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Original article

Biochemical characteristics of inhaled antibiotics related to tolerability

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ABSTRACT

Introduction: Inhaled antibiotics are used in the treatment of various respiratory diseases, including cystic fibrosis (CF), non-CF bronchiectasis, and ventilator-associated pneumonia. While some of these drugs are marketed as ready-to-use formulations, others require prior manipulation, such as dilution or reconstitution procedures that are often not standardized. Furthermore, certain antibiotics are only approved for intravenous administration, making it necessary to develop specific protocols for their preparation and use via the inhaled route. Their biochemical properties may also compromise patient safety and tolerability. The aim of this study was to assess how frequently preparation methods and biochemical parameters of inhaled antibiotic solutions are described in the scientific literature. Additionally, we explored their prevalence of use in our country and evaluated their biochemical characteristics to assess tolerability.
Methods: A literature review was conducted using the MEDLINE database to identify studies describing the dilutions used for the administration of inhaled antibiotics. In addition, a nationwide survey was carried out to assess the dilutions currently used in hospital clinical practice. Biochemical analyses were performed in parallel to determine the pH, osmolality, and sodium and chloride ion concentrations of the solutions employed. Excipients present in each formulation were recorded based on information from the product's summary of characteristics.
Results: The literature review identified 533 full-text publications describing 737 different inhaled antibiotic mixtures. Of these, 476 were not standardized. Only 190 mixtures included precise dilution instructions, while just 31 provided data on pH and 28 on osmolality. The national survey revealed a high prevalence of inhaled antibiotic use among participating hospitals, with 22 centres (64.7%) reporting the use of intravenous formulations administered via inhalation. Laboratory analyses showed that some of the evaluated dilutions fell outside the acceptable tolerability range, particularly those involving reconstitution of dry powders or dilution of concentrated intravenous solutions.
Conclusion: There is limited information in the scientific literature regarding preparation methods and the biochemical characteristics of inhaled antibiotic solutions. Off-label use of intravenous formulations for inhalation is widespread, and some of the dilutions used exhibit biochemical parameters outside the recommended tolerability range, which may compromise both the safety and effectiveness of treatment.

Características bioquímicas de los antibióticos para inhalación relacionados con la tolerabilidad

Palabras clave:
Bronquiectasias
Seguridad
Tolerabilidad
Agentes antibacterianos

RESUMEN

Introducción: Los antibióticos inhalados se utilizan en el tratamiento de diversas enfermedades respiratorias, como la fibrosis quística (FQ), las bronquiectasias no relacionadas con FQ y la neumonía asociada a ventilación mecánica. Mientras que algunos de estos fármacos se comercializan listos para su administración, otros requieren manipulaciones previas, como su dilución o su reconstitución, procedimientos que a menudo carecen de

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Uso fuera de indicación

estandarización. Además, ciertos antibióticos solo cuentan con autorización para su uso por vía intravenosa, lo que hace necesario establecer protocolos específicos para su preparación y administración por vía inhalada. Sus propiedades bioquímicas también pueden comprometer la seguridad y la tolerabilidad en los pacientes. El objetivo de este estudio fue analizar con qué frecuencia se describen en la literatura los métodos de preparación y los parámetros bioquímicos de las soluciones de antibióticos inhalados. Asimismo, se exploró su prevalencia de uso en nuestro país y se evaluaron sus características bioquímicas con el fin de valorar su tolerabilidad.

Métodos: Se realizó una revisión bibliográfica en MEDLINE para identificar estudios que describieran las diluciones empleadas en la administración de antibióticos por vía inhalada. Además, se llevó a cabo una encuesta a nivel nacional con el objetivo de evaluar las diluciones utilizadas en la práctica clínica hospitalaria. Paralelamente, se realizaron análisis bioquímicos para determinar el pH, la osmolalidad y las concentraciones de iones sodio y cloruro de las soluciones empleadas. Los excipientes presentes en cada formulación se registraron según la información recogida en la ficha técnica del producto.

Resultados: La revisión bibliográfica identificó 533 publicaciones a texto completo, en las que se describían 737 mezclas diferentes de antibióticos inhalados. De estas, 476 carecían de estandarización. Solo 190 mezclas incluían instrucciones precisas de dilución, mientras que únicamente 31 proporcionaban datos sobre el pH y 28 sobre la osmolalidad. La encuesta nacional evidenció una alta prevalencia en el uso de antibióticos inhalados en los hospitales participantes, con 22 centros (64,7%) que reconocieron el empleo de formulaciones intravenosas administradas por vía inhalada. Los análisis de laboratorio revelaron que algunas de las diluciones evaluadas se encontraban fuera del rango considerado tolerable, especialmente aquellas correspondientes a reconstituciones de polvos secos o diluciones de presentaciones intravenosas concentradas.

Conclusión: Se observó una escasa disponibilidad de información en la literatura científica sobre los métodos de preparación y las características bioquímicas de las soluciones de antibióticos administrados por vía inhalada. El uso fuera de indicación de formulaciones intravenosas para esta vía resulta generalizado, y algunas de las diluciones empleadas presentan parámetros bioquímicos fuera de los rangos recomendados de tolerabilidad, lo que podría comprometer la seguridad y la efectividad del tratamiento.

