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GENEBU Project. Equipment and drugs used for home nebulizer therapy in Italy

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ABSTRACT: ***GENEBU Project. Equipment and drugs used for home nebulizer therapy in Italy. A.S. Melani, M. Pirrelli, P. Sestini, M. Del Donno, M. Bonavia, P. Canessa, C. Giacomelli, V. Cilenti, P. Martucci, A. Sena, G. Grande, V. Cappiello, M. Aliani, M. Neri, on behalf of the Associazione Italiana Pneumologi Ospedalieri Educational Group.***

The GENEBU Project is an open, observational survey evaluating home nebulizer practices in Italy. It consecutively included patients who were referred to one of the 27 participating chest clinics from May to December 1999 and who had been using a home nebulizer in the previous six months.

The information source was a self-administered questionnaire compiled by the enrolled subjects. We collected 1257 questionnaires.

The nebulizer equipment was heterogeneous, with at least 92 different models. Jet nebulizers were 90% of the total; 53% of these had a glass reservoir. Almost 80% of the patients selected the nebulizer themselves without any medical advice. In addition, most patients (>80%) did not receive information on both the interface system and the optimal fill volume of the nebulizer.

Corticosteroid nebulisation was widespread (74%), for both occasional and regular daily use, for both acute and chronic diseases from upper to lower airways. Beta$_2$-agonist (55%), anticholinergic (37%), mucolytic (32%) drugs were also often nebulised. More than 90% of patients mixed some active drugs.

We conclude that the nebulizer equipment for home aerosol therapy was very heterogeneous and, probably, not always utilised at its best in Italy. The mixing of drugs and the widespread use of corticosteroids were peculiarities of home nebulizer therapy in Italy.
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Keywords: Aerosol, nebulizer therapy, asthma, chronic obstructive pulmonary disease, clinical practice, home care.

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Introduction

Aerosolisation is advantageous in comparison with other routes of administration in respiratory medicine, because it permits to active drugs be delivered directly to the airways with rapid onset of action and minimal systemic effects.

A therapeutic aerosol is currently produced by nebulizers, Metered Dose Inhalers (MDIs) and Dry Powder Inhalers (DPIs).

Nebulizers are cumbersome, time-consuming and not very efficient, and as a result many physicians consider them as a second-choice for delivering an aerosol therapy. Although not extensively evaluated in the literature [1–3], many patients prefer nebulizers in home clinical practice.

Nebulizers have been used for many years to deliver bronchodilator, corticosteroid, antibiotic and mucolytic drugs [1–3], but their use seems to vary largely between different countries. In 1992, an international asthma survey was carried out by chest physicians from 19 European countries. Vermeire found [4] that β_2-agonists were the most commonly nebulised drugs, but corticosteroid, anticholinergic and mucolytic drugs were also used; corticosteroids were seldomly employed in U.K., but were more common in Germany, Austria and Switzerland; mucolytic drugs appeared mainly utilised in the Eastern Europe, but also in Germany and Austria.

Guidelines stress that the nebulizer equipment largely influences the dose of active drug delivered to the airways [1–3]. However, to our knowledge, no nation-wide survey has investigated what equipment is used for home nebulizer therapy in clinical practice and whether the choice of nebulizer equipment depends on both the appropriate airway target site and the characteristics of the nebulised solution.

The AIPO (Italian Association of Hospital Pneumologists) Educational Group has carried out the GENEBU (Gruppo Educativo per i NEBUlizzatori) Project with the aim of evaluating home nebulizer practices in Italy. This survey analyses the current equipment and the most commonly used drugs with relative dosages for home nebulizer therapy. It also evaluates the patients' perceived effectiveness of nebulizer therapy and the comparison with other inhalers in terms of effectiveness, ease of use and personal preference.

Material and methods

The GENEBU Project is an open, cross-sectional, observational study carried out in 27 Respiratory Centres throughout Italy, from 1st May to 31st December 1999. Although the enrolment of investigators was voluntary, the participating centres encompassed several geographical and environmental conditions, therefore, we believe that this survey has a nation-wide value (see centres listing in footnote 1).

