Resumen

Objetivo: Describir las dosis de los antíinfecciosos inhalados descritas en la literatura tanto en la población adulta como en la pediátrica. Para aquellos antíinfecciosos que no tienen la vía inhalatoria aprobada, proponer la forma óptima de preparación para conseguir una osmolaridad y un pH lo más cercano posible a los valores fisiológicos.

Método: Se realizó una búsqueda en PubMed (entre 1960 y 2005) con cada uno de los antíinfecciosos y las palabras “inhalation OR inhaled OR aerosol OR aerosolized OR nebulized”. También se consultaron libros de texto, Micromedex y las fichas técnicas de las especialidades farmacéuticas. De los fármacos que se encontró información se prepararon las soluciones para nebulizar. Los fármacos con vía inhalada aprobada se prepararon según las recomendaciones del laboratorio fabricante. Para los antíinfecciosos que no tienen la vía inhalatoria aprobada se prepararon diluciones de la materia prima o de las presentaciones comerciales por vía intravenosa disponibles en nuestro hospital con solución salina fisiológica y/o agua para inyección hasta un volumen final de 4-5 ml. Se midió la osmolaridad y pH de todas las soluciones. Se consideró como forma óptima de preparación, la más próxima posible a una solución de una osmolaridad entre 150 y 550 mOsm/kg y a un pH de 7 ± 0.5.

Resultados: Se encontró información sobre dosificación por vía inhalatoria de 18 antíinfecciosos (12 antibióticos, 5 antifúngicos y 1 antivírico), de los cuales en 9 se describe la dosis pediátrica. Tres de los antíinfecciosos revisados tienen la vía inhalatoria aprobada en adultos y 4 en pediatría. De las 48 recomendaciones de dilución propuestas para la administración, dos tienen una osmolaridad > 1.100 mOsm/kg y 5 una osmolaridad < 100 mOsm/kg. Dos diluciones tienen el pH > 8 y 14 un pH < 5.

Conclusiones: La información bibliográfica sobre las dosificaciones de los antíinfecciosos por vía inhalatoria es escasa. La mayoría de antíinfecciosos no tienen aprobada la administración por vía inhalatoria. La dilución de la materia prima o de las especialidades por vía intravenosa con agua o solución salina fisiológica consigue soluciones con osmolaridad adecuada en la mayoría de los casos. Algunas de las soluciones tienen valores extremos de osmolaridad y/o pH con lo que cabe esperar un riesgo mayor de broncoespasmo.


Summary

Objective: To report the doses of inhaled anti-infective agents described in the literature for both the adult and paediatric population. In the case of anti-infective agents which were not approved for inhaled administration, to propose the optimum manner in which these should be prepared in order to achieve osmolality and pH values as similar as possible to physiological values.

Method: A search was carried out of PubMed (between 1960 and 2005) for each of the anti-infective agents using the words “inhalation OR inhaled OR aerosol OR aerosolized OR nebulized”. We also consulted text books, Micromedex and the technical specifications of the pharmaceutical products. Nebulised solutions were prepared using the drugs for which information was found. The drugs approved for inhaled administration were prepared according to the manufacturers’ recommendations. For anti-infective agents which were not approved for inhaled administration, the raw materials and the branded drug products for intravenous administration available at our hospital were diluted using physiological saline solution and/or water for injection up to a final volume of 4-5 ml. The osmolality and pH values of all the solutions were measured. The optimum form of preparation was considered to be one with values as close as possible to between 150 and 550 mOsm/kg for osmolality and 7 ± 0.5 for pH.

Results: Information about doses of 18 inhaled anti-infective agents was found (12 antibiotics, 5 antifungals and 1 antiviral); paediatric doses were described in 9 of these. Three of the anti-
infec_tive agents reviewed were approved for inhaled use in adult patients and four in paediatric patients. Of the 48 recommenda_tions for dilution suggested for administration, two had an osmo_lality > 1,100 mOsm/kg and 5 an osmolality of < 100 mOsm/kg. Two dilutions had a pH > 8 and 14 a pH < 5.

