Cocamidopropyl Betaine Surfactant 0.075% Solution in Physiological Serum for Hygiene Process of COVID-19 Intubated Patients

HOSPITAL COVID HEALTHCARE WORKERS DURING AN INTUBATION PROCEDURE TO A COVID PATIENT

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EXPRESSION OF SYMPATHY:

The authors remember those who lost their lives during the COVID-19 pandemic.

ABSTRACT

When using ventilators in the management of the coronavirus disease 2019 patient, dense and abundant mucous secretions are formed, obstructing the endotracheal tube and making its aspiration difficult. This situation is worsened if in order to minimize the risk of infection of the medical personnel, the humidifier is disconnected. This circumstance forces the tube to be removed, cleaned, or changed, increasing the workload of the intensive care unit staff. Other therapies tested until now, like mesna, acetylcysteine, or hypertonic saline solution, are valid alternatives, although they have not shown great efficacy for this specific procedure in the past. The sanitary emergency forced the collaboration between a pharmacist and an otorhinolaryngologist to develop the cocamidopropyl betaine surfactant formula, after several tests with different concentrations of the surfactant. The objective of this compounding formula was to resolve a mechanical problem and avoid reintubation due to obstruction of the ventilator tube. The cocamidopropyl betaine surfactant solution 0.075% in saline 0.9% (physiological serum) solution demonstrated to be a well-tolerated formula, using inexpensive materials, was simple to prepare, and was easy to use in clinical practice.

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INTRODUCTION

When using ventilators in the management of the coronavirus disease 2019 (COVID-19) patient, dense and abundant mucous secretions are formed, obstructing the endotracheal tube (ETT) and making its aspiration difficult. This situation is worsened if, in order to minimize the risk of infection of the medical personnel, the humidifier is disconnected. This circumstance forces the tube to be removed, cleaned, or changed, increasing the workload of the intensive care unit (ICU) staff.

Other therapies tested until now, like mesna, acetylcysteine, or hypertonic saline serum, have not demonstrated great efficacy resolving the mechanical obstruction of ventilators tubes.[1] This mechanical issue during the sanitary emergency of COVID-19 has brought out the need of the clinicians to collaborate between compounding pharmacists and otorhinolaryngologists (ORLs) to develop a surfactant formula and test the formulas with different concentrations of the surfactant.

The physicians considered the use of cocamidopropyl betaine (CAPB) as a surfactant based on its previous use in baby shampoo, which contains the ingredient CAPB, to remove mucus and bacteria biofilms. Irrigations of the nasal mucosa with CAPB 1% solution in saline serum have demonstrated an improvement in symptoms, good tolerance, and synergic effects with antibiotics.[2,3]

On the other hand, CAPB is a widely used component in cosmetic products (child hygiene, intimate hygiene). CAPB is also one of the components of a nasal hygiene product called Sinusurf[4] (NeilMed Pharmaceuticals, Inc.) that can be used to relieve the common cold, nasal allergies, bacterial infections, and fungal infections. This product is commercialized in the U.S. and Canada.

The CAPB surfactant solution 0.00075-mg/mL in 0.9% saline solution

is a well-tolerated formula, uses inexpensive materials, is simple to compound, and is easy to use in clinical practice.

The objective of this compounded formula was to try to resolve, with no pharmacologic interaction and minimal adverse effects, the obstruction problems that occur while using the ventilators on patients suffering from COVID-19.

MATERIALS, EQUIPMENT, AND METHODS

Materials

Materials for the formulations included personal protective equipment (following *United States Pharmacopeia [USP]* <797> guidelines[5]), as follows:

- Protective glasses
- Face Mask
- Gowning
- Hair cover
- Sterile gloves

Equipment

- 0.22-µm filter for the final sterility process
- pH meter
- Graduate cylinder
- Glassware

Methods

The formula used in this study was a sterile compounded formulation that was compounded in an International Organization for Standardization (ISO) Class 7 cleanroom environment and under an ISO Class 5 laminar flow hood, following *USP* <797> standards.[5] The SOPs for a sterile compounded solution were followed.

The CAPB 0.075% formula was trialed in three ICU areas: at the Salamanca University Assistance Complex (CAUSA), at the Nuestra Señora de Sonsoles de Ávila Hospital, and at the University Hospital of Ciudad Real. The ICU physicians at these hospitals estimated that the formula was tried on approximately 62 patients. The patients presented with obstruction and the risk of repeated reintubations during the process for ETT suctioning.