Introduction

Inhaled antibiotics are a cornerstone of treatment for various diseases such as cystic fibrosis (CF), non-CF bronchiectasis, and ventilator-associated pneumonia. The variety of available antibiotics is vast, and clinicians typically select them based on the local prevalence of microorganisms, specific antibiograms, antibiotic availability in their hospital, and patient-specific factors such as tolerability test results or administration preferences. The advantages of inhaled antibiotic administration include delivering higher drug concentrations directly to the infection site, avoiding the systemic side effects associated with parenteral or oral antibiotics, rapid action, and bypassing the liver's first-pass metabolism. Their therapeutic potential is considerable.[1]

However, inhaled antibiotics are not free from side effects. The most commonly reported adverse events are cough, tachycardia, hyper- or hypotension, and hypoxemia.[2,3] Bronchospasm, often thought to be a common side effect of nebulization, is infrequently reported.[3] To minimize these adverse effects, inhaled antibiotic solutions should be non-pyrogenic, sterile, preservative-free, with a pH level between 4 and 8, and an ideal osmolality between 150 and 550 mOsm/kg.[4] Some experts contend that osmolality up to 1100 mOsm/kg can be used,[5] but most authors agree that side effects increase as osmolality rises.[6,7] In addition, tolerability is improved when solutions contain at least 30 mEq/L of permeant anions.[7] Most researchers agree that chloride is the preferred anion, and aerosols with <30 mEq/L of chloride induce coughing.[7] The ideal concentration is approximately 70 mEq/L of chloride.[6]

Although some studies suggest that dry powder inhalers may have better outcomes than nebulized solutions (such as time to first exacerbation, quality of life, or pharmacokinetics[8,9]), their tolerability may often be worse.[10] Moreover, dry powder formulations for many antibiotics are not always commercially available, and when they are, they are generally more expensive than diluted formulations. Regarding nebulized solutions, there are three categories: (1) antibiotics approved for inhalation and commercialized as ready-to-use liquids (e.g., tobramycin 300 mg/5 mL), (2) antibiotics indicated for inhalation but requiring patient manipulation, such as powder reconstitution (e.g., colistimethate or aztreonam lysine), and (3) off-label use of intravenous antibiotics for inhalation, where patients must reconstitute (e.g., ampicillin) and dilute (e.g., gentamicin). In the latter two cases, and particularly in the third, there is little consensus on how to reconstitute and dilute antibiotics, especially regarding dose and diluent, and only 50% of studies report how the mixtures are prepared.[11] Furthermore, fewer than 10% report data on osmolality, pH, or ion concentrations, which directly affect tolerability.[11]

If possible, intravenous solutions should be avoided as they may contain particles that induce inflammation and bronchospasm upon contact with the bronchial epithelium.[12] Additionally, intravenous formulations often contain additives that can cause bronchospasm or coughing, among other side effects.[13] Moreover, their biochemical suitability for inhalation has often not been tested, and some parameters may worsen tolerability.[11] Similarly, intravenous antibiotics are formulated with different salts, and some may be better tolerated than others, which requires clarification. For instance, colistin sulfate is used orally or topically, while the inactive prodrug sodium colistimethate is more suitable for injection or inhalation.[9,14] Interestingly, most studies on tobramycin use the sulfate salt, but one small study suggests that the free base form may be better tolerated in terms of reducing coughing.[15] Lastly, manipulating intravenous vials to reconstitute powders or dilute solutions increases the risk of contamination and potential infection.[13]

Therefore, intravenous formulations should be thoroughly studied for their osmolality, pH, ion concentrations, and the presence of additives that are not recommended for nebulization before they are administered to patients. This study aimed to assess how frequently the literature reports the preparation methods and biochemical parameters of inhaled antibiotic solutions through a systematic review. We also aim to explore the use of these solutions in our country and analyze their biochemical characteristics to identify which could be potentially safer and better tolerated.

Materials and methods

The study was divided into three parts: a literature review, a hospital survey, and biochemical analysis.

Literature review

The MEDLINE database was searched on 01 October 2023, using keywords related to inhaled antibiotics used in different hospitals: (antibiotics[Title] OR amikacin[Title] OR ampicillin[Title] OR aztreonam[Title] OR cefotaxime[Title] OR ceftazidime[Title] OR colistin[Title] OR colistimethate[Title] OR gentamicin[Title] OR imipenem[Title] OR levofloxacin[Title] OR meropenem[Title] OR tobramycin[Title] OR vancomycin[Title]) AND (inhalation[Title] OR inhaled[Title] OR aerosol [Title] OR aerosolized[Title] OR nebulized[Title]) without language or date filters. One reviewer downloaded all the studies. If an article was unavailable, the reviewer contacted the primary authors. If contact failed, the article was excluded. Four reviewers checked the complete texts after downloading all possible articles. We included all studies on inhaled antibiotic solutions. Exclusion criteria included manuscripts solely referring to inhalation powders, substances that were not antibiotics, animal studies, pharmacokinetic or pharmacodynamic studies, antibiotics used for other routes of administration, and adherence studies.

The reviewers recorded the methods used to prepare inhaled antibiotics when available, and any data regarding pH, osmolality, or ion concentrations. Mixtures were categorized as ready-to-use liquids approved in the technical datasheet (e.g., Tobi®, Quinsair®), approved inhalation drugs requiring reconstitution or dilution (e.g., Cayston®, Promixin®), and non-approved antibiotics for inhalation (e.g., intravenous gentamicin vials). Some studies included more than one antibiotic.

