Deflazacort treatment of Duchenne muscular dystrophy

W. Douglas Biggar, MD, Michele Gingras, MD, Darcy L. Fehlings, MD, Vivien A. Harris, RN, and Catherine A. Steele, PhD

**Objective:** We report the long-term effects on muscle strength and side effects with deflazacort in Duchenne muscular dystrophy (DMD).

**Study design:** Boys with DMD between the ages of 7 and 15 years were reviewed retrospectively; 30 had been treated with deflazacort, and 24 had not. Muscle function, pulmonary function, and side effects were compared.

**Results:** The boys not treated with deflazacort stopped walking at 9.8 ± 1.8 years. Seven of 30 treated boys had stopped walking at 12.3 ± 2.7 years (P < .05), and of the 23 boys who were still walking, 21 were older than 10 years. Pulmonary function (percent predicted functional vital capacity) was significantly greater in treated boys at 15 years (88% ± 18%) than in boys not treated (39% ± 20%) (P < .001). Between 9 and 15 years, treated boys were shorter. Between 9 and 15 years, treated boys weighed less. After 15 years the treated boys maintained their weight, whereas boys not treated lost weight. Asymptomatic cataracts developed in 10 of 30 boys who received deflazacort. Other potential side effects of deflazacort such as hypertension, glucosuria, acne, infection, or bruising were not more common.

**Conclusions:** We conclude that deflazacort can preserve gross motor and pulmonary function in boys with DMD with limited side effects. (J Pediatr 2001;138:45-50)

Duchenne muscular dystrophy is an X-linked recessive disorder affecting primarily skeletal and cardiac muscle. Boys with DMD exhibit a progressive and predictable deterioration of muscle function.1-6 As young boys, walking may be delayed and awkward. Although variable, most boys lose the ability to walk between 7 and 12 years of age.1,2 Progressive respiratory insufficiency begins early in their second decade.1 Scoliosis develops in most boys who are full-time wheelchair users.

Prednisone has been shown to preserve muscle function in DMD,3-8 but the mechanism(s) of action is not clear. It is associated with an increase in muscle mass5,9 and a slower rate of muscle degradation.10 Prednisone is, however, also associated with significant side effects.5-8 There has been interest recently in an oxazolone derivative of prednisolone: deflazacort.11 In short-term studies deflazacort and prednisone were equally effective in preserving muscle function in DMD.12,13 Weight gain and cataracts were the most important side effects in the deflazacort group.13 In a second short-term study with 2 mg/kg deflazacort on alternate days, side effects after 9 months were believed to be fewer than with prednisone while comparable muscle strength was maintained.14 In a third double-blind placebo-controlled trial, alternate-day deflazacort (2 mg/kg) was significantly better than the placebo in preserving muscle function, and side effects were described as mild.15 Preliminary data suggest that pulmonary function also benefits from deflazacort treatment.16 There is little information on longer term effects (>2 years) of deflazacort on muscle function.

**METHODS**

**Patients**

All 54 boys who met the following criteria were included: between 7 and 15 years old with a diagnosis of DMD and monitored in our comprehensive neuromuscular clinic between January 1993 and July 1999. All patients fulfilled the following 5 diagnostic criteria for DMD: (1) onset of weakness before 5 years, (2) male sex, (3) proximal muscle weakness, (4) increased serum

---

From the Bloorview MacMillan Centre and Department of Paediatrics, University of Toronto, Toronto, Ontario, Canada.

Submitted for publication Dec 22, 1999; revision received May 3, 2000; accepted June 16, 2000.
Copyright © 2001 by Mosby, Inc.
0022-3476/2001/$35.00 + 0 921/109601

---

**DMD** Duchenne muscular dystrophy

**FVC** Forced vital capacity

**FVC-PP** Percent predicted values for forced vital capacity
creatinine kinase, and (5) a muscle biopsy and dystrophin analyses consistent with DMD or DNA mutation and analysis by polymerase chain reaction or Southern blot techniques to detect gene deletions. All boys were given the option of deflazacort treatment when they were ambulatory and there was early clinical evidence of decreasing muscle function. This was usually indicated by parents reporting that their son was falling more frequently, having more difficulty getting up after falling, and having more difficulty climbing stairs. Information about deflazacort was shared both verbally and in writing.

Thirty boys were treated with deflazacort; 24 were not. Their pulmonary function (Fig 1), height (Fig 2), and weight (Fig 3) were similar for both groups before deflazacort was administered. All 54 boys were walking at 7 years. The most common reason for not choosing to take deflazacort was the fear of side effects.