The design of the GENEBU Project has been extensively described elsewhere [5]. Briefly, during the study period, all the patients who were referred to one of the participating centres, were and had been using a home nebulizer in the six months prior to the enrolment and agreed to take part in this study, giving written informed consent, were included. Once enrolled, all the patients compiled a self-administered questionnaire on their home nebulizer practices. The diagnosis of the respiratory disease, written from the investigators, was the only exception to self-compilation.

The present manuscript includes the results to some close-ended answers mainly on both the perceived effectiveness of nebulizer therapy to relieve symptoms and the comparison with other inhalers in terms of effectiveness, ease of use and personal preference. It also includes some open answers, which analysed the model of the current nebulizer equipment and the nebulised solution with the initial fill volume, and the dosages of active drugs.

Chi square statistics and multiple logistic regression were used for the analysis of categorical variables. Unless stated otherwise, all logistic models included gender, age and presence of bronchopulmonary diseases to adjust to these possible confounders. A p value of 0.05 or less for a two tailed test was considered as significant. Data analysis was performed using the Stata v7.0 program (Stata corp., College Station, TX, USA).

Results

1,157 subjects answered and returned the questionnaire. Almost 90% of patients mainly suffered from bronchopulmonary diseases and the remaining ones (10.3%) only of upper airways diseases. Almost 95% of the patients with bron-

Table 1. – The most common types of nebulizers

Type of nebulizer	No.
Artsana Project II ultrasound	53
Artsana jet unspecified	44
Artsana Record jet type diaphragm compressor	10
Alleanza e Salute jet unspecified	13
Atomizer 3A Elettromedicali unspecified	10
CAMI Pharmasol jet type diaphragm compressor	12
Farmac-Zabban Zeta-Sol jet type diaphragm compressor	20
Farmac-Zabban Neosol jet type rotary piston compressor	11
FLAEM Linea F Angelini jet type diaphragm compressor	117
FlAEM Universal II ultrasound	22
Ico Air Lister Rapid ultrasound	10
Ico Air Lister Plus unspecified	15
Ico Air Lister 2000 jet type diaphragm compressor	45
IMETEC jet unspecified	26
Markos Mobyneb jet type rotary piston compressor	10
Markos Nebula jet type rotary piston compressor	167
Markos Soffio jet type rotary piston compressor	47
Medel Aerofamily jet type rotary piston compressor	25
Medel Microlux jet type diaphragm compressor	35
Medel Microgen jet type diaphragm compressor	14
Nord Italia Elettromedicali Constellation jet unspecified	14
Nord Italia Elettromedicali Concorde jet unspecified	10
Nucleo Pharma Mercury Super jet unspecified	16
Pari Boy LC Plus jet type rotary piston compressor	9
Others	335

chopulmonary diseases had chronic problems, such as COPD (46%) and bronchial asthma (31%).

In Italy patients needing a home nebulizer, took charge of their the device directly. Just under 80% of patients made a decision regarding their nebulizer equipment, without any advise from the prescribing physician. One thousand and ninety-nine patients reported the model name of their nebulizer: ninety-two different models were reported at all, being the most common ones reported in table 1. Jet nebulizers were the most commonly used systems, but ultrasound ones accounted for around 7% of the total. Ultrasound nebulizers were similarly diffused between patients with upper and lower airways disease, as well as between those with occasional (less than 60 days per year) and regular daily use (6.9% vs. 6.5%). Most patients powered the jet nebulizer using a compressor; approximately half of the specified compressors were rotary piston types, and the others, diaphragm ones, with no difference between patients with prevalent lower or upper airways diseases. A few subjects (9.7%) used oxygen as a source of compressed gas for nebulisation and more often were patients suffering with bronchopulmonary disturbances (10.6% vs. 1.2%, $p<0.001$). All patients were using a jet nebulizer employed disposable reservoirs. Among jet nebulizers, a glass reservoir was used in 53.4% cases, mainly often in patients with only upper airways diseases (66.3% vs. 50.4%, $p<0.01$).

Eighty-three-per-cent of patients reported that they decided to use the interface system with the nebulizer equipment themselves, without any medical information. Subjects who mainly suffered with lung diseases mainly used the mouthpiece (24.5% vs. 17.9%, $p<0.05$) and face mask (71.3% vs. 52.8%, $p<0.01$), but less frequently the nose adaptor (7.5% vs. 34.9%, $p<0.001$). With respect to those patients with only upper airways disturbances, some patients gave more than one answer, probably because they used more systems due to their medical circumstances.