Conclusions: There is limited literature regarding the doses of anti-infective agents for inhaled administration. The majority of anti-infective agents are not approved for inhaled administration. The dilution of the raw material or proprietary drugs with water or physiological saline solution for intravenous administration achieved solutions with appropriate osmolality in the majority of cases. Some of the solutions have extreme osmolality and/or pH levels, implying that it is reasonable to expect a greater risk of bronchospasm.


INTRODUCTION

Anti-infective agents are basically administered through the inhaled route to prevent or treat respiratory infections of the respiratory apparatus in patients with cystic fibrosis (CF), in patients with bronchiectasis which is not secondary to CF and immunodepressed patients, as well as for the treatment of tracheobronchitis and pneumonia in patients on mechanical ventilat-ion1-6.

The use of anti-infective agents through the inhaled route has been controversial due to a lack of clear indications for initiating the therapy, a lack of proprietary drugs formulated for administration via this route, lack of knowledge of the dosage to follow, fear of creating resistance and the associated inconvenience and difficulties, especially in patients who are intubated1,6. Nonetheless, several anti-infective agents, including beta lactams, polymyxin and aminoglycoside have been shown to be clinically beneficial to patients with CF7,8.

Inhaled administration of anti-infective agents has the advantage of obtaining high concentrations of the drug in the infection site, reducing undesirable systemic effects. However, this method of administration, the physicochemical properties of the drug (pH and osmolality), the dose used and the particular characteristics of the patient can affect its efficacy9-14.

To administer anti-infective agents via the inhaled route when there is no suitable branded drug product, the raw materials were used or the proprietary drug for intravenous administration was reconstituted or diluted with water for injection (WFI) or physiological saline solution (PSS) according to the physicochemical stability of the anti-infective agent, osmolality and pH of the solution. Ideally, values for osmolality and pH of these solutions should be as close as possible to physiological values (300-400 mOsm/kg, and 7 ± 0.5, respectively) for them to be well-tolerated. The literature suggests that an ideal nebuliser solution should have an osmolality of between 150 and 550 mOsm/kg. Certain patients experience coughing or bronchoconstriction during nebuliser therapy, an event that has been specifically connected with the use of solutions with osmalalities < 100 or > 1,100 mOsm/kg, extreme pH values and with preservatives included in some of the intravenous products from which they have been prepared. In these cases, using a bronchodilator may reduce bronchial irritation and the frequency of bronchospasms15,16,17,18.

The volume of the solution to be nebulised should be between 4-5 ml. Lower volumes can mean increased viscosity of the solution, which can make it difficult to nebulise, while higher volumes do not improve performance, and, on the contrary increase the nebulising time, making treatment adherence difficult.

There are few clinical trials and studies backing the use of anti-infective agents administered through the inhaled route. The only recommendations available deal with posology, length of treatment and form of preparing the solution for nebulising the anti-infective agents approved for inhaled use. For the remaining anti-infective agents, the data appearing in the literature regarding dosage guidelines is not very homogeneous and their use is basically empiric.

The objective of this study is to record the doses of anti-infective agents with inhaled administration described in the literature for both adult and paediatric populations. In the case of anti-infective agents without approval for inhaled administration, to propose the optimum manner in these should be prepared to achieve osmolality and pH values as similar as possible to physiological values.

METHOD

A systematic, sequential and repetitive search was carried out of the Pubmed database for the years 1960 to 2005 using the key words “inhalation OR inhaled OR aerosol OR aerosolized OR nebulized” followed by each of the anti-infective agents cited in the Guía de Antinfectiosos en Pediatría (Guide of anti-infective agents in pediatrics) by C. Barroso and F. Moraga (2003)19. This guide was chosen because it is complete, and at the same time it is simple and practical and presents the anti-infective agents by groups enabling a systematic, orderly search.