Components of the Formula

COCAMIDOPROPYL BETAINE

CAPB is derived from coconut fatty acids and betaines with surfactant properties. It is a good foam former (fine and stable) and is very easy to handle due to its low viscosity. It is compatible with anionic, cationic, and non-ionic substances. CAPB is a clear, colorless, or very pale-yellow liquid and is very soluble in water. Commonly used in children and for mucosal hygiene, CAPB is a very mild surfactant with great tolerance.[6-8] The CAPB solution contains 0.5% sodium benzoate as a preservative.

The product information is as follows:

- Synonyms: Tegobetaina L; CAPB
- CAS number: 61789-40-0
- Manufacturer: Laboratorios Guinama
- Laboratory Reference Number: 405035

The commercialized CAPB solutions are usually diluted in a range of 30% to 50% of active raw material.[7,8] We recommend to always review the supplier's technical data sheet. The solution of CAPB contained between 30% and 32% of raw material. A 25% dilution was prepared from the commercial preparation at 30% for the formulation.

SODIUM BENZOATE

The commercially available solutions of CAPB may contain sodium benzoate[9] as a preservative (approximately 0.5%, equivalent to about 0.4% benzoic acid) to protect against microbial contamination during the normal life of the product. Sodium benzoate has antibacterial and antifungal properties and is used as a preservative in pharmaceutical and cosmetic formulations. It can cause hypersensitivity reactions, with irritation of the eyes, skin, and mucosa. There have been cases of nonimmune contact urticaria.

It should be noted that the concentration of sodium benzoate in the final formula is negligible, about 0.001%. It is important in a case of obtaining the product from another supplier that the technical data sheet be reviewed since the concentration of the preservative may vary. The authors have not found any pharmaceutical supplier's medications on the market that are preservative free. Some suppliers use it as a preservative; this information is not always mentioned in the technical data sheet.

PHYSIOLOGICAL SERUM

The commercial 0.9% sodium chloride solution, also known as physiological serum,[10] was used for the hygiene procedure by endotracheal suctioning of secretions of the respiratory mucosa and endotracheal lavage. The solution has a pH between 4.5 and 7. In the event of a shortage of the commercial 0.9% sodium chloride solution, the compounding pharmacy will compound this solution, following the standard operating procedures (SOPs) for compounding sterile preparations.

COMPOSITION

CAPB at 0.00075 g/mL (i.e., 0.075 g/100 mL [0.075%]) is the final concentration of the physiological serum (0.9% sodium chloride solution) for cleaning/flushing the ventilator tube. For clarification,

This compounding formula was an emergency tool in response to a request in the middle of a sanitary crisis.

FORMULA

COCAMIDOPROPYL BETAINE SURFACTANT 0.075% SOLUTION IN PHYSIOLOGICAL SERUM

INGREDIENTS FOR 1000 ML	CONCENTRATION OF USED PERCENT/ WEIGHT/VOLUME	QUANTITY REQUIRED
Cocamidopropyl betaine commercially available at 30%	0.25%	2.5 mL
Sodium chloride sterile solution	0.9%	997.5 mL
Total Yield		1000 mL

CALCULATION NOTES:

- Basic calculations for the dilution of CAPB 30% to 0.25% were used in the study formula.
- The commercial sodium chloride 0.9% sterile solution was used for the formula. If not available, the compounding pharmacists can prepare it following sterile compounding standard operating procedures.

METHOD OF PREPARATION

1. Measure, accurately, 997.5 mL of the 0.9% sodium chloride solution in a graduate cylinder. *Note: A calibrated sterile beaker also could be used, adding the 0.9% sodium chloride solution in to the beaker.*
2. Pour the mixture from step 1 into a beaker of adequate capacity.
3. Add 2.5 mL of CAPB slowly to the 0.9% sodium chloride solution with a syringe.
4. Add a clean magnetic bar to the beaker to homogenize the mixture on a magnetic stirrer at low speed for 2 minutes to 3 minutes, avoiding foam formation.
5. Verify the solution's pH.
6. Filter the solution with a 0.22-µm filter for sterility into an empty sterile glass bottle in the laminar flow hood.
7. Seal the glass bottle and include an adapter to connect a syringe.
8. Label correctly.

PACKAGING

Package the preparation in a sealed sterile topaz glass bottle and include an adapter for the syringe.

LABELING/STORAGE

Store refrigerated between 2°C and 8°C, protected from light and moisture.

STABILITY

Expiration Date: 3 days (This expiration date is based on *United States Pharmacopeia 41–National Formulary 36* Chapter <797>.)[5]

USE

The CAPB 0.075% solution in physiological serum is used in endotracheal lavage when administered through the ventilator tube intended to remove secretions in intubated patients with COVID-19.

the concentration expressions are: 0.075 g/100 mL - 0.00075 g/mL - 0.75 mg/mL in the final product.