The most commonly used drugs with relative dosages are reported in table 2. Some drugs were mainly nebulised for less than 60 days per year, others had a regular or almost regular daily use, as shown in table 3. Table 3 also shows that some drugs were used mainly for bronchopulmonary diseases, others for upper airways disturbances; only corticosteroids had widespread use (78% of total) for both acute and chronic diseases from upper to lower airways. After adjustment for gender, age, frequency of use and disease, patients using ultrasound nebulizers nebulised corticosteroids more often than those using jet ones (85.5 vs. 74.4%, $p<0.05$). We did not observe any difference in the average dosage of beclomethasone dipropionate (BDP), the most commonly used corticosteroid, between subjects with acute and chronic diseases, as well as with upper and lower airways disturbances.

Less than 10% of patients (112 cases) used only one active drug for each nebulisation. Mixing active drugs was quite ubiquitous: of 745 patients with lung diseases who used bronchodilators, 659 (88%) mixed them with steroids. There were no significant difference in the mean dose of both salbutamol and ipratropium bromide, the most commonly used bronchodilators, between patients who used them either alone or mixed to corticosteroids, as well as in the mean dose of

Table 2. – Drugs nebulised with home nebulizers, their frequency of use and dosages

Drug	No. of users	Median, mg	95% IC, mg
MUCOLYTICS	*396*		
Ambroxol	251	15	15-15
N-acetylcysteine	97	300	300-300
Sobrerol	34	40	30-40
MESNA	13	600	300-600
Bromhexin	8	4	2-4
Tiopronin	3	200	200-200
ANTIBIOTICS	*62*		
Tiamfenicol	43	500	500-500
Tobramycin*	14	100	90-108.30
Gentamicin*	5	20	0.3-40
Ceftazidime*	1	1000	1000-1000
CORTICOSTEROIDS	*935*		
BDP	736	0.8	0.8-0.8
Flunisolide	192	1	1-1
Betamethasone*	23	0.5	0.5-1
Methylprednisolone*	3	3	3-3
Hydrocortisone*	4		
CROMONS	*59*		
Nedocromil sodium	41	10	10-10
Cromoglycate disodium	18	20	20-20
BRONCHODILATORS	*745*		
Salbutamol°	608	2	1.87-2
Ipratropium bromide°	456	0.25	0.25-0.25
Fenoterol	82	1.25	1.25-1.25
Oxitropium°	8	0.5	0.42-0.6

* These drugs are currently unlicensed for the aerosol route in Italy.
° These drugs are available only as multiple dose vials in Italy.

Table 3. – Some modalities of use for nebulised drugs

Drug	Use for broncho-pulmonary diseases	Use only for upper airways diseases	Occasional use*	Regular daily use
Steroids	77.7	61.5°°	71.2	85.2°°
Antibiotics	3.4	11.3°	6.1	1.8°°°
Mucolytics	24.8	53.8°°	38.2	12.6°°
Anticholinergics	44.4	7.1°°	27.1	65.4°°
Beta-agonists	63.5	14.1°°	47.3	75.6°°
Cromons	5.1	3.2	5.4	2.8°°

Results are reported as percentage of the group; * Occasional use means nebulisation for less than 60 days per year; ° $p<0.01$; °° $p=0.01$; $p=0.05$.

BDP, nebulised either alone or mixed to bronchodilators.

The mean total volume of the solution into the reservoir before starting nebulisation was 3.5 ± 1.2 ml. (mean ± SD), without any significant difference at least for the most commonly used types of jet nebulizer. Although the initial volume of solution varied largely, it did never resulted in less than 2.5 ml for single nebulisation. Forty-three per cent of patients added physiologic saline to active drugs, 5.1% distilled water, 1.8% tap water, while the remaining ones did not add any solvent to the active drug. Most patients (97.3%) reported that they never received any information from health care advisors on the optimal and the minimal fill volume of drug solution before starting nebulisation.