Articles and publications on the subject were reviewed. The Micromedex® database, text books15-18 and specifications of the proprietary drugs were also consulted19-32. Only information giving the dose, osmolality and pH values was taken into account. The rest was excluded.

The nebuliser solutions were prepared for all of the drugs for which information was found (except for zanamivir, which has a presentation in powder form which can be inhaled). The drugs approved for inhaled administration were prepared according to the manufac-
turers’ recommendations. For the anti-infective agents which are not approved for inhaled administration, dilutions of raw material or branded drug products for intravenous administration were prepared by reconstituting/diluting with WFI or PSS according to the doses recorded in the literature, if permitted by their physicochemical stability, to a final volume of 4-5 ml. The branded drug product available at the time from the pharmacy department of our hospital was always used as a starting point, except in the case of niastatin, when the raw material was used. The metabisulphite content of the different aminoglycosides was also taken into account, and the preparations with the lowest levels were chosen.

Osmolality was measured with a micro-osmometer (model 3MO® Advanced Instruments, Inc., Medical Europa, S.A.) and the pH of all the dilutions was measured using a portable pH meter (PHM80® Radiometer Copenhagen), except for caspofungin, the pH of which was obtained from information contained in the literature. If more than one dilution was made using different diluents and/or different concentrations were made for the same dose of the drug, the optimum form of preparation was considered that with values as close as possible to an osmolality of between 150 and 550 mOsm/kg and a pH of 7 ± 0.5.

RESULTS

Eighteen anti-infective agents are described in the literature in the form of solution to be inhaled in adult patients, 12 of which are antibiotics (amikacin, amoxicillin, aztreonam, cefotaxime, ceftazidime, colistin, gentamicin, imipenem/cilastatin, ticarcillin, tobramycin, sulphite-free tobramycin and vancomycin), 5 antifungals (conventional amphotericin B, liposomal amphotericin B, caspofungin, nystatin and pentamidine), and 1 antiviral (ribavirin).

Nine anti-infective agents have been described for the paediatric population, seven of which are antibiotics (amikacin, colistin, gentamicin, ticarcillin, tobramycin, sulphite-free tobramycin and vancomycin), one antifungal (pentamidine) and one anti-viral (ribavirin).

Of the 18 anti-infective agents described, only three were approved for inhaled administration in adults: sulphite-free tobramycin (Tobi®), colimycin (Colistimethate GES®), and pentamidine (the product Pentacarinat® and not Pentam® which is currently imported by the Ministry of Health). In paediatrics, of the nine agents found, four were approved for inhalation: the three described above plus ribavirin (Virazole®).

In table I, the doses of the inhaled anti-infective agents described in the literature are shown, for both adult and paediatric populations, as is the form of preparing each of the doses found, the pH and osmolality of the solution corresponding to the dilution described, the approval or lack of approval of the inhaled route of administration and the level of clinical evidence found in the literature. The bibliographical references appearing in the dose boxes correspond to the doses or intervals of the doses described; the pH values and the osmolality corresponding to the form of preparation referred to. Meropenem was also included in this table, even though no information has been found in the literature, as it had been used via the inhaled route in our hospital after being authorised for compassionate use.

The scale used to classify the quality of evidence for each anti-infective agent per population group is that used in our hospital to prepare clinical practice guidelines and is basically an adaptation of the Scottish model (Table II). If for each of the anti-infective agents, there are different sources of information with different qualities of evidence, in table I the level of the greatest evidence found is shown (lower level).

The proprietary drugs tobramycin, gentamycin gentamicin and amikacin contain sodium metabisulphite as an excipient. To make the solutions of gentamycin gentamicin and tobramycin, the proprietary drug with the lowest content of sodium metabisulphite per milligram (mg) of drug was chosen. There was the exception of the 20 mg gentamycin gentamicin preparation, for which a presentation of 80 mg/2 ml was preferred to 240/3 ml due to the lower bisulphite content of the latter. In the case of amikacin, the presentation made no difference, as they contain the same amount per mg of drug. Table III shows the bisulphite content of the different presentations of these proprietary drugs.