Records were excluded if the primary study was a review or a letter to the editor, but the authors searched the studies cited in the references. One author downloaded the articles, and two reviewers registered data from the full texts. Similarly, if an article was unavailable, the reviewer contacted the primary authors, and if contact failed, the article was excluded.

Hospital survey

In March 2022, a mass email was sent via the Spanish Society of Hospital Pharmacy platform "ListaSEFH" to all members, informing them about the study and requesting data on any antibiotics dispensed for inhalation, including the drug, brand name, national drug code, and preparation method (including the type and volume of the diluent). In addition to the email, all Spanish public hospital pharmacies were contacted by telephone to inform them about the study. The list of hospitals was compiled through a Google search for each region in Spain. In September 2022, a second round of phone calls was made. In September 2023, the complete list of preparations from all hospitals was sent to the respondents to verify and update the data.

Biochemical analysis

Each of the compounded preparations reported in the survey was prepared by the hospital pharmacy department and sent to the biochemistry laboratory for analysis. We also included the analysis of normal saline and water for injection. pH was determined using litmus paper and a pH meter (OAKTON Instruments, Vernon Hills, USA). An automatic osmometer (OSMO STATION OM-6050, ARKRAY EUROPE, Amstelveen, The Netherlands) was used to measure osmolality. Sodium and chloride ion concentrations were measured using an indirect ion-selective electrode on an Alinity c (Abbott Diagnostics, Abbott Park, Illinois, USA). Osmolality and ion concentrations were measured twice. Excipients were consulted using the product information.

Based on the test results, we classified the solutions in terms of potential tolerability according to pH (ideal between 4 and 8),[4] osmolality (between 150 and 550 mOsm/kg),[4] chloride (ideal around 70 mEq/L or higher),[6] and excipients (ideal without bisulfites, ethylenediaminetetraacetic acid (EDTA), or phenol). If all four parameters were ideal, the mixture was marked green. If one parameter was not ideal, the mixture was marked orange. The mixture was marked red if two or more parameters were outside the ideal range. Commercialized ready-to-use liquid mixtures with approved indications were marked blue, as well as dry powders with inhalation indications and with their specific reconstitution instructions.

Results

Literature review

We identified 796 articles in MEDLINE. After including primary studies cited in reviews and letters to the editor, excluding papers based on the exclusion criteria, and removing duplicates, a total of 533 records were evaluated, from which 737 mixtures were extracted. Of these, we carefully analyzed data from 476 mixtures that patients must prepare at home and that are not commercially available as ready-to-use products or provided with ampules containing the exact volume needed to dilute the powder. Of the 476 mixtures, only 190 (39.9%) included precise instructions for preparation (mainly dose and diluent volume), and only 31 (6.5%) reported pH data, while 28 (5.9%) provided information on osmolality. Data are shown in Fig. 1.

Hospital survey

In March 2022, 20 hospitals responded and completed the form with the requested data. In September, another 14 hospitals were added, bringing the total to 34. A total of 178 hospitals were contacted, resulting in a 19.1% response rate. Of the 34 hospitals, 22 (67.4%) reported using intravenous antibiotics for inhalation. The Biochemistry Laboratory analyzed all the mixtures they use.

Biochemical analysis

Table 1 shows the results for 66 different mixtures. All commercialized inhalation drugs approved for inhalation were marked in blue and were within the recommended parameters, except for levofloxacin and aztreonam lysine, which had low chloride ion concentrations. For intravenous antibiotics, most mixtures had one or more parameters that did not meet the recommendations. For hyposmolal mixtures, diluting with normal saline, as in the case of amikacin, is beneficial. On the other hand, for hyperosmolal mixtures, such as ceftazidime, dilution with water for injection is preferable.

Discussion

The results of the review highlight the need for more reporting on the biochemical parameters related to the safety and tolerability of non-commercial dilutions of antibiotics for inhalation. Less than 10% of the studies identified in the review reported data on pH, osmolality, or relevant ion concentrations in non-standardized mixtures that patients must prepare at home. Moreover, it is clear that there is a lack of standardized protocols for preparing these solutions. To the best of our knowledge, we could not find reference texts in the literature that provide detailed instructions on preparing such solutions, despite their widespread use.

Regarding the hospitals surveyed, 67.4% reported using intravenous preparations for inhalation, including ampicillin, amikacin, aztreonam, cefotaxime, ceftazidime, gentamicin, imipenem, meropenem, tobramycin, and vancomycin. A notable issue is that some hospitals continue to prepare inhalation solutions from vials designed for parenteral use, even when commercial inhalation formulations exist, as is the case with aztreonam. The reasons may vary, including the lack of availability of these drugs in certain hospitals (due to cost, for instance[16]) or clinicians' preference for parenteral formulations based on their historical success and reluctance to adopt new formulations. However, it is important to remember that inhalation formulations have been tested in

