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Effect of succimer chelation therapy on postural balance and gait outcomes in children with early exposure to environmental lead

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Abstract

This study investigated the influence of succimer chelation therapy in eliminating and/or minimizing lead-associated impairments of motor functions such as postural balance and locomotion or gait activities. In this study, postural balance and functional locomotion or gait were quantitated in 161 children in Cincinnati enrolled in a randomized, placebo-controlled, double blind clinical trial. In comparison to the placebo group, the succimer therapy group showed significantly decreased postural sway during dynamic task performance implying improved postural balance. The results from locomotion tests demonstrated significant improvements in functional tasks of obstacle crossing and normal walking in the succimer treated group. While some beneficial neuromotor effects of succimer therapy were observed in the present study there remains several unanswered questions such as how long these effects will persist and how succimer therapy modifies lead-associated cerebellar deficits manifesting as perturbations in vestibular and/or proprioception systems for postural balance and functional locomotion.

Keywords: Succimer therapy; Postural balance; Functional locomotion; Gait; Children; Force platform

1. Introduction

This study investigated the neuromotor effects of chelation therapy in children with early chronic exposure to lead (Pb). The overall aim of this study was to determine whether the succimer chelation therapy regimen produced beneficial effects on gross motor performance such as postural balance or sway during static standing and semi-dynamic tasks and functional locomotion activities such as walking and obstacle crossing.

Previous studies have documented that early childhood exposure to Pb is associated with both neurocognitive and neuromotor dysfunctions (Bellinger et al., 1992; Benetou-Marantidou et al., 1988; Bhattacharya et al., 1995, 2006; Dietrich et al., 1993a,b; Needleman, 2000; Needleman et al., 1990; Wasserman et al., 2000). Our research group has specifically shown that early childhood Pb exposure is associated with increased postural instability in the Cincinnati Lead Study cohort (Bhattacharya et al., 1990, 1995, 1998, 2006). The data from our postural balance research study implicated Pb-associated potential damage to functional abilities of the vestibular and/or proprioception systems which is modulated by the cerebellum (Shambes et al., 1978; Shumway-Cook and Woollacott, 2001). Recent MRI data in the same cohort reported by Cecil et al. (2005) indicated Pb-associated gray matter loss in the cerebellum, thereby providing further support for our postural balance findings.

The importance of chelation therapy to help reduce Pb burden has been documented in the literature (Chisolm, 1968; Ruff et al., 1993). In particular, the use of a chelating agent such as CaEDTA in the treatment of acute and chronic Pb intoxication in childhood has been reported by Chisolm (1968). In 1991, 2,3-meso-dimercaptosuccinic acid (succimer or CHEMET®) was approved by the Food and Drug Administration (FDA) as a chelating drug in children with blood lead (PbB) levels of 45 μg/dL and higher. Several studies have provided data showing that succimer is safe and effective (Graziano, 1993). While previous studies have shown that succimer reduces the Pb level in the blood, there are only a few studies that have investigated succimer associated changes in neuromotor and neurocognitive performances. A recent clinical

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trial at the University of Cincinnati along with three other institutions was undertaken to investigate its effectiveness in preventing developmental deficits at PbB levels between 20 and 44 μg/dL (Rogan et al., 2001). The results from the Rogan et al. (2001) and Dietrich et al. (2004) studies showed that, while chelation therapy initially decreased PbB levels, no improvements in neurocognitive measures were found. However, there are no data available regarding the influence of chelation therapy in eliminating and/or minimizing Pb associated impairments of motor functions such as postural balance and locomotion or gait activities. The results presented here are the first regarding how succimer therapy may impact postural balance and functional gait performance.

The physiological rationale for potential benefits of succimer can be inferred from some studies in the literature. Studies with Pb workers (Lee et al., 1995) and confirmed in animal models (Cory-Slechta, 1988) have shown that succimer chelates Pb from soft tissue compartments (brain and kidney) which may have a direct impact on measures of health-effects such as neuromotor and renal functions. To date, comprehensive data related to succimer associated changes in neuromotor function such as postural balance/locomotion do not exist. In our laboratory, a clinical case study has been completed which provides suggestive evidence to support the hypothesis that a combination of CaEDTA and succimer therapy might modify one of the neuromotor functions, i.e. ability to maintain postural balance in a child with early Pb exposure (Bhattacharya et al., 1998). Briefly, this case study showed that, with pharmacologic intervention the postural sway response of the patient improved markedly for three of four postural sway test conditions. The fourth test required relatively higher reliance on the vestibular system. Since this fourth test is purported to involve the higher cortical centers much more than the remaining three tests, a deteriorated response for this test implies that succimer might be redistributing Pb to the sites which are critical to the functionality of the vestibular/cerebellar pathways relevant for postural balance. Alternately, succimer might be sluggish in removing Pb concentrations from sites specific to the vestibular/cerebellar functions (Press, 1977). These case findings were preliminary in nature and therefore further investigation with a larger cohort of succimer treated subjects was carried out and results are presented in this paper.

