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Daily salbutamol in young patients with SMA type II

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Abstract

The aim of this open pilot study was to establish the profile of tolerability and clinical response of salbutamol (albuterol) in a cohort of young children affected by type II spinal muscular atrophy (SMA). Twenty-three children between 30 months and 6 years of age were treated with salbutamol (2 mg three times a day) for 1 year. All children were longitudinally assessed using the Hammersmith motor functional scale 6 months before treatment started (T0), at baseline (T1) and 6 and 12 months later.

There was no significant change in function between T0 and T1 assessments, but the functional scores recorded after 6 and 12 months of treatment were significantly higher than those recorded at baseline ($p = 0.006$).

Our results suggest that salbutamol may be beneficial to SMA patients without producing any major side effect. Larger prospective randomized, double-blind, placebo controlled trials are needed to confirm these preliminary findings.

Keywords: Spinal muscular atrophy; Salbutamol; Therapy; Children; β2 Agonists

1. Introduction

Several studies have documented the effect of β-adrenergic agonists in animals [1], in human healthy volunteers [2,3] and in subjects with muscle weakness due to acute or chronic conditions [4]. Evidence of a positive effect of salbutamol (albuterol) has also been reported in open pilot studies in patients with muscle disorders, such as facio-scapulo-humeral muscular dystrophy (FSH) or congenital myopathies, [5–7] though the only double blind placebo study, performed in FSH, has suggested that the positive effect was not maintained over time [8]. In 2001 a pilot study using salbutamol in patients with spinal muscular atrophy (SMA) type II and III reported a significant improvement in myometry and on DEXA scan scores between baseline and 6 months after treatment [5].

Following these encouraging results and in absence of any medication capable of improving the course of SMA, salbutamol has become part of clinical management of SMA patients in several centers. However the original pilot study had not been followed by a further randomized placebo controlled study that is considered to be the gold standard to establish the possible effect of a treatment. As the initial pilot study had been carried out in a relatively small

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and heterogeneous cohort, including both SMA type II and III patients with a wide age range, we reasoned that further information using appropriate disease-specific outcome measures in a more homogeneous cohort was needed before considering the effort of a larger randomized placebo-controlled study. We were also interested in establishing the possible effect of salbutamol in younger children compared to those studied in the original pilot study [5].

This paper reports the effect of salbutamol in 23 children with SMA type II, who started treatment before the age of 6 years.

1.1. Subjects and methods

Twenty-three consecutive children affected by SMA type II of age between 30 months and 6 years followed at three Italian Tertiary Referral centers, Catholic University and Bambino Gesù Children's Hospital in Rome and Nigrisoli Hospital in Bologna were offered treatment with salbutamol between January 2005 and May 2006. All children had a diagnosis of SMA type II confirmed by genetic analysis with homozygous absence of *SMN1*. SMA II was classified according to the International Classification for SMA [9], based on age at disease onset and maximum function achieved (i.e. onset age over 6 months, and being able to sit unsupported but not to walk). None of children was taking part in any other pharmacological trial or was on any other concurrent medication. None had corrective surgery for scoliosis before or during the treatment with salbutamol.

The families were informed of the preliminary published results and of possible side effects of salbutamol, and agreed to treatment. Patients were started on oral salbutamol at an initial dose of 1 mg three times a day. After the first week, if the initial dosage was tolerated, it was increased to 2 mg three times a day. A 24 h electrocardiogram (ECG) was performed in all patients before starting treatment to exclude possible baseline tachycardia or other ECG abnormalities.

1.2. Functional assessment

Each child was longitudinally assessed using the Hammersmith functional motor scale, that is part of our routine clinical assessment. The scale consists of 20 items, investigating the child's ability to perform various activities. A total score can be achieved by summing the scores for each item. The total score, obtained by adding up the answers to all items, ranges from 0 (all items failed) to 40 (all items met) [10].

All 23 patients had at least one preliminary assessment 6 months before baseline (T0) and a baseline assessment immediately before beginning treatment (T1). Subsequently, they were evaluated 6 (T6) and 12 months (T12) after the start of the treatment.

Each child was always assessed by the same examiner, and the three examiners from the three centers had formal training sessions with the physiotherapist who developed the scale (MM). Interobserver reliability among the three examiners was formally assessed and the correlation coefficient was 0.96, showing similar results to the inter-rater reliability found in previous studies using the same scale [10–12].

All the children also had a detailed assessment of joint mobility in order to exclude possible deterioration in contractures as observed in the previously published pilot study on salbutamol in SMA [5]. Mean value was calculated for each measurement between sides at baseline and added subtracted to the mean value at 6 and 12 months (worsening symbolized with plus and improvement with minus).