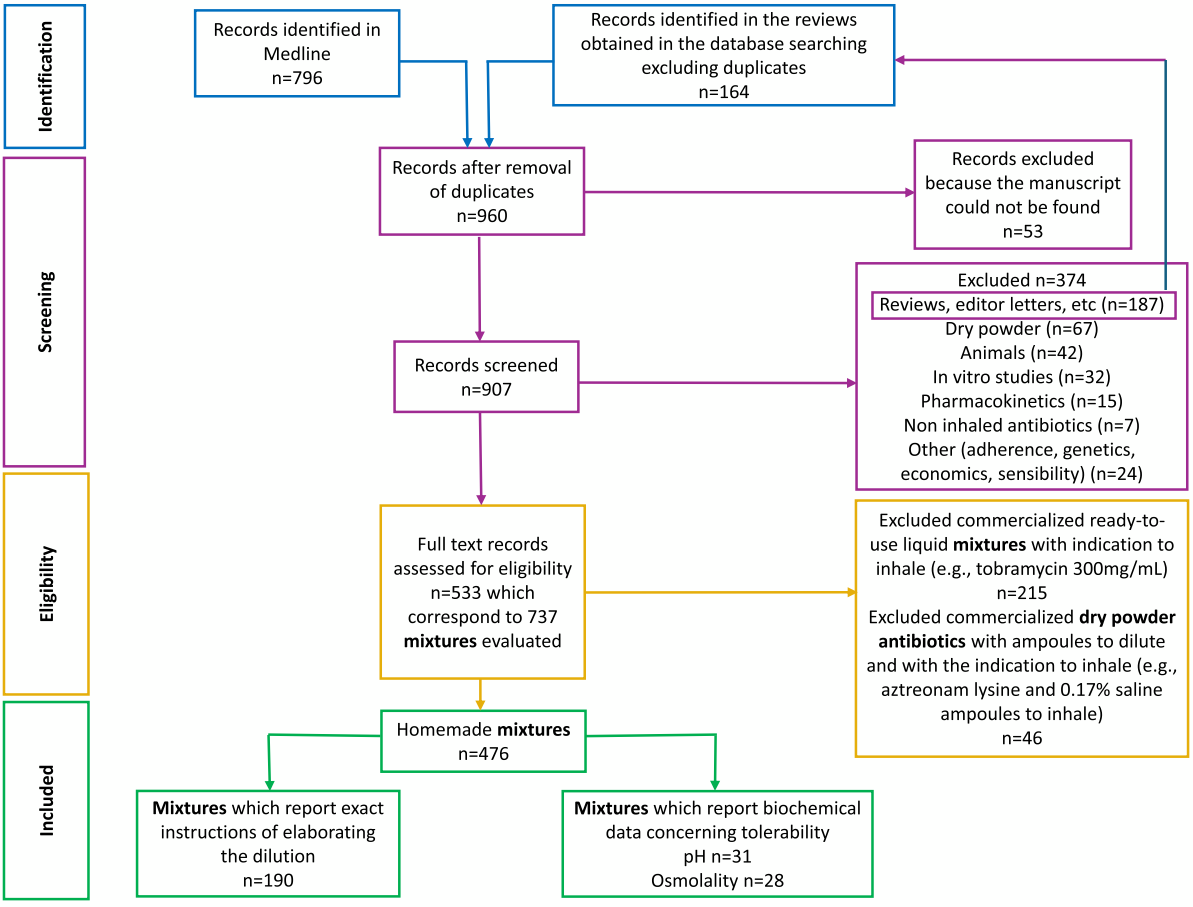

Figure 1. Flow chart of the study revision process.

clinical trials and are specifically designed for efficacy and safety in this route of administration. Their biochemical parameters are optimized for inhalation, ensuring stability. For example, aztreonam has been co-formulated with lysine. Studies show that the pH for optimal compatibility between the powder and diluent should range from 4.0 to 8.2 (with maximum solubility and stability at pH 4.5–6.0), osmolality should be between 150 and 550 mOsm/kg, and permeant anion (e.g., chloride) concentrations should be kept to a minimum.[17] The powder is more stable when refrigerated before reconstitution, which is why the commercial brand of aztreonam lysine is sold as a refrigerated powder, with the diluent containing minimal sodium chloride.

Our biochemical tests showed that not all mixtures fell within the established safety and tolerability ranges reported in the literature. In terms of pH (ideal range: 4–8),[4] vancomycin and gentamicin mixtures were too acidic. The FDA has granted orphan drug status to AeroVanc™ (vancomycin hydrochloride inhalation powder) for treating pulmonary methicillin-resistant *Staphylococcus aureus* (MRSA) infections in CF patients.[18] Although this drug is not approved in Europe, it addresses a crucial therapeutic need, and thus, off-label use of intravenous vials is common, compromising safety and tolerability. Vancomycin is also classified as a vesicant.[19] In the case of gentamicin, the pH was also outside the recommended range; however, some authors propose broader pH margins (2.6–10), within which gentamicin would be acceptable.[20] Furthermore, the greater tolerability of colistimethate observed in a recent study conducted at our centre, compared to nebulized intravenous ampicillin and gentamicin, may be partly explained by its more favorable biochemical profile, particularly its pH and osmolality, falling within the recommended tolerability ranges.[21]

Regarding osmolality, the ampicillin solution, with an osmolality exceeding 1700 mOsm/kg, is noteworthy as it falls far outside the recommended range. This drug is highly hyperosmolal, and moreover with a pH above 8. Hospitals in our study reported reconstituting 1000 mg vials with 4 mL of normal saline. In the review, we found four studies that reported the use of this drug for inhalation.[22–25] In the study by Máiz et al., researchers reconstituted 1000 mg in 4 mL of water for injection, lowering the osmolality to 1250 mOsm/kg.[22,23] The authors specified the brand used for this mixture, which was the same as in our study. Two other studies reported even lower osmolalities (around 650 mOsm/kg) because they used half the dose (500 mg) while maintaining the same volume.[24,25] Based on our findings, reconstituting ampicillin powder with water for injection, rather than normal saline, to reduce osmolality would seem advisable for doses of 1000 mg. Two other antibiotics in our study, cefotaxime and ceftazidime, also showed even higher osmolality levels, exceeding the measurement capabilities of our tools, although only one hospital reported their use.

