Pediatric Neurology 73 (2017) 78–87

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

Effect of Salbutamol on Respiratory Muscle Strength in Spinal Muscular Atrophy

Sonia Khirani PhD [a,b], Ivana Dabaj MD [c,d,e], Alessandro Amaddeo MD [b,f,g], Jorge Olmo Arroyo MSc [b], Jacques Ropers PharmD [h], Stéphane Tirolien RT [c], Véronique Coudert MD [c], Brigitte Estournet MD [c,d,e], Brigitte Fauroux MD, PhD [b,f,g], Susana Quijano-Roy MD, PhD [c,d,e,i,*]

[a] *ASV Santé, Gennevilliers, France*
[b] *AP-HP, Hôpital Necker-Enfants Malades, Pediatric Noninvasive Ventilation and Sleep Unit, Paris, France*
[c] *AP-HP, Hôpital Raymond Poincaré, Hôpitaux Universitaires Paris-Ile-de-France Ouest, Pôle pédiatrique, Service de Pédiatrie, Garches, France*
[d] *Centre de Référence Maladies Neuromusculaires Garches-Necker-Mondor-Hendaye (GNMH), Garches, France*
[e] *Réseau National de Maladies Neuromusculaires FILNEMUS, Garches, France*
[f] *INSERM U955, Créteil, France*
[g] *Paris Descartes University, Paris, France*
[h] *Hôpitaux Universitaires Paris Île-de-France Ouest, Unité de Recherche Clinique, Boulogne, France*
[i] *INSERM U1179, Université Versailles Saint-Quentin (UVSQ), UFR des sciences de la santé Simone Veil, Montigny, France*

ABSTRACT

BACKGROUND: Oral salbutamol has shown clinical benefits in spinal muscular atrophy (SMA). We studied its effect on the respiratory muscle strength in children with different types of SMA. **METHODS:** Lung and respiratory muscle functions were assessed in children receiving daily oral salbutamol for at least one year. The respiratory data of age-matched SMA II historical control subjects were compared with data of SMA II patients receiving salbutamol. **RESULTS:** Seven children (6.4 ± 2.0 years old, range four to ten; one SMA I, five SMA II, and one SMA III) treated with salbutamol (duration 23 ± 8 months) were assessed. Maximal static inspiratory pressure, sniff nasal inspiratory pressure, and slow vital capacity were significantly better in the salbutamol-treated SMA II group compared with control subjects ($P < 0.05$). **CONCLUSIONS:** Long-term oral salbutamol showed benefits in respiratory function in children with SMA and appeared to increase the strength of the inspiratory muscles in a small cohort of SMA II patients.

Keywords: spinal muscular atrophy, salbutamol, respiratory muscles, lung function, motor function

Pediatr Neurol 2017; 73: 78-87

Introduction

Spinal muscular atrophy (SMA) is a common genetic neuromuscular disease caused by a deficit of the survival motor neuron (SMN) protein encoded by two closely related genes, *SMN1* and *SMN2*, located on chromosome 5q13. Patients have usually no functional *SMN1* gene, although they retain at least one copy of the *SMN2* gene.[1] The clinical severity of the disease depends on the amount of SMN protein,[2,3] and this is related to the number of copies of *SMN2* gene.[4] SMA represents the second most common cause of mortality from a recessive genetic disorder.

Owing to the wide phenotypic presentation, patients are classified in different types based on age of onset, severity of disease, and achieved motor milestones,[5,6] but there is a continuous spectrum of severity with intermediary forms.[7]

SMA causes a predominantly bilateral proximal muscle atrophy and weakness.[5,8] The respiratory muscles are also

The present work was performed at AP-HP, Hôpital Raymond Poincaré, Hôpitaux Universitaires Paris-Ile-de-France Ouest, Pôle pédiatrique, Service de Pédiatrie, Garches and AP-HP, Hôpital Necker-Enfants Malades, Pediatric Noninvasive Ventilation and Sleep Unit, Paris, France.

Conflicts of Interest: The authors have no conflicts of interest.

Article History:
Received December 9, 2016; Accepted in final form April 12, 2017

* Communications should be addressed to: Prof. Quijano-Roy; Service de Pédiatrie; AP-HP; Hôpital Raymond Poincaré; 92380 Garches, France.
E-mail address: susana.quijano-roy@aphp.fr

0887-8994/$ – see front matter © 2017 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pediatrneurol.2017.04.013

involved with weakness of the intercostal muscles and a relatively spared diaphragm.[9] This respiratory muscle weakness translates into an impairment of cough, resulting in poor clearance of airway secretions and recurrent pulmonary infections, restrictive lung disease because of poor or insufficient chest wall and lung growth, nocturnal hypoventilation, and finally respiratory failure in the most severe patients.[8]

Short-acting β-adrenergic agonists have been showed to increase skeletal muscle strength in healthy humans[10,11] and in subjects with muscle weakness because of acute or chronic conditions.[12-14] Recent studies have suggested that salbutamol may induce a rapid and significant increase in *SMN2* full-length messenger RNA and SMN protein in human SMA fibroblasts.[15,16] Moreover, it has been shown that the significant increase in full-length *SMN2* transcript levels was directly proportional to *SMN2* gene copy number.[16] However, the mechanism of action of β2 agonists on human skeletal muscle is not completely understood, requiring further investigations.

A few studies have also evidenced motor and respiratory function improvements in SMA patients after treatment with oral salbutamol,[17,18] but no study has addressed its effect on respiratory muscle function. The lack of defined respiratory outcome measures was specifically pointed out recently in an international SMA workshop.[7] The aim of this study was to assess the effect of oral salbutamol on respiratory muscle strength and to describe the clinical effects in a series of SMA children.