We have reported the preparation of 48 solutions using anti-infective agents for nebulisers. Some of these are outside the recommended parameters, 2 have osmolality > 1,100 mOsm/kg and 5 < 100 mOsm/kg, and 2 have a pH > 8 and 14 a pH < 5.

DISCUSSION

Although anti-infective therapy through the inhaled route is widely used, there is not a great deal of literature on the subject. There are very few drugs that have been legally approved for inhaled administration. The majority of them are used empirically with the only evidence, in many cases, being the description in the literature of a clinical case or the opinion of a group of experts.

In our study we have tried to show the current situation of inhaled antibiotherapy, taking into consideration the inhaled anti-infective agents used, highlighting the descriptions of the doses used and the method of administration for agents which do not have an accepted inhaled route, with the intention of facilitating clinical use and helping nursing personnel with this type of therapy. The pH and osmolality measurements of the dilutions allow possible intolerance to be foreseen in the administration when using a proprietary drug not designed to be administered through the inhaled route.

S. Clemente Bautista et al. Farm Hosp 2007; 31: 112-119
Table I. Dose and preparation of anti-infective agents through the inhaled route

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Form of preparation</th>
<th>Osmolality (mOs/kg)</th>
<th>pH</th>
<th>Approved Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin (AK)</td>
<td>400 mg every 8 h&lt;sup&gt;15&lt;/sup&gt;</td>
<td>1.6 ml AK 500/2 ml + 2.4 ml WFI</td>
<td>331</td>
<td>4.6</td>
<td>No Ib</td>
</tr>
<tr>
<td></td>
<td>100 mg every 12 h&lt;sup&gt;13,16&lt;/sup&gt;</td>
<td>1.6 ml AK 125/2 ml + 2.4 ml SSF</td>
<td>254</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>500 mg every 12 h&lt;sup&gt;11&lt;/sup&gt;</td>
<td>2 ml AK 500/2 ml + 2 ml WFI</td>
<td>412</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Children</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 12 years: 250 mg every 12 h&lt;sup&gt;17&lt;/sup&gt;</td>
<td>1 ml AK 500/2 ml + 3 ml SSF</td>
<td>430</td>
<td>4.6</td>
<td>No IV</td>
</tr>
<tr>
<td>Amoxicillin (AX)</td>
<td>500 mg every 12 h&lt;sup&gt;9,18,40&lt;/sup&gt;</td>
<td>4 ml AX 1g/8 ml WFI</td>
<td>596</td>
<td>8.8</td>
<td>No III</td>
</tr>
<tr>
<td>Amphoterin B (AB)</td>
<td>5-6 mg every 6-12 h&lt;sup&gt;22,23&lt;/sup&gt;</td>
<td>5-6 ml of 50 mg AB/50 ml WFI</td>
<td>9</td>
<td>5.5</td>
<td>No Ib</td>
</tr>
<tr>
<td></td>
<td>10 mg every 6-8 h&lt;sup&gt;16&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liposomal amphoterin B (LAMB)</td>
<td>24 mg three times/week (1-2 month post lung transplant)&lt;sup&gt;43&lt;/sup&gt;</td>
<td>24 mg of liposomal AB/2 ml WFI</td>
<td>285</td>
<td>7.5</td>
<td>No IIb</td>
</tr>
<tr>
<td></td>
<td>24 mg three times/week (3-6 month post lung transplant)&lt;sup&gt;43&lt;/sup&gt;</td>
<td>24 mg of liposomal AB/2 ml WFI</td>
<td>285</td>
<td>7.5</td>
<td>No IIb</td>
</tr>
<tr>
<td>Aztreonam (AZ)</td>
<td>1,000 mg every 12 h&lt;sup&gt;11&lt;/sup&gt;</td>
<td>1,000 mg AZ/4 ml WFI</td>
<td>1,134</td>
<td>4.9</td>
<td>No IV</td>
</tr>
<tr>
<td></td>
<td>500 mg every 12 h&lt;sup&gt;13&lt;/sup&gt;</td>
<td>500 mg AZ/4 ml WFI</td>
<td>570</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Caspofungin (CP)</td>