In terms of ion concentrations, various authors emphasize the importance of high anion concentrations,[7] particularly chloride, to improve tolerability.[6] For example, several manufacturers produce inhalation solutions of tobramycin containing 300 mg of the drug in 4 or 5 mL. According to our tests, the pH, osmolality, and chloride ion concentrations were within acceptable ranges. However, some hospitals still use pure intravenous vials without chloride. Other hospitals use the same vials but dilute them with normal saline, improving the ion balance and making the solution more tolerable. From this perspective, dilution is recommended, provided the drug's concentration is properly considered.

Finally, in terms of excipients, it is preferable to use antibiotics specifically formulated for nebulization.[1] These solutions typically contain drugs dissolved in aqueous, isotonic solvents that may include tested

Table 1
Biochemistry laboratory analysis.

Drug	Brand	Laboratory	Liquid (L) / Powder (P)	Volume to reconstitute	Diluent to reconstitute	Volume of the drug	Volume of the diluent	Diluent	Final dose and final volume	Osmolality mOsm/L	pH	Na mEq/L	Cl mEq/L	Excipients*
Amikacin	Amikacin 500 mg/2 ml	BRAUN	L	-	-	2 ml	2 ml	WFI	500 mg in 4 ml	241	4,19	<20	<20	Edetate disodium, E-216, E-218, E-223, WFI
Amikacin	Amikacin 500 mg/2 ml	BRAUN	L	-	-	2 ml	2 ml	NS	500 mg in 4 ml	390	4,32	85	71	Edetate disodium, E-216, E-218, E-223, WFI
Amikacin	Amikacin 500 mg/2 ml	NORMON	L	-	-	2 ml	1 ml	WFI	500 mg in 3 ml	541	4,94	202	<20	Sodium citrate, E-223, E-513, WFI
Amikacin	Amikacin 500 mg/2 ml	NORMON	L	-	-	2 ml	2 ml	WFI	500 mg in 4 ml	392	5,07	153	<20	Sodium citrate, E-223, E-513, WFI
Amikacin	Amikacin 500 mg/2 ml	NORMON	L	-	-	2 ml	3 ml	WFI	500 mg in 5 ml	297	4,77	122	<20	Sodium citrate, E-223, E-513, WFI
Amikacin	Amikacin 500 mg/2 ml	NORMON	L	-	-	0.4 ml	2.6 ml	WFI	100 mg in 3 ml	117	4,82	40	<20	Sodium citrate, E-223, E-513, WFI
Amikacin	Amikacin 500 mg/2 ml	NORMON	L	-	-	2 ml	2 ml	NS	500 mg in 4 ml	544	5,03	230	76	Sodium citrate, E-223, E-513, WFI
Amikacin	Amikacin 500 mg/2 ml	NORMON	L	-	-	2 ml	3 ml	NS	500 mg in 5 ml	489	5,09	213	85	Sodium citrate, E-223, E-513, WFI
Ampicillin	Gobemicina 1 g	NORMON	P	4 ml	NS	4 ml	-	-	1000 mg in 4 ml	1738	8,88	>400	189	-
Aztreonam	Azactam 1g	BRISTOL	P	4 ml	WFI	4 ml	-	-	1000 mg in 4 ml	1106	5,04	<20	25	Arginine
Aztreonam	Azactam 1g	BRISTOL	P	4 ml	WFI	2 ml	2 ml	WFI	500 mg in 4 ml	460	4,67	<20	<20	Arginine
Aztreonam lysine	Cayston 75 mg	GILEAD	P	1 ml	NaCl 0.17%	1 ml	-	-	75 mg in 1 ml	417	4,59	28	38	Powder: L-lysine; Diluent: sodium chloride, WFI
Cefotaxime	Cefotaxima 1g	REIG-JOFRE	P	2 ml	WFI	2ml	-	-	1000 mg in 2 ml	> 1700	6,07	>400	56	-
Cefotaxime	Cefotaxima 1g	REIG-JOFRE	P	5 ml	WFI	5 ml	-	-	1000 mg in 5 ml	645	5,61	343	24	-
Cefotaxime	Cefotaxima 1g	REIG-JOFRE	P	10 ml	WFI	5 ml	-	-	500 mg in 5 ml	347	5,50	191	<20	-

(continued on next page)

