean turbidity measurement >2 NTU, suggesting the combination of rocuronium and glycopyrrolate was physically compatible. No precipitate formation was noted during the experiment; therefore, no statistical analysis was performed regarding precipitate formation.

The physical compatibility of glycopyrrolate and rocuronium was previously untested, and scientific evidence of their compatibility will increase confidence of practitioners should coadministration occur in the clinical environment. No universally accepted protocol has been established for experimental design to test for drug compatibility; however, many studies use the 5 metrics employed in this study.[7] While glycopyrrolate and rocuronium appear physically compatible when combined in vitro, they may be incompatible in vivo. Testing to further evaluate physiochemical compatibility using high-performance liquid chromatography for example may be necessary to strengthen the results of this study.[8]

One weakness of this study was that the researchers were not blinded to the experiment, which could have created unintentional bias. In addition, only a total 5 trials were run for the experiment, which may have caused the study to have been underpowered. More trials could have been run to increase confidence in the data, making the study more robust.

CONCLUSION

Medications administered simultaneously must be physically compatible to avoid adverse drug interactions and reactions. The combination of glycopyrrolate and rocuronium produced no significant differences in any of the 5 metrics measured from baseline to 60 minutes. The data from this study suggest the physical compatibility of glycopyrrolate and rocuronium, 2 drugs that have potential for coadministration during anesthesia. Practitioners can now have more confidence should simultaneous administration of glycopyrrolate and rocuronium occur in the clinical environment.

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