<td>50 mg&lt;sup&gt;15&lt;/sup&gt;</td>
<td>50 mg CP/5 ml PSS</td>
<td>301</td>
<td>&lt; 6.3</td>
<td>No III</td>
</tr>
<tr>
<td></td>
<td>150 mg&lt;sup&gt;15&lt;/sup&gt;</td>
<td>150 mg CP/5 ml PSS</td>
<td>326</td>
<td>&lt; 6.3</td>
<td>No III</td>
</tr>
<tr>
<td>Cefotaxim (CX)</td>
<td>500 mg every 6-12 h&lt;sup&gt;13&lt;/sup&gt;</td>
<td>5 ml CX 1.000 mg/10 ml WFI</td>
<td>364</td>
<td>5.1</td>
<td>No IV</td>
</tr>
<tr>
<td></td>
<td>1,000 mg every 12 h&lt;sup&gt;13&lt;/sup&gt;</td>
<td>1,000 mg CX/5 ml WFI</td>
<td>706</td>
<td>5.4</td>
<td>No IV</td>
</tr>
<tr>
<td>Ceftazidime (CZ)</td>
<td>1,000 mg every 12 h&lt;sup&gt;22,23,44&lt;/sup&gt;</td>
<td>1,000 mg CZ/5 ml WFI</td>
<td>596</td>
<td>7.3</td>
<td>No Ib</td>
</tr>
<tr>
<td></td>
<td>500 mg every 6-12 h&lt;sup&gt;22,23&lt;/sup&gt;</td>
<td>5 ml CZ 1,000 mg/10 ml WFI</td>
<td>335</td>
<td>7.5</td>
<td>No Ib</td>
</tr>
<tr>
<td></td>
<td>250 mg every 12 h&lt;sup&gt;48&lt;/sup&gt;</td>
<td>2.5 ml CZ 1,000 mg/10 ml API + 2.5 ml PSS</td>
<td>352</td>
<td>7.6</td>
<td>No Ib</td>
</tr>
<tr>
<td>Colistin (CL)</td>
<td>0.25 mU every 6 h&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1 ml CL 1 mU/4 ml WFI + 4 ml WFI</td>
<td>20</td>
<td>8.5</td>
<td>Yes Ib</td>
</tr>
<tr>
<td></td>
<td>1 mU every 8-12 h&lt;sup&gt;2,24,41&lt;/sup&gt;</td>
<td>1 mU CL/4 ml WFI</td>
<td>77</td>
<td>7.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 mU every 8-12 h&lt;sup&gt;2,24,41&lt;/sup&gt;</td>
<td>2 mU CL/4 ml WFI</td>
<td>137</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 mU every 12 h&lt;sup&gt;2,41&lt;/sup&gt;</td>
<td>3 mU CL/4 ml WFI</td>
<td>183</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Children</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 2 years: 1-2 mU every 8-12 h&lt;sup&gt;13&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 6 years: 1-3 mU every 12 h&lt;sup&gt;19&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 6 years: 0.5 mU every 12 h&lt;sup&gt;13&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 6 years: 1-2 mU every 12 h&lt;sup&gt;13&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentamicin (GT)</td>
<td>40 mg every 6-12 h&lt;sup&gt;12&lt;/sup&gt;</td>
<td>0.5 ml GT 240/3 ml + 3.5 ml PSS</td>
<td>293</td>
<td>4.4</td>
<td>No Ib</td>
</tr>
<tr>
<td></td>
<td>80 mg every 6-12 h&lt;sup&gt;12,14&lt;/sup&gt;</td>
<td>1 ml GT 240/3 ml + 3 ml PSS</td>
<td>296</td>
<td>4.4</td>
<td>No Ib</td>
</tr>
<tr>
<td></td>
<td>160 mg every 6-12 h&lt;sup&gt;12&lt;/sup&gt;</td>
<td>2 ml GT 240/3 ml + 2 ml PSS</td>
<td>277</td>
<td>3.5</td>
<td>No Ib</td>
</tr>
<tr>
<td></td>
<td><strong>Children</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 2 years: 40 mg every 12 h&lt;sup&gt;19&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>No Ib</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 years: 80 mg every 12 h&lt;sup&gt;12,14&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>No Ib</td>
</tr>
<tr>
<td></td>
<td>&lt; 1 year: 80 mg every 12 h&lt;sup&gt;19&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>No Ib</td>
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<tr>
<td></td>
<td>&gt; 1 year: 120 mg every 12 h&lt;sup&gt;19&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>No Ib</td>
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<tr>
<td></td>
<td>Adolescents: 160 mg every 12 h&lt;sup&gt;19&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>No Ib</td>
</tr>
</tbody>
</table>