Ceftazidime	Ceftazidima 1 g	REIG-JOFRE	P	4 ml	WFI	4 ml	-	-	1000 mg in 4 ml	836	7,34	>400	20	Sodium carbonate
Ceftazidime	Ceftazidima 1 g	REIG-JOFRE	P	5 ml	WFI	5 ml	-	-	1000 mg in 5 ml	683	7,20	378	<20	Sodium carbonate
Ceftazidime	Ceftazidima 1 g	REIG-JOFRE	P	4 ml	NS	4 ml	-	-	1000 mg in 4 ml	1130	7,37	>400	142	Sodium carbonate
Ceftazidime	Ceftazidima 2 g	REIG-JOFRE	P	10 ml	WFI	5 ml	-	-	1000 mg in 5 ml	666	7,23	361	<20	Sodium carbonate
Ceftazidime	Ceftazidima 2 g	REIG-JOFRE	P	20 ml	WFI	2.5 ml	2.5 ml	NS	250 mg in 5 ml	325	6,99	170	77	Sodium carbonate
Ceftazidime	Ceftazidima 2 g	REIG-JOFRE	P	20 ml	WFI	5 ml	-	-	500 mg in 5 ml	355	7,05	199	<20	Sodium carbonate
Ceftazidime	Ceftazidima 2 g	KABI	P	3 ml	NaCl 0.45%	3 ml	-	-	2000 mg in 3 ml	> 1700	7,44	>400	97	Sodium carbonate
Colistimethate	Colfinair 1 MUI	PARI PHARMA	P	3 ml	NS	3 ml	-	-	1 MUI in 3 ml	361	7,31	214	151	-
Colistimethate	Colfinair 2 MUI	PARI PHARMA	P	3 ml	NS	3 ml	-	-	2 MUI in 3 ml	442	7,00	278	150	-
Colistimethate	Colfinair 2 MUI	PARI PHARMA	P	4 ml	NS	4 ml	-	-	2 MUI in 4 ml	390	7,24	237	152	-
Colistimethate	Colistimetato 1 MU	ACCORD	P	2 ml	WFI	2 ml	-	-	1 MUI in 2 ml	118	8,03	94	<20	-
Colistimethate	Colistimetato 1 MU	ACCORD	P	3 ml	WFI	3 ml	-	-	1 MUI in 3 ml	74	8,03	60	<20	-
Colistimethate	Colistimetato 1 MU	ACCORD	P	4 ml	WFI	4 ml	-	-	1 MUI in 4 ml	61	7,51	48	<20	-
Colistimethate	Colistimetato 1 MU	ACCORD	P	5 ml	WFI	5 ml	-	-	1 MUI in 5 ml	50	7,62	40	<20	-
Colistimethate	Colistimetato 1 MU	ACCORD	P	4 ml	NS	4 ml	-	-	1 MUI in 4 ml	349	7,59	198	149	-
Colistimethate	Colistimetato 2 MU	ACCORD	P	2 ml	WFI	2 ml	-	-	2 MUI in 2 ml	229	6,85	177	<20	-
Colistimethate	Colistimetato 2 MU	ACCORD	P	4 ml	WFI	4 ml	-	-	2 MUI in 4 ml	90	7,41	72	<20	-
Colistimethate	Colistimetato 2 MU	ACCORD	P	4 ml	NS	4 ml	-	-	2 MUI in 4 ml	402	6,96	242	151	-
Colistimethate	Colistimetato 1 MU	ALTAN	P	1 ml	WFI	1 ml	-	-	1 MUI in 1 ml	223	7,00	173	<20	-
Colistimethate	Colistimetato 1 MU	ALTAN	P	2 ml	WFI	2 ml	-	-	1 MUI in 2 ml	114	7,13	86	<20	-
Colistimethate	Colistimetato 1 MU	ALTAN	P	3 ml	WFI	3 ml	-	-	1 MUI in 3 ml	86	7,32	63	<20	-
Colistimethate	Colistimetato 1 MU	ALTAN	P	4 ml	WFI	4 ml	-	-	1 MUI in 4 ml	61	7,38	46	<20	-
Colistimethate	Colistimetato 1 MU	ALTAN	P	2 ml	NS	2 ml	-	-	1 MUI in 2 ml	399	6,71	234	150	-
Colistimethate	Colistimetato 1 MU	ALTAN	P	4 ml	NS	4 ml	-	-	1 MUI in 4 ml	339	7,09	191	150	-
Colistimethate	Colistimetato 2 MU	ALTAN	P	2 ml	WFI	2 ml	-	-	2 MUI in 2 ml	228	7,00	178	<20	-