The mean length of each nebulisation was less than 15 minutes in 65.4% of cases, from 15 to 30 minutes, in 30.4%, and beyond 30 minutes in 3%. There was no difference in the average duration of each nebulisation between patients with upper and lower airways disease. However, the concept of "time of nebulisation" was considered differently between groups of patients: a greater percentage of patients with bronchopulmonary disease continued their nebulisation until "ending the drug solution" than those with upper airways disturbances (58.3% vs. 38.9%, $p<0.01$). On the contrary, the latter group stopped the aerosolisation more often, either after a prefixed time (27% vs. 15.2%), or when the subject felt better (25% vs. 19.2%). Nearly all the respondents (98%) prepared the drug solution into the reservoir just before the nebulization. Most patients, who did not reach dryness, threw the residual solution away, but 12% of subjects, who did not end the drug solution, again used it after some hours from the first interruption.

The subjects perceived the effectiveness of the nebulizers for aerosol therapy from their own symptoms is analysed in table 4.

Only 36% of the respondents never used any other delivery devices other than nebulizers for aerosol therapy. The perceived value of home aerosol therapy using nebulizers in contrast to other inhalers for subjects with no or previous experience with delivery devices other than nebulizers is reported in table 5. For both nebulizer users with little or no previous experience of other inhalers, the preference always remained the same related to the ease of use and efficacy using a multiple regression model ($p<0.001$).

Table 4. – Perceived effectiveness of aerosol therapy with home nebulizers

Symptom	Positive result in patients with lower airways disease, %	Positive result in patients with upper airways disease, %
Reduction of cough	27.5	23.8
Easier expectoration	34.2	29.3
Reduction of running and closed nose	12.7	60.7*
Reduction of wheezing	22.7	8.3*
Reduction of dyspnea	80.4	39.7*

Results are reported as percentage of the group; * $p<0.001$.

Table 5. – Perceived value of aerosol therapy with home nebulizers with respect to other inhalers

	Nebulizer	MDI/DPI	No difference
Patients with no previous experience with inhalers other than nebulizers considered:			
The most effective delivery device:	72.9	6.8	20.3
The easiest device to use:	63.5	23.1	13.4
The preferred device:	67.3	13.5	19.2
Patients with previous experience with inhalers other than nebulizers considered:			
The most effective delivery device:	49.0	33.1	17.9
The easiest device to use:	19.3	70.1	11.6
The preferred device:	36.7	49.2	14.1

Percentage of subjects in the group.

Discussion

This is the first survey evaluating the nebulised drugs and the nebulizer equipment for aerosol therapy in Italy among patients using a home nebulizer and referring to chest clinics. We have previously shown that home nebulizer therapy has several applications in Italy, for both acute and chronic diseases from upper to lower airways, ranging from the paediatric to the elderly [6]. The different uses of home nebulizer therapy may require one or several different drugs, each with an explanation of that particular nebulizer system for optimal compatibility as we found many different types of nebulizers. However, our study does not seem to support this possibility. In fact, the choice of nebulizer equipment did not base itself on technical reasons, because most patients selected it without any medical advice. Their choices were based on the minimal characteristics required for an effective delivery device. Likewise, to date, there has been no source of unbiased information regarding the quality of available nebulizers in Italy. In addition reliable functions cannot automatically be assumed for a specific nebulizer simply because it has been accepted in the market. Since adequate information on commercially available nebulizers is scarce in Italy, physicians who prescribe a home nebulizer, when make purchasing decisions, either simply follow only their own clinical experience, or, more often, do not advice any specific model of nebulizer, as we have observed. Obviously, further studies should accurately evaluate this topic.

Nevertheless, this study has not been devised to investigate whether the nebulizer equipment used by our patients was always consistent in delivering an adequate amount of drugs into the targeted airways. The length of nebulisation has been considered as a rough estimation of nebulizer performances [7], but this is not possible for our study because, both the drugs, the initial amount of nebulised solution and the same concept of nebulisation time were too different. However, we suggest that there is certainly the possibility to improve home nebulizer equipment in Italy. Firstly, more than half of our patients used a glass and not disassemblable reservoir for nebulisation; and it is well known that the quality control by manufacturers is not as high in blown glass, as current moulded plastic reservoirs [1]. Secondly, for reason of convenience and compliance nebulization should deliver the effective dose of drug to the airways in as short a time as possible, but more than a third of our patients required at least 15 minutes for each nebulisation (1). Thirdly, although jet nebulizers were the most commonly used devices in our study, a significant number of our patients employed ultrasonic nebulizers and, more often, they were compelled to nebulise corticosteroids for lower airways diseases. British Thoracic Society does not support the use of current ultrasound nebulizers for nebulising drug suspension, such as corticosteroids, which are ubiquitously used from our patients, at least until their effectiveness has been effectively demonstrated in clinical practice [1].