(See the following page)
Table I. Dose and preparation of anti-infective agents through the inhaled route (continuation)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Form of preparation</th>
<th>Osmolality (mOsm/kg)</th>
<th>pH</th>
<th>Approved</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem-cilastatin (IC)</td>
<td>Adults</td>
<td>500 mg every 8 h&lt;sup&gt;11,14&lt;/sup&gt;</td>
<td>500 mg IC/10 ml PSS</td>
<td>651</td>
<td>7.4</td>
<td>No</td>
</tr>
<tr>
<td>Meropenem (MP) Adults</td>
<td>500 mg every 12 h</td>
<td>500 mg MP/10 ml WFI</td>
<td>350</td>
<td>7.9</td>
<td>No</td>
<td>IV</td>
</tr>
<tr>
<td>Nystatin (N) Adults</td>
<td>50.000-500.000 UI every 4-12 h&lt;sup&gt;5,65&lt;/sup&gt;</td>
<td>50,000 UI N5 ml PSS</td>
<td>303</td>
<td>6.9</td>
<td>No</td>
<td>IV</td>
</tr>
<tr>
<td>Pentamidine (P) Adults</td>
<td>300 mg/month&lt;sup&gt;14,17,62-65&lt;/sup&gt;</td>
<td>300 mg P/5 ml WFI</td>
<td>193</td>
<td>6.1</td>
<td>Yes</td>
<td>Ib</td>
</tr>
<tr>
<td>Ribavirin (R) Adults</td>
<td>6 g/day&lt;sup&gt;14,20,72&lt;/sup&gt;</td>
<td>6 g R/100 ml of WFI (3 sessions of 2 h)</td>
<td>225</td>
<td>4</td>
<td>No</td>
<td>III</td>
</tr>
<tr>
<td>Ticarcillin (TC) Adults</td>
<td>1.000 mg every 12 h&lt;sup&gt;14&lt;/sup&gt;</td>
<td>1.000 mg TC/4 ml WFI</td>
<td>2.156</td>
<td>6.2</td>
<td>No</td>
<td>III</td>
</tr>
<tr>
<td>Tobramycin (TB) Adults</td>
<td>40 mg every 6 h&lt;sup&gt;14&lt;/sup&gt;</td>
<td>0.8 ml TB 100/2 ml + 3.2 ml PSS</td>
<td>270</td>
<td>5.7</td>
<td>No</td>
<td>Ib</td>
</tr>
<tr>
<td>Sulphite-free TB (SFTB) Adults</td>
<td>300 mg every 12 h&lt;sup&gt;14,19,21,71,78&lt;/sup&gt;</td>
<td>5 ml de SFTB</td>
<td>173</td>
<td>6.1</td>
<td>Yes</td>
<td>Ib</td>
</tr>
<tr>
<td>Vancomycin (V) Adults</td>
<td>120 mg every 6 h&lt;sup&gt;15&lt;/sup&gt;</td>
<td>2.5 ml of 500 mg V/10 ml PSS + 2.5 ml PSS</td>
<td>304</td>
<td>3.7</td>
<td>No</td>
<td>IV</td>
</tr>
</tbody>
</table>