Colistimethate	Colistimetato 2 MU	ALTAN	P	4 ml	WFI	4 ml	-	-	2 MUI in 4 ml	129	7,21	97	<20	-
Colistimethate	Promixin 1 MUI	ZAMBON	P	1 ml	WFI	1 ml	-	-	1 MUI in 1 ml	217	7,07	166	<20	-
Colistimethate	Promixin 1 MUI	ZAMBON	P	2 ml	WFI	2 ml	-	-	1 MUI in 2 ml	123	7,66	95	<20	-
Colistimethate	Promixin 1 MUI	ZAMBON	P	3 ml	WFI	3 ml	-	-	1 MUI in 3 ml	82	8,37	62	<20	-
Colistimethate	Promixin 1 MUI	ZAMBON	P	4 ml	WFI	4 ml	-	-	1 MUI in 4 ml	63	7,98	52	<20	-
Colistimethate	Promixin 1 MUI	ZAMBON	P	1 ml	NS	1 ml	-	-	1 MUI in 1 ml	517	6,52	329	151	-
Colistimethate	Promixin 1 MUI	ZAMBON	P	2 ml	NS	2 ml	-	-	1 MUI in 2 ml	405	7,13	236	149	-
Colistimethate	Promixin 1 MUI	ZAMBON	P	3 ml	NS	3 ml	-	-	1 MUI in 3 ml	361	6,85	212	152	-
Colistimethate	Promixin 1 MUI	ZAMBON	P	4 ml	NS	4 ml	-	-	1 MUI in 4 ml	327	7,01	185	142	-
Colistimethate	Promixin 1 MUI	ZAMBON	P	1 ml	NaCl 0.45%	1 ml	-	-	1 MUI in 1 ml	373	6,86	234	71	-
Colistimethate	Promixin 1 MUI	ZAMBON	P	3 ml	NaCl 0.45%	3 ml	-	-	1 MUI in 3 ml	235	7,21	138	74	-
Gentamicin	Genta GOBENS 80 mg/2 ml	NORMON	L	-	-	1 ml	3 ml	NS	40 mg in 4 ml	244	2,90	113	108	E-216, E-218, E-524, E-223, WFI
Gentamicin	Genta GOBENS 80 mg/2 ml	NORMON	L	-	-	2 ml	2 ml	NS	80 mg in 4 ml	221	2,82	89	74	E-216, E-218, E-523, E-224, WFI
Gentamicin	Genta GOBENS 80 mg/2 ml	NORMON	L	-	-	2 ml	3 ml	NS	80 mg in 5 ml	230	3,01	101	90	E-216, E-218, E-523, E-224, WFI
Gentamicin	Genta GOBENS 80 mg/2 ml	NORMON	L	-	-	4 ml	1 ml	NS	160 mg in 5 ml	180	2,75	55	31	E-216, E-218, E-523, E-224, WFI
Imipenem/cilastine	Imipenem/cilastine 500 mg	AUROVITAS	P	10 ml	NS	10 ml	-	-	500 mg in 10 ml	620	7,24	301	152	sodium bicarbonate
Levofloxacin	Quinsair 240 mg	CHIESI ESPAÑA	L	-	-	2.4 ml	-	-	240 mg in 2.4 ml	410	4,96	<20	<20	Magnesium chloride hexahydrate, WFI
Meropenem	Meropenem 500 mg	AUROVITAS	P	10 ml	WFI	10 ml	-	-	500 mg in 10 ml	583	7,51	323	148	Sodium carbonate
Tobramycin	Bramitob 300 mg/4 ml	CHIESI ESPAÑA	L	-	-	4 ml	-	-	300 mg in 4 ml	244	4,82	75	69	Sodium chloride, E-513, E-524, WFI
Tobramycin	Tobramicina 300 mg/5 ml	TEVA	L	-	-	5 ml	-	-	300 mg in 5 ml	169	5,60	38	36	Sodium chloride, E-513, E-524, WFI
Tobramycin	Tobramicina 300 mg/5 ml	ACCORD	L	-	-	5 ml	-	-	300 mg in 5 ml	166	4,34	40	36	Nitrogen, Sodium chloride,

(continued on next page)

														E-513, E-524, WFI
Tobramycin	Tobramicina 300 mg/5 ml	ALTAN	L	-	-	5 ml	-	-	300 mg in 5 ml	166	5,56	38	36	Sodium chloride, E-513, E-524, WFI
Tobramycin	Tobramicina 300 mg/5 ml	SUN	L	-	-	5 ml	-	-	300 mg in 5 ml	163	5,67	37	36	Sodium chloride, E-513, E-524, WFI
Tobramycin	Tobramicina 100 mg/2 ml	NORMON	L	-	-	2 ml	-	-	100 mg in 2 ml	155	5,04	<20	<20	Edetate disodium, phenol, E-223, E-513, WFI
Tobramycin	Tobramicina 100 mg/2 ml	NORMON	L	-	-	2 ml	2 ml	NS	100 mg in 4 ml	227	5,56	82	76	Edetate disodium, phenol, E-223, E-513, WFI
Tobramycin	Tobramicina 100 mg/2 ml	NORMON	L	-	-	2 ml	3 ml	NS	100 mg in 5 ml	243	5,47	97	91	Edetate disodium, phenol, E-223, E-513, WFI
Vancomycin	Vancomicina 500 mg	NORMON	P	10 ml	NS	5 ml	-	-	250 mg in 5 ml	309	3,00	145	184	Chlorhydric acid
Vancomycin	Vancomicina 500 mg	REIG-JOFRE	P	10 ml	NS	5 ml	-	-	250 mg in 5 ml	312	1,85	140	175	-
Vancomycin	Vancomicina 500 mg	REIG-JOFRE	P	10 ml	NS	2.5 ml	1.5 ml	NS	125 mg in 4 ml	320	2,96	147	171	-
Vancomycin	Vancomicina 500 mg	REIG-JOFRE	P	10 ml	NS	2.5 ml	2.5 ml	NS	125 mg in 5 ml	305	3,01	147	164	-
Vancomycin	Vancomicina 1 g	PFIZER	P	20 ml	WFI	5 ml	-	-	250 mg in 5 ml	41	2,64	<20	39	-
Vancomycin	Vancomicina 1 g	REIG-JOFRE	P	20 ml	WFI	5 ml	-	-	250 mg in 5 ml	47	3,14	<20	35	-
NS	NS	MEINSOL	L	-	-	-	-	-	-	285	5,36	148	151	Chlorhydric acid, E-524, WFI
WFI	WFI	MEINSOL	L	-	-	-	-	-	-	0	5,75	<20	<20	-