Materials and Methods

Patients

We retrospectively reviewed the charts of all SMA patients followed in our multidisciplinary pediatric neuromuscular clinic who received daily treatment with oral salbutamol (GlaxoSmithKline, UK) started before December 2013. The diagnosis of SMA had been confirmed by mutation analysis of the *SMN*1 gene. We used the functional criteria of the International SMA Consortium to classify the patients[19]: type I SMA (SMA I): early infantile onset, patients are never able to sit without support; type II SMA (SMA II): onset before 18 months, patients are able to sit but are unable to walk unaided; type III SMA (SMA III): onset during childhood, patients are able to walk unsupported.

Treatment with oral salbutamol was initiated after clinical and cardiological assessment (electrocardiogram and 24-hour holter electrocardiogram) to rule out contraindications. A first test dose was performed (1 mg if weight was under 10 kg, 2 mg otherwise) to assess tolerance, heart rate, and blood pressure, each hour for 3 hours. The salbutamol dose was progressively increased over several weeks or months to a maximal dose of 6 mg/day (2 mg three times per day),[18] provided it was well tolerated. Patients continued their usual treatment, including trunk and limb orthosis, motor and respiratory physical therapy, intermittent positive pressure breathing or high-frequency intrapulmonary percussive ventilation, and/or noninvasive ventilation (NIV) when indicated. They were followed by the clinical team at least every 6 months, and height, weight, heart rate, and blood pressure were systematically recorded. Lung function tests and motor function tests, using motor function measurement (MFM) scores MFM 32,[20] were performed when possible. In children younger than seven years, the short version (MFM 20) was used.[21]

The study was approved by the institutional review board of the French learned society for respiratory medicine "Société de Pneumologie de Langue Française," and all patients and parents gave their informed consent.

Lung function and respiratory muscle tests

All the patients had a complete assessment of the lung function and respiratory muscle tests between March 2014 and January 2015 when they were clinically stable. This evaluation was performed after at least one year with salbutamol treatment and at least four months with maximal daily dose.

Spirometry

The patients were asked to perform at least three acceptable slow vital capacity (SVC) curves and the curve with the highest SVC was used for the analysis, as per American Thoracic Society/European Respiratory Society standards.[22] Predicted SVC was calculated.[23] The measurements were done without a brace. Only measurements in the supine position were available for all patients and were therefore considered for subsequent analysis.

Respiratory muscle tests

Nonvolitional tests. An esogastric catheter was inserted pernasally after local anesthesia (lidocaine 2%; AstraZeneca, Rueil-Malmaison, France).[24] This 2.1 mm external diameter catheter mounted pressure transducer system (Gaeltec, Dunvegan, Isle of Skye, UK) has two integral transducers mounted 1 (for the gastric pressure [Pgas]) and 21 cm (for the esophageal pressure [Pes]) from the distal tip. Appropriate placement of the catheter was checked.[25] Transdiaphragmatic pressure (Pdi) was obtained by subtracting on line the Pes signal from the Pgas signal.

The Pgas to Pes swing ratio (ΔPgas/ΔPes) was used to assess the relative contribution of the respiratory muscles to tidal breathing.[26-29] A value ranging between −1 and 1 indicates an ever-increasing contribution of the ribcage and expiratory muscles, compared with the diaphragm, to tidal breathing. This ratio becomes equal to 1 in case of complete diaphragmatic paralysis.[29]

The patient's global inspiratory muscle and diaphragmatic effort during quiet breathing were assessed by calculating the esophageal (PTPes) and diaphragmatic pressure-time products (PTPdi), respectively. The PTPes per breath (PTPes/breath) was obtained by measuring the area under the Pes signal between the onset of inspiratory effort and the end of inspiration and was referred to the chest wall static recoil pressure-time relationship according to a methodology adapted from Sassoon et al.[30] The PTPdi/breath was obtained by measuring the area under the Pdi signal from the onset of its positive deflection to the end of inspiratory flow. Both PTPes and PTPdi were expressed per minute (PTPes/minute and PTPdi/minute).[31]

Volitional tests. To determine the strength of the inspiratory muscles, the patient was asked to perform 10 to 20 short, sharp maximal sniffs and the maximum sniff nasal inspiratory pressure (SNIP) was recorded.[32] Predicted values were calculated.[33] Concomitantly, maximal sniff Pes (Sniff Pes) and sniff Pdi (Sniff Pdi) were measured. The strength of the expiratory muscles was measured by asking the patient to perform a maximal cough. The peak Pgas value among at least five maximal coughs was measured (Pgas Cough).[34]

When possible, maximal static inspiratory pressure (MIP) and maximal static expiratory pressure (MEP) were measured from residual volume and total lung capacity, respectively. Patients were asked to perform at least five maneuvers until two reproducible maneuvers were obtained. The best maneuvers were retained for analysis and the mean value that could be maintained for one second was calculated, otherwise the peak value was used.[35,36] Predicted values were calculated.[35,36]

The diaphragmatic tension time index (TTdi), which estimates the endurance of the diaphragm, was calculated as TTdi = (Pdi/Sniff Pdi) × Ti/Ttot, where Pdi = mean Pdi during quiet spontaneous breathing, Sniff Pdi = Pdi during a maximal sniff, Ti = inspiratory time, and Ttot = total breath time during quiet breathing.[37] The esophageal tension time index (TTes), which estimates the overall endurance of the inspiratory muscles, was calculated as TTes = (Pes/Sniff Pes) × Ti/Ttot, where Pes = mean Pes during quiet spontaneous breathing and Sniff Pes = Pes during a maximal sniff.