The formulation for the preparation used in this study is provided within this article.

QUALITY CONTROL

Quality-control tests for the final formulation can include the following:

- Organoleptic characteristics (color, odor, appearance): A transparent and colorless liquid. The appearance of the solution should be homogeneous and free of foreign particles.
- Degree of transparency
- Volume of the finished formula
- pH control: 4.5 to 7.0

POSOLOGY

For the hygiene procedure by endotracheal suctioning of secretion process, 3 mL of the surfactant solution was instilled with a cannula via the artificial airway. An additional 5 mL of physiological serum was instilled to clean the remains of the surfactant solution from the tube.

The solution was allowed to loosen the secretions for 10 minutes, then suctioned through the aspiration tube. If the patient tolerated this procedure well, some physicians allowed the surfactant solution to work for 1 hour or 2 hours or until secretions were produced, and then aspirated. This protocol was repeated in each nursing work shift (every 8 hours), which may vary depending on the medical criteria as well as the practical management of the professionals.

POSSIBLE CONTRAINDICATIONS

Contraindications could include hypersensitivity or an allergic reaction to any of its components.

POSSIBLE INTERFERENCES

- The sodium benzoate content in the formula, despite being almost negligible (0.001% in the final product), could interfere with the extraction of culture aspirates, although we consider this a remote possibility.
- The benzoates used have antimicrobial and antifungal properties. Its antimicrobial activity is due to undissociated benzoic acid, and, therefore, depends on the pH. They are relatively inactive at a pH above 5.
- Benzoates are used as preservatives in various pharmaceutical specialties. Because of this use, we consider that, if taken by the same route (endotracheal aspiration), there is a very low possibility of interference with the samples for microbiological cultures from the patient.[9]

We wanted more time and resources in order to focus on an extremely urgent solution through a formulation requested by a physician.

POSSIBLE INTERACTIONS

At the present, there are no documented interactions between this formulation and other medicinal products.

PRECAUTIONS

Some general precautions include:

- In case of sensibility or irritation in the application area, the treatment should be discontinued.
- In case of bronchospasm, the treatment should be discontinued.
- Pregnancy
- Use of other medications

RESULTS

This compounding formula was an emergency tool in response to a request in the middle of a sanitary crisis. After several tests were performed, we developed this surfactant formula with different concentrations of the surfactant until the minimum effective concentration of CAPB to remove the secretions was found. We also tested the combination of CAPB with other vehicles like hypertonic saline (3%, 5%, 7%). These tests did not show improved results; neither did the isotonic. We selected the isotonic 0.9% sodium chloride solution due to its better tolerance profile.

Due to stability reasons,[10] we recommend refrigerated storage of the compounded formula, but it is important to remember that it requires time to reach room temperature prior to administration to prevent a possible risk of bronchospasm due to the airway's membrane contact with cold fluids. We recommend using a single-dose, ready-to-use, pre-filled syringe with a short expiration date as a primary container package, to be used within a period of 3 days, keeping them refrigerated until use.[10]

Two of the three ICUs reported a good response to the procedure in the 60 patients that received the formula due to the avoidance of blockages in the orotracheal tubes of the ventilators and possible derived complications. Doctors and healthcare professionals from the Complejo Asistencial Universitario of Salamanca and from the ICU of the Hospital Nuestra Señora de Sonsoles in Ávila were satisfied with the results and began using this formula for intubated patients. Only a few cases of bronchospasm occurred in previous trials when the solution was administered without allowing the formula to reach room temperature; this was corrected to avoid bronchospasm.

DISCUSSION

In this health-emergency situation, treatments and techniques have been tried despite the lack of comparative studies. The treatments and techniques discussed in this article are being administered and used because of the current state of emergency and the need of provision of life support during the difficult process of airway management. We believe that it is important to provide patients with the best and appropriate therapy in the emergency setting. In our assessment, we evaluated and recognized the circumstances of COVID-19 where a problem must be solved for an issue that is more of a mechanical than a pharmacological issue; a comparative study was ruled out. We wanted more time and resources in order to focus on an extremely urgent solution through a formulation requested by a physician.

In order to reach the final preparation, other compositions were previously tested: hypertonic saline, combinations at different concentrations of CAPB, and combinations of CAPB in hypertonic saline at different concentrations of sodium chloride that included 3%, 5%, and 7%. In our findings, the CAPB 0.075% in 0.9% sodium chloride solution was adequate and effective.