The initial dose of deflazacort was 0.9 mg/kg/d. The boys treated with deflazacort were given daily oral supplements of vitamin D, 1000 IU, and calcium, 750 mg. All 30 boys had been taking deflazacort for >1 year.

**Protocol**

Patient monitoring in both treated and nontreated groups was normally done every 4 to 6 months with a standard clinical protocol. Muscle function was evaluated by history and observation of the following 3 functions: climbing 4 standard stairs (17 cm rise) with a railing, getting up from the floor, and walking on a level floor. End points for each were not able to climb stairs, not able to get up from the floor independently, and not able to walk with or without long leg braces.

Pulmonary function testing as forced vital capacity was determined with an electronic spirometer. This spirometer, in our laboratory, gives values similar to the standard values of a Stead-Wells spirometer.\(^{17}\) Percent predicted values for FVC were calculated based on normal published values.\(^{18}\) The testing was performed by the same person to enhance patient cooperation and reduce interobserver variability. The best of 3 trials was recorded. Clinical side effect data included height, weight, blood pressure (sitting), an eye examination, and questions about possible side effects. Clinic visits were usually in the morning and included independent clinical evaluations by a nurse, physiotherapist, occupational therapist, and physician. Boys receiving deflazacort were seen by an ophthalmologist yearly. The clinic nurse gave dietary recommendations on each visit. A referral to a nutritionist was made if their weight exceeded expected weight by 5% to 10%. Discussion about operative intervention for scoliosis began when the boys became full-time wheelchair users. Surgery was usually recommended when curves developed and began to progress and their FVC-PP was >30%.

**Laboratory Evaluation**

Blood specimens for fasting blood glucose, complete blood count, calcium, phosphorus, and bilirubin and creatinine kinase were obtained every 8 months. Urine was tested for glucose by Dipstix every 4 months. A 24-hour urine specimen was tested for calcium every 8 months.

**Statistical Analysis**

Statistical analyses were performed by SAS, version 6.\(^{19}\) Means and SDs were calculated for each variable (height, weight, FVC-PP) yearly for ages 7 to 15 years for all 54 boys. Unpaired \(t\) tests determined whether significant differences existed over a 7- to 15-year period between the treated and nontreated boys. The 2-tailed Fisher's exact test was used to compare motor function for both groups at 10 years. Ten years was chosen so that most of the boys were included.

**RESULTS**

The mean age of starting deflazacort was 8.4 ± 2 years; the mean duration of...
therapy was 3.2 ± 1.3 years. Twelve boys had been taking deflazacort for >3 years, 5 of the 12 boys for >5 years. The dose of deflazacort (milligrams per kilogram) for the 30 boys gradually declined over time as they grew and gained weight or was reduced because of side effects. By the time the boys were 10 years old, the mean dose was 0.76 ± 0.19 mg/kg, and by 15 years it was 0.61 ± 0.2 mg/kg.

**Motor Function**

**Walking.** All 24 boys not treated with deflazacort stopped walking at 9.8 ± 1.8 years of age. The 7 boys treated with deflazacort who had stopped walking (12.3 ± 2.7 years of age) did so significantly later than boys not treated (P < .05). Of the 23 boys who were still walking, 21 were older than 10 years. At 10 years the 2-tailed Fisher’s exact test showed that the number of treated boys walking was significantly greater than that of the boys not treated (P < .0001).

**Climbing Stairs.** All 24 boys who were not treated with deflazacort stopped climbing stairs at 9.2 ± 1.1 years of age; 21 of the 30 boys treated with deflazacort stopped climbing stairs (10.9 ± 1.9 years) significantly later than boys not treated (P < .001). Of the 9 boys still able to climb stairs, 8 were older than 9 years. At 10 years the 2-tailed Fisher’s exact test showed that the number of treated boys able to climb stairs was significantly greater than that of nontreated boys (P < .0001).

**Getting Up from the Floor.** All 24 boys who were not treated with deflazacort required assistance getting up from the floor by 8.8 ± 1.4 years of age. By contrast, 19 of 30 boys treated with deflazacort who required assistance (10.7 ± 1.9) did so significantly later than the boys not treated with deflazacort (P < .001). Of the remaining 11 boys who could get up from the floor without assistance, 9 were older than 9 years.
Pulmonary Function

Both groups of boys, treated and nontreated, had similar FVC-PP from 7 to 9 years of age (9 years of age treated, 85.3% ± 15% vs nontreated, 85.2% ± 19%, P > .05) (Fig 3). When the boys were 10 years old, the FVC-PP in the treated group was unchanged, whereas that in the nontreated group had fallen to 74% ± 25% (P > .05). By the time the boys were 15 years old, the FVC-PP in the treated group was significantly greater than that in the boys not receiving deflazacort (82.5% ± 14% vs 43.2% ± 9%, P < .002). The differences at 14 years (P < .0002) and 15 years (P < .001) were also significant, at which time the FVC-PP for the treated boys was 88% ± 18%, and that of the nontreated boys was 59% ± 20%.