Osmolality, pH, and ion concentrations were measured twice, and the table reports the mean values. Data from the litmus paper test are not included, as this test was performed solely for internal verification of the pH results. Information on excipients was obtained from the product's official documentation.
Key:
NaCl: Sodium chloride; NS: Normal saline; WFI: Water for injection.
Propylparaben (E-216); Methylparaben (E-218); Sodium metabisulfite (E-223); Sulfuric acid (E-513); Sodium hydroxide (E-524).
Blue: Commercialized liquid drug ready to use or commercialized drug in powder with exact instructions of volume to reconstitute.
Green: The following four parameters are correct (1) pH = 4–8, (2) osmolality = 150–550 mOsm/kg, (3) chloride ≥70 mEq/L, and (4) no contraindicated inhalation excipients.
Orange: One parameter is outside the range but the other three are correct.
Red: Two, three or four parameters are outside the range.

preservatives to reduce microbial growth. Sodium chloride and other salts are commonly used to adjust osmolality, while acids and bases such as hydrochloric acid, sodium hydroxide, citric acid, or phosphates are used to adjust pH. It is noteworthy that all marketed inhalation preparations in our study contained excipients classified in Group 1 in the FDA's Generally Recognized as Safe (GRAS) database. This means that there is no evidence to suggest a hazard to the public when these excipients are used at current levels.[26] By contrast, intravenous antibiotics may contain additives designed to enhance chemical stability. Some excipients, such as sodium bisulfite and EDTA, are approved for inhalation, despite studies linking their use to side effects such as coughing and bronchospasm.[27,28] In our study, intravenous formulations of gentamicin, tobramycin, and amikacin contained sulfites, and some brands of amikacin and tobramycin contained EDTA. Despite this, no increase in adverse drug reactions or deterioration in quality of life has been reported in our centre compared to patients using preservative-free formulations.[11] Additionally, intravenous antibiotics may contain preservatives like phenol, which can cause airway irritation, coughing, and bronchoconstriction and is not recommended for inhalation.[27,29] Phenol is also classified as a neurotoxin by the National Institute for Occupational Safety and Health.[30] In our case, intravenous tobramycin contained this substance. Other intravenous formulations, such as vancomycin, ampicillin, or cefotaxime, contained no additives.

We must acknowledge several limitations in our study. First, the literature review could have been more extensive, as we could have reviewed other databases. Additionally, we focused exclusively on antibiotics used in our setting and excluded other commonly used substances such as antifungals.[31] However, we believe that focusing on this topic allowed us to identify a significant proportion of relevant studies. Second, regarding the survey, the response rate was low, despite our efforts to contact hospitals via email and telephone. The reasons may vary (e.g., workload, lack of incentives, lack of prioritization). Third, the tests we conducted only measured pH, osmolality, and key ion concentrations. We did not assess factors such as viscosity, temperature, other chemical compounds, or inhalation devices, all of which are known to

influence tolerability.[32] Moreover, it is important to note that these biochemical parameters were measured under ideal conditions, whereas some delivery devices, particularly ultrasonic nebulizers, heat the solution, thereby increasing osmolality and ion concentrations.[33] Finally, it should be noted that this study does not include certain antibiotics that, although not identified in the national survey, are used in specific clinical scenarios. One example is nebulized linezolid in transplant patients colonized by MRSA or VRE (vancomycin-resistant Enterococci). This absence may limit the generalizability of our findings to all possible clinical contexts.

Among the study's strengths, this review is, to our knowledge, the first to summarize the biochemical parameters of antibiotic solutions and provide recommendations based on accepted ranges in the literature. Furthermore, it addresses current clinical practices and offers alternatives for achieving better tolerability. We analyzed the biochemical parameters used in numerous hospitals, which strengthens the external validity and applicability of our findings.

In conclusion, more information should be reported in the literature on the procedures for preparing inhalation mixtures. Many hospitals use intravenous antibiotics for inhalation, and some of these solutions have biochemical parameters that fall outside the recommendations for optimal tolerability and safety. By considering pH, osmolality, chloride concentration, and the presence of certain excipients, we can better predict which solutions may be more tolerable for patients.

CRediT authorship contribution statement

Manuel Vélez-Díaz-Pallarés: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **María Ángeles Parro-Martín:** Supervision, Investigation. **Hilario Martínez-Barros:** Supervision, Investigation. **Beatriz Montero-Llorente:** Supervision, Investigation. **Miriam Menacho-Román:** Supervision, Investigation. **Ana Gómez-Lozano:** Supervision, Investigation. **Rosa Nieto Royo:** Visualization, Validation. **Luis Máiz Carro:** Visualization, Validation. **Ana Álvarez-Díaz:** Validation, Supervision.

Ethical considerations

Not applicable.

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Declarations of interest

None.

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Statement of authorship

The conception of the article was conceived by all authors.

Manuel Vélez-Díaz-Pallarés was responsible for drafting the document, Miriam Menacho-Román and Ana Gómez-Lozano for collecting biochemical results, and María Ángeles Parro-Martín, Hilario Martínez-Barros, and Beatriz Montero-Llorente for the rest of the results.

All authors have read and approved the final manuscript.

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