1.3. Statistical analysis

Data were analyzed with the Stata package, version 9 [13]. Descriptive statistics (mean, median, range and centiles) of the Hammersmith score at T0, T1, T6, and T12 were computed. The variation of total score after treatment start was assessed through the Friedman test for non-parametric repeated measures comparisons [14]. To assess whether the child's condition at preliminary assessment (T0) influenced the treatment effect, a multivariate regression analysis, clustered to allow for the repeated measurements carried out within the same child, was performed using the score values as dependent variable, and patient's age, time of measurement (T1, T6 or T12) and preliminary score status (T0 < 18 versus $\geqslant 18$) as independent variables.

2. Results

All 23 children completed 12 months of treatment. On direct questioning, the parents of all patients reported some subjective improvement in strength and endurance and increased stamina. Three patients who had already been walking in calipers but had been stable for several months, succeeded to take a few steps without calipers after a few months of treatment.

Table 1 shows details of the scores at T0, T1, T6, and T12.

Median score values were 19 at baseline, 21 at 6 months and 22 at 12 months assessment (Fig. 1). The mean values were 20.8 (SD 9.2), 23.7 (SD 9.5), and 24.7 (SD 9.0), respectively. The increase in score values after treatment was statistically significant (Friedman test 42.05, $p = 0.006$).

Table 2 shows the results of the multivariate cluster analysis. Significantly higher score values are associated with pre-study better conditions (score 18 or more at preliminary assessment, T0) and with treatment. The average increase of score after the first 6 months of treatment was 2.91 (95%CI 1.97–3.85); improvement continued between 6 and 12 months, although to a lesser degree (additional average score increase 0.91, 95%CI 0.07–0.25) (Table 2). No statistically significant interaction was detected between

Table 1
Details of the scores at T0, T1, T6, and T12

	Age	T0	T1	T6	T12
1	2.3	21	20	21	24
2	2.4	18	18	22	26
3	2.7	18	19	21	21
4	2.7	14	14	15	15
5	2.8	14	14	18	22
6	2.8	36	37	40	40
7	2.8	34	34	40	40
8	2.9	14	10	14	15
9	2.9	16	17	18	17
10	3.1	26	24	28	29
11	3.2	28	27	30	29
12	3.2	19	19	21	22
13	3.2	27	27	31	32
14	3.5	21	19	22	22
15	3.6	18	18	19	19
16	3.6	2	2	2	6
17	4.1	18	16	19	20
18	4.3	17	19	20	19
19	4.3	37	38	40	40
20	4.4	34	34	36	37
21	5.2	11	11	21	22
22	5.3	29	30	32	32
23	6.01	12	12	16	18

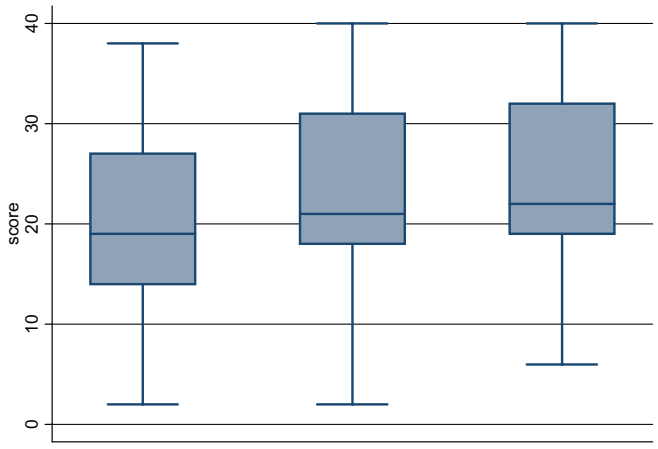

Fig. 1. Distribution of score values at baseline (1), and after six (6) and twelve (12) months of treatment. (The line intersecting the middle of each box representing the median. The box extends from the 25th to the 75th centile, and therefore represents interquartile range.)

pre-study conditions (score at preliminary assessment) and degree of improvement after treatment, indicating a similar effect of salbutamol independently from score at T0. Patient's age was not significantly associated with score (Table 2).

2.1. Side effects

Salbutamol was generally well tolerated and there was no severe side effect. Six of the 23 children noticed increased hand tremor a few days after they went to the full dose but this was mild, subsided after a few days and did not require any drug adjustment. Major joint's ranges

Table 2
Adjusted changes of score values after treatment: results of multivariate cluster regression analysis

	Coefficient (95%CI)	*p* value
Time of assessment		
Baseline (T1)	–	
Six months (T6)	2.91 (1.97–3.85)[a]	<0.001
Twelve months (T2)	0.91 (0.07–0.25)[#]	0.011
Score values at preliminary assessment (T0)		
Below 18	–	
18 or more	13.76 (8.46–19.07)	<0.001
Patient's age (months)	0.58 (−1.35 to 2.51)	0.541

[a] Average increase in score between baseline and 6 months assessment, and [#]between 6 and 12 months assessment. Average increases are adjusted for the other variables in the model (patient's age and preliminary assessment status).