Scoliosis Surgery

Thirteen of the 24 boys not treated with deflazacort had scoliosis surgery at a mean age of 13.7 ± 0.9 years. Of the remaining 11, 1 family refused surgery, 3 boys had a stable hyperextended spine and will probably not require surgery, and 7 boys were <13.5 years of age. None of the boys treated with deflazacort have yet required spine surgery.

Side Effects

Height. When the boys were 7 years old, the mean heights for both the treated and nontreated boys were similar (Fig 2). The mean height of the treated boys was significantly less (P < .05) than that of the nontreated boys between 11 and 15 years of age. The mean height of the treated boys then continued along the 3rd percentile until 15 years. The mean height for boys not treated remained between the 25th and 50th percentile between 7 and 15 years.

Weight. At 7 years the mean weights for both the nontreated (21 ± 6 kg) and treated (21 ± 5 kg) boys were similar (Fig 3). Four months after deflazacort was begun, their mean weight increased from 25.7 ± 7.6 kg to 27.3 ± 7.5 kg. This was not significantly more than that of the boys not treated (P > .8). The mean weight for the treated group remained between the 25th and 50th percentile. The mean weight for the nontreated group increased to between the 75th and 90th percentile at 13 years (50 ± 13 kg). After 15 years their mean weight declined. At 14 years their mean weight was between the 25th and 50th percentile (46 ± 7 kg), and by 15 years it had fallen to between the 5th and 10th percentile (42 ± 17 kg).

Cataracts. Cataracts developed in 10 of the 30 boys treated with deflazacort. In 9 of the 10 boys the cataracts were bilateral. The earliest cataracts were noted 4 months after deflazacort was begun; the latest was 5.8 years. No correlation was found between the presence of cataracts and their age at the start of deflazacort, the dose per kilogram taken, or the total amount of deflazacort taken before the cataracts were noted. Other side effects were not more prevalent in these 10 boys. That is, they were not the shortest boys or the boys with the most weight gain. The cataracts were asymptomatic in all 10. Intraocular pressures and visual acuity remained normal. None of the boys in the nontreated group had cataracts.

Other Side Effects

When the boys were 7 years old, the mean heights for both the treated and nontreated groups had normal systolic and diastolic blood pressures. In addition, throughout the study period there was no glucosuria, acne, or excessive hair growth reported. There was no apparent increased susceptibility to infection or bruising. Gastrointestinal complications and headaches were not more common, and no gastrointestinal bleeding was reported. Blood specimens for fasting blood glucose, complete blood count, calcium, phosphorus, albumin, and bilirubin were all within normal limits. Increased calcuria was not found in any 24-hour urine specimens.

Discussion

Deflazacort is an oxazolone derivative of prednisolone, which has an anti-inflammatory effect and an immunosuppressive effect. The therapeutic equivalence is approximately 1.2 mg deflazacort to 1 mg prednisolone. Short-term studies in Germany, Italy, and Argentina suggest that deflazacort can delay the loss of muscle function in DMD. In those studies the ability to walk continued significantly longer in boys treated with deflazacort. Our findings extend those observations and indicate that deflazacort has an important role in maintaining muscle function.

Respiratory muscle weakness contributes in a major way to the morbidity and mortality in DMD. Pulmonary function follows 3 typical phases: ascending, plateau, and descending. The descending phase typically begins at approximately 10 to 12 years of age. The rate of decline in FVC-PP varies between approximately 5% and 10% per year. In the 21 boys not treated with deflazacort, the FVC-PP began to decline at 10 years of age from 85.2% ± 19% at 9 years to 74% ± 25% at 10 years. By 15 years of age their FVC-PP was 59% ± 20%. In contrast, boys receiving deflazacort had no significant decline in their mean FVC-PP during the same time interval. Similar observations were reported recently in 50 boys with DMD treated with 0.5 to 1.0 mg/kg/d deflazacort. Boys 12 to 14 years of age who were treated with deflazacort had an FVC-PP of 86 ± 19.6 compared with 51.7 ± 29.1 for boys not treated with deflazacort. In our study boys 12 to 14 years of age who were treated with deflazacort had an FVC-PP of 80 ± 17 compared with
52 ± 25 for boys not treated with deflazacort. On the basis of these findings, we do not usually recommend stopping deflazacort after the boys become full-time wheelchair users.