Amikacin: Amikacin Normon®; Amoxicillin: Amoxi Gobens®; Amphotericin B desoxycholate: Fungizone®; Amphotericin B liposomal: Ambisome®; Aztreonam: Azactam®; Cefotaxime: Claforan®; Ceftazidime: Kefamin®; Cefoxitin: Kefoxitin®; Colistin: Colistimethate GES®; Gentamicin: Gent-Gobens®; Imipenem-cilastatin: Tienam®; Meropenem: Meronem®; Nystatin; raw material; Pentamidine: Pentam®; Ribavirin: Virazole®; Ticarcillin: Ticarpen®; Sulphite free tobramycin: Tob®; Tobramycin: Tobra-Gobens®; Vancomycin: Vancomicina Normon®.
Table II. Scale for classifying the quality of the evidence (levels I to IV)

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Randomised clinical studies, meta-analysis or systematic reviews of randomised clinical trials, without any methodological limitations (regarding variations, precision and heterogeneity of the results)</td>
</tr>
<tr>
<td>Ib</td>
<td>Randomised clinical trials, meta-analysis or systematic reviews of randomised studies, with no methodological limitations</td>
</tr>
<tr>
<td>Ila</td>
<td>Semi-experimental studies, cohort studies, control case studies, without any methodological limitations (regarding variations and confusion factors)</td>
</tr>
<tr>
<td>IIb</td>
<td>Semi-experimental studies, cohort studies, control case studies, with no methodological limitations (regarding variations and confusion factors)</td>
</tr>
<tr>
<td>III</td>
<td>Descriptive studies (longitudinal or follow-up, cross-sectional, ecological correlation and others). Temporal series. Records and databases</td>
</tr>
<tr>
<td>IV</td>
<td>Reports from expert committees. Opinions based on clinical experience. Case studies</td>
</tr>
</tbody>
</table>

Table III. Sodium bisulphite content

<table>
<thead>
<tr>
<th>Proprietary drugs</th>
<th>mg of sodium bisulphite/mg of antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin Normon® 125 mg/2 ml</td>
<td>0.0264 mg</td>
</tr>
<tr>
<td>Amikacin Normon® 500 mg/2 ml</td>
<td>0.0264 mg</td>
</tr>
<tr>
<td>Genta-Gobens® 40 mg/2 ml</td>
<td>0.16 mg</td>
</tr>
<tr>
<td>Genta-Gobens® 80 mg/2 ml</td>
<td>0.08 mg</td>
</tr>
<tr>
<td>Genta-Gobens® 240 mg/3 ml</td>
<td>0.04 mg</td>
</tr>
<tr>
<td>Tobra-Gobens® 50 mg/2 ml</td>
<td>0.056 mg</td>
</tr>
<tr>
<td>Tobra-Gobens® 100 mg/2 ml</td>
<td>0.028 mg</td>
</tr>
</tbody>
</table>

One limitation of our study was the fact that that preparations were only made from the proprietary drugs (branded products) available in our hospital. Therefore, in many cases, the results will only act as a basis when it is necessary to use other proprietary drugs, since osmolality and pH values could vary.

Clinical trials could establish the dose, frequency and duration of the treatment, in addition to showing their efficacy and safety.

References

40. Hill SL, Morrison HM, Burnett D, Stockley RA. Short term response of patients with bronchiectasis to treatment with amoxicillin given in standard or high doses orally or by inhalation. Thorax 1986; 4: 559-65.
41. Connealy E, Cafferkey MT, Daly PA, Keane CT, McCann SR. Nebulized amphotericin B as prophylaxis against invasive aspergillosis in granulocytopoenic patients. Bone Marrow Transplantation 1990; 5: 403-6.

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