(hips, knees, tendon Achilles, and elbows) measured at baseline and after 12 months showed differences within 5°.

All the families elected to remain on treatment at the end of the trial, as they felt an overall positive effect.

3. Discussion

Our results suggest that salbutamol administered for 12 months in non-ambulant young SMA patients may improve muscle function without significant adverse effects. All the families of the young children who received treatment for 12 months reported an increase in stamina and function, and this was confirmed by our assessment showing an improvement on the functional scale in 21 of the 23 patients assessed. The peak of the improvement was noticed after 6 months of treatment, but further improvement was also observed between 6 and 12 months. It is remarkable that 3 of the 23 children who were relatively stronger compared to the others and were able to stand but not to walk independently, acquired the ability to walk independently for a few steps following administration of salbutamol. All three had been relatively stable before salbutamol was started, and the acquisition of this improvement was not expected. As most of our children were below the age of 4, when spirometry and assessment of forced vital capacity is not easily recordable, we do not have systematic data about respiratory function, but it is of note that many families also reported a subjective improvement in the efficacy of cough.

The functional improvement observed after 6 and 12 months of treatment is not typical of the natural history of the disease. All the children in our cohort had at least one assessment performed 6 months before treatment started and all but three had no changes or only minimal changes (±1 point) between the functional scores recorded at prebaseline (T0) and baseline (T1). Furthermore, in a previous study validating the Hammersmith scale in 90 untreated Italian children with type II SMA assessed at baseline, we also found that, when reexamined after 3 months and 6 months, less than 5% of the children

assessed had an improvement of more than 2 points [11]. The difference between the two studies is remarkable as, in our cohort 15 of the 23 children (65%) treated with salbutamol had an improvement of more than 2 points and this was already present after 6 months in 12 of the 15.

The results of the present study should be interpreted with caution, because of the relatively small sample size and possible placebo effect. In our recent randomized placebo controlled study using phenylbutyrate (Pb) for 13 weeks in 90 children with SMA type II we also found an improvement in functional scores that was found in both treated and placebo groups [12]. In view of these findings we cannot therefore exclude that the improvement noticed in our cohort may be partially due to a placebo effect rather than specifically to salbutamol administration. The changes observed in the Pb study, however, were much smaller than in our cohort treated with salbutamol as only 15 of the 90 patients (16.6%) (7 treated with Pb and 8 with placebo) had improvements of more than 2 points after 13 weeks of treatment opposed to 15 of the 23 (65%) found in the present cohort. In the present study it is also remarkable that in most children the changes were already obvious after 6 months of treatment and the improvement appeared to continue between 6 and 12 months, a trend that is different from the temporary early response typically associated with a placebo effect. It should also be noticed that 3 of the 23 subjects hit the ceiling of the Hammersmith scale, suggesting that the statistical analysis may have underrepresented the full effect in these subjects. A future randomized, placebo-controlled study would need to consider this issue in its design.

Our results raise questions about the disease natural history and response to treatment in young SMA children. There is contrasting evidence about the progression of the disease in this age range. While some authors report that children with type II SMA show a progressive loss of function between 2 and 4–5 years [15], other studies report little changes over time [11,16]. In our cohort we found a relevant and statistically significant improvement in functional scores over a 12 month period. Although we cannot be certain that the improvement is related to salbutamol, these findings suggest that there is a potential for improvement in young children. This would be in keeping with recent pathological data derived from SMA-like mice suggesting that SMA motoneuron death is a late phenomenon, preceded by a severe chronic dying-back axonopathy [17] and with our observation in previous clinical trials with Pb showing that children in this age range were more likely to show motor function improvement compared to older children [11,12]. These observations suggest that young children should be included, if not specifically targeted, when designing clinical trials in SMA type II as at this age other variables such as scoliosis or contractures are also less frequent than in older children.

In conclusion, our results suggest that salbutamol appears to be well tolerated and may have a beneficial effect on muscle function in young patients with SMA type II. The mechanism of action of β2 agonists on human skeletal muscle is not completely understood. Most of the published experimental work has been linked to β2 agonist used by athletes or healthy volunteers which have been shown to cause large increases in muscle mass in normal muscle. Other studies have suggested that β2 agonist may reduce wasting in dystrophic [18] or denervated muscle [4], also enhancing functional repair of regenerating muscle fibres following an injury [19]. Recent studies have however suggested that in SMA salbutamol may also have a different mechanism of action by determining a rapid and significant increase in SMN2-full length mRNA and SMN protein in SMA fibroblasts, predominantly by promoting exon 7 inclusion in SMN2 transcripts [20]. Although it is not known if the splicing of SMN in motoneurons is also influenced by the administration of β2 agonists, these pharmacological agents are capable of crossing the blood–brain barrier and could therefore potentially have an effect also at the motor neuron level. These recent findings and the encouraging results obtained in our pilot study highlight the need for a more appropriate study investigating the efficacy of the treatment in SMA.

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