The objective of our study was to develop a formula capable of improving an ETT bronchial hygiene procedure for the patients on mechanical ventilators, and we assert that considerable progress has been made. However, these are only the first steps to continue the improvement of the compounded formula and to continue further studies of its functionality. It would also be positive if possible limitations associated with the administration of this formulation were assessed against the risks of a reintubation procedure. The heads of the ICU at the University Hospital of Salamanca and Hospital of Ávila have included the CAPB 0.075% solution in their practice. Their decision to do so has increased our confidence in the rationale implemented by our proposal.

During this crisis, this proposal has provided an alternative for the patients on mechanical ventilators. Other formulations could be developed in an effort to help these cases, with the objective to clear the patient's airways and improve survival outcomes.

Some Limitations of the Study

COCAMIDOPROPYL BETAINE

CAPB is the main component of the formula; it is classified as a cosmetic product by the European Medicines Agency and the U.S. Food and Drug Administration. Other regulatory agencies, such as the Therapeutic Goods Administration in Australia, classify CAPB as a drug excipient, included in their Permissible Ingredients Determination (No.4) 2019, which specifies that those ingredients listed in the Register may be contained in a medication.[11]

CAPB is also the main ingredient of some cosmetic products, without bibliographic support, for clinical application that has been related to type IV hypersensitivity reactions mediated by T lymphocytes. These T lymphocytes, in turn, activate macrophages, so it seems contraindicated in COVID-19 patients in their second inflammatory phase with macrophage activation syndrome.[12]

In the available bibliography on the allergenicity of CAPB, it is described that all the individuals with a CAPB allergy are sensitized to 3-dimethylaminopropylamine (DMAPA) and to amidoamine (AA).

These molecules are intermediates in the synthesis of CAPB, and persist as impurities in the commercialized product in variable amounts, depending on the quality of the CAPB in the final product. While it is concluded that the allergy to 1% CAPB is very low, we propose a formulation with a CAPB concentration 13 times below the 1%.

BENZOIC ACID

The CAPB raw material available in Spain contains sodium benzoate as a preservative in a concentration between 0.1% to 0.55%. This component is widely used in food industry as an antifungal and preservative. In the final preparation used in the formula, it is highly diluted (0.001%), and the possibility of adverse reactions (bronchospasm) or analytical interference (microbiological cultures) is very low but not negligible. Also, as we have already reported, we have not found any pharmaceutical suppliers in Spain for a commercially available medication without preservatives. An example of a medication with this preservative is Valium (diazepam) for intravenous use; it contains 95 mg of benzoic acid per vial (as described in its data sheet).

Sodium benzoate is a traditional component of ORL's prescriptions and is referred to in the *Spanish Military Pharmacy Formulary.*[13] In 2005, the United States Environmental Protection Agency declared no sub-chronic or chronic data on human health effects resulting from inhalation exposure to benzoic acid in the literature reviewed.[14] As a simple example, the doses for the treatment of pathologies such as non-ketotic hyperglycinemia (NKH) or disorders of the urea cycle are much higher in the pediatric population, so we believe that this is an aspect that we should take into account. However, we claim that the possibility of adverse reactions, as well as the possible generation of analytical interferences, is very low.

We mentioned that the sodium benzoate content, despite being almost negligible, *could* interfere with the extraction of culture aspirates, but we believe that at the final concentration, it is highly improbable.

STERILITY

Based on the *Good Manufacturing Guidelines to Elaborate Medicaments at the Hospital Pharmacy Units*,[15] we recommend that the compounding of this formula be conducted under a strict sterility environment. The objective of this compounded formula is to reduce the probability of obstruction of the ventilators, especially when the humidity system is disconnected.

We contemplate that if the addition of a preservative is necessary, the compatibility with the route of administration and the physiological and clinical status of the patient should be considered. However, this is something we do not completely know at this moment and will need to further study.

CONCLUSION

This initiative is the outcome of an increased demand during the COVID-19 crisis. The formula was developed in the two aforementioned hospitals that reported a positive reaction to the CAPB surfactant solution 0.075% in saline 0.9% (physiological serum) solution due to the increased workload in the ICUs, and the procedure was administered to improve the ETT bronchial hygiene for the patients on mechanical ventilators. The data was collected, evaluated, and published by the LASEMI as a scientific society whose essence came from the need to share knowledge about individualized medicine between healthcare professionals and the patients. The community pharmacists, hospitalists, physicians, nurses, and patients had become members of LASEMI to search for alternatives to improve a patient's quality of life. As united professionals, we have developed a new emergency alternative to avoid airway obstructions with the use of a well-tolerated formula that is simple to prepare and easy to use in clinical practice. Under the benefit-risk criteria, we recognize the need to continue studying this formula and document and report any adverse events that could arise during its use. This work is an original idea, in a new field of study. We recommend further studies about the use of surfactants in the endotracheal lavage.

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