This study provides good support for long-term maintenance of muscle function and respiratory muscle strength. However, this maintenance must be balanced by the side effects of deflazacort. Overall, deflazacort was very well tolerated, with the main side effects being growth suppression and cataracts. As a group, the 30 boys who received deflazacort were shorter than the 24 boys who did not. Nine of the 30 boys between 11 and 13 years of age were <3rd percentile for height. Although the number of boys with heights <3rd percentile is too small for statistical comparison, it is interesting that when the motor function of these 9 boys was compared with the motor function of the 21 boys whose height was >3rd percentile, their ability to climb stairs and to get up from the floor tended to be better. We know in some muscle disorders, for example, spinal muscular atrophy, that when there is no change in muscle strength, rapid growth can lead to a deterioration in motor function. Growth suppression, although a side effect, can therefore also have a beneficial effect in DMD. Furthermore a patient with growth hormone deficiency had a remarkably benign form of DMD. On the basis of these observations, we suggested to the boys and their parents that there could be an advantage in being short. If the boys were very concerned about their short stature, we reduced their dose of deflazacort by 20% to 30%.

Excessive weight gain, defined as personally unacceptable to the child and his family, was not common in the boys treated with deflazacort. Furthermore the commonly observed early excessive weight gain after prednisone therapy is begun was not observed with deflazacort. As was reported by McDonald et al, boys not receiving deflazacort tended to put on weight between 8 and 10 years of age. In our own study both groups were at the 25th percentile for weight at 7 years of age, but by 10 years the mean weight of the boys not treated with deflazacort was 35.7 ± 8.1 kg, and that of the boys treated with deflazacort was 30.4 ± 4.6 kg. We attribute this partly to education, strict dietary management, and increased motor activity in the boys treated with deflazacort. Another important difference between the 2 groups was noted after they were 15 years old. The mean weight for the boys receiving deflazacort continued to be between the 25th and 50th percentiles. By contrast, the mean weight for the boys not receiving deflazacort fell from the 75th percentile at 13 years of age to between the 5th and 10th percentile by 15 years of age. Six of the 24 boys lost approximately 20% of their total body weight. The 6 boys with the most severe weight loss were not those with the most compromised cardiac or pulmonary function. No cause for their weight loss was identified; specifically, coughing, choking, and vomiting were not more common. During this time period most of the boys had surgical instrumentation to stabilize their spine. Their weight loss may have been related to several factors: having spinal surgery, loss of muscle mass, progression of respiratory insufficiency, difficulties with self-feeding and swallowing, and not wanting to eat. It is important to note that to date, none of the 30 boys treated with deflazacort have required scoliosis surgery. Our findings suggest that with deflazacort, the timing for scoliosis surgery is delayed. The impact of delaying surgery is unknown.

Asymptomatic cataracts were documented in 10 of the 30 boys. Most were documented within 3 years of starting deflazacort. None of the boys has required cataract surgery. The reported incidence of cataracts in boys with DMD treated with steroids varies. Ten of 87 boys receiving prednisone (0.75 mg/kg/d) for 2 years had cataracts. These were mild and asymptomatic and did not progress. A double-blind study from 14 German centers compared prednisone (0.75 mg/kg/d) with deflazacort (0.9 mg/kg/d) in 100 boys with DMD. Sixteen of 50 boys treated with deflazacort but only 1 of 50 in the prednisone-treated group had cataracts. In our experience most cataracts were documented within 3 years of treatment. Cataracts were not reported in boys treated for 24 months with alternate-day deflazacort (2 mg/kg). There are, however, some limitations to the study. This study was retrospective. The control group was a convenience sample of boys not treated with deflazacort, and the similarity of the 2 groups at baseline may be in question. All boys could walk at age 7 years. It is reassuring that pulmonary function testing, which is representative of overall muscle strength, was also similar at baseline. The heights and weights for both groups were also similar. A number of factors can influence the age when the boys stop using the stairs. For example, a frequent one is that they do not need to use stairs. Their home and school are on one floor, or they use an elevator. Some parents choose to carry their children up stairs. Some stairs at home do not have railings for support. Thus identifying the end point for not using stairs based on muscle weakness is in our experience more difficult than identifying the time when the boys stop walking. We are confident, however, that with parental reporting combined with frequent assessments by the clinic team, our reported end points for walking, getting up from the floor, and using stairs are reliable and consistent. Studies are currently underway to determine the impact of deflazacort on osteoporosis.
REFERENCES