The conjunction system of patients with the nebulizers is another question, which may largely influence the drug delivery to the lungs. Most of our subjects chose the face-mask as interface system for their nebulisations. We did not investigate whether these subjects breathed through either the mouth or the nose, but the counselled interface system for patients who use home nebulizers mainly for lung diseases is a mouth-piece and nose-clips [1–3]. Alternatively, care has to be taken when using the face-masks to avoid nasal inhalation, as the nose is a very effective filter of aerosols. However most of our patients never received any information on the interface system of nebulizer and its optimal modality for use from their respective physician.

The optimal fill volume of the drug solution into the reservoir varies depending on the nebulizer [8]. Such a volume fill is another important variable for optimising nebulizer performances, but neither the prescribing physicians, nor patients seemed to perceive this point as a problem in our survey.

With reference to Vermeire's data [4], the widespread use of corticosteroids and the mixing of more active drugs seem to be peculiarities of home nebulizer therapy in Italy. Interestingly, corticosteroids were used for both occasional and daily use, for treatment of both acute and chronic diseases from upper and lower airways. With respect to its use in chronic lung diseases, inhaled corticosteroids may be useful in COPD and are a mainstay in bronchial asthma, but most available studies establishing their role used either MDIs or DPIs. There are currently good evidence to suggest that nebulised budesonide may have the same value of budesonide, given by MDI and spacer [9], but the clinical significance of nebulised BDP or flunisolide is substantially unknown. At present few studies have been performed *in vivo* and have shown contrasting results [10–14]. In an *in vitro* study O'CALLAGHAN [15] showed that BDP suspension, the first formulation designed to deliver a corticosteroid by way of nebulization in Italy, nebulises poorly. In these conditions it would be advisable to use BDP only with nebulizers which are able to delivered effectively to the lungs. Similarly, dose recommendations for nebulised corticosteroids have little significance and this, perhaps, may explained the discrepancies that we have observed between the dosages of flunisolide and BDP.

The mixing of nebulised drugs has been reported in other countries [16–18], but it was usually limited to bronchodilators [16–17]. The mixing of bronchodilators and corticosteroids was almost the rule in our patients. Mixing nebulised anticholinergic and β_2-agonist drugs is not considered to reduce their clinical value, but it is unknown whether the association with other drugs may be disadvantageous. To date, with respect to the mixing of nebulised steroids and bronchodilators, DI BERARDINO *and* FRASCHINI [19] have shown in an *in vitro* study using Mobyneb®, a commonly used

nebulizer in Italy, that there is a significant reduction of the respirable fraction of particles of both salbutamol and, above all, either flunisolide or BDP when nebulised together compared to the single aerosolisation of each active drug.

This study has not been designed to investigate whether the prescription of home nebulisations was always consistent. However, it is interesting to note that even patients with previous experience of several delivery devices for aerosol therapy, perceived inhalers easier to handle, but, often, not so effective as nebulizers. We believe that is illogical to doubt patients' beliefs and preferences, above all for those patients with chronic lung disease where a multiple drugs therapeutic regimen is common and often reduces the adherence to the prescribed treatment. Likewise, several studies have shown that home nebulizer therapy may give more subjective and objective benefits than maximal therapy administered by other inhalers [20–23].

We conclude that the nebulizer equipment for home aerosol therapy is very heterogeneous in Italy, but its choice does not seem to depend on both the appropriate airway target site and the characteristics of the nebulised solution. The performances of the available nebulizers remain poor documented and, probably, they are not utilised to their maximum potential in Italy. The mixing of different nebulised drugs and the widespread use of corticosteroids are peculiarities of home nebulizer therapy in Italy, but their ultimate clinical value still has to be evaluated. We think that the implementation of guidelines in clinical practice may secure the best results in home nebulizer therapy in Italy.

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