2. Methods

2.1. Study population and protocol

The results presented here include subjects who participated at the Cincinnati Clinical Center of a multi-center, randomized, placebo-controlled, double blind clinical trial of succimer (dimercaptosuccinic acid) (Rogan et al., 2001). The Treatment of Lead-Exposed Children (TLC) study was approved by the institutional Review Boards at the clinical sites, data coordinating center, the United States Centers for Disease Control and Prevention, and the National Institute for Environmental Health Sciences. The TLC clinical sites were Philadelphia, PA; Newark, NJ; Cincinnati, OH; and Baltimore, MD. Parents or guardians signed informed consent documents covering three phases of the study including all activities leading up to randomization (if qualified), and for later follow-up studies as described in this report. Methods are presented in detail elsewhere (Rogan et al., 2001). TLC accepted referral of children 12–33 months of age, with PbB levels between 20 and 44 μg/dL (0.96–2.12 μmol/L), and who could be tested in English or Spanish (Newark site only). TLC measured PbB concentration in a venous sample and inspected the child's home to determine whether cleaning and minor repair could be expected to suppress further exposure to Pb dust. Each family was given a month's supply of TLC vitamin and mineral supplements, that included iron, zinc, calcium and copper. Children with confirmed venous PbB concentrations between 20 and 44 μg/dL and who lived in cleanable housing had a second visit. The child was randomized if a second venous PbB level was also between 20 and 44 μg/dL (0.96–2.12 μmol/L). TLC cleaned the child's home with a high efficiency particle arrestor vacuum, damp mopped or wiped with a tri-sodium phosphate solution, performed minor carpentry when necessary and paint stabilization.

To be eligible to participate in the postural balance and gait evaluations, the subject had to be at least 5 years old and have completed the succimer or placebo therapy regimen. Out of those who qualified to be in the postural balance and gait evaluations, 81 subjects were randomly assigned to the placebo group and 80 subjects to the succimer group. The investigators were blinded to the group assignments and PbB levels. Treatment assignments were randomized within strata of clinical center, body surface area, baseline PbB level, and Spanish language. McNeil Consumer Products provided 100 mg unmarked succimer (dimercaptosuccinic acid) and placebo capsules of identical appearance. Because succimer has a strong, sulfurous, mercaptan odor, TLC packed 200 mg of succimer in a vented plastic cylinder in each bottle of placebo and succimer. Courses of therapy were 26 days and aimed to provide 1050 mg/M^2 day for the first 7 days and then 700 mg/M^2 day thereafter (Rogan et al., 2001).

Children could receive up to three courses of drug or placebo. TLC patients were scheduled to return for clinic visits at 7, 28, and 42 days after the beginning of each treatment course. If a child receiving succimer had a PbB level of $\geq$15 μg/dL (0.72 μmol/L) at the 6–8 week follow-up visit of the first or second course (median = 48 days, 95% range = 41–101 days for the first course, similarly for the second), an additional course of treatment was initiated.

The postural balance and locomotion (gait) studies were carried out once the subjects reached at least the age of 60 months and completed the succimer or placebo therapy regimen. The postural balance and gait data from subjects were excluded for medical reasons affecting postural balance and gait or inability or unwillingness to complete test protocol. Only one subject was excluded for a medical reason (Rett Syndrome). Out of 195 children from the Cincinnati Center, data from 158 and 152 subjects met the inclusion criteria for statistical analysis for the postural balance and gait tests, respectively. Fig. 1 provides mean PbB levels of both groups

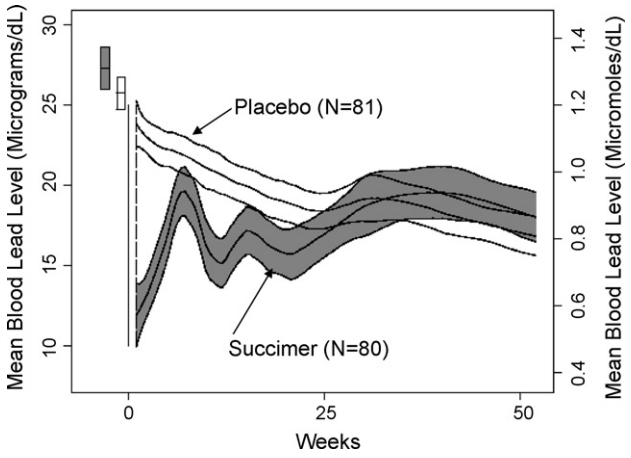

Fig. 1. Mean blood levels and 95% confidence intervals (adapted from Rogan et al., 2001). (▮) Base line values of succimer group measured 9 days before the start of treatment. (▯) Base line values of placebo group measured 9 days before the start of treatment. (¦) Dotted vertical line refers to 1 week after randomization when the first blood lead. Levels were measured after the start of treatment.

between 1 week before succimer or placebo administration (or pre-randomization visit) started and 50 weeks later when PbB levels of the 2 groups were overlapping (Fig. 1). Blood samples were collected again at the time of the postural balance test only if the previous PbB levels were obtained more than 1 year ago.

2.2. Postural balance test

The child's postural balance was quantified with a microprocessor-based force platform system along with a custom developed experimental protocol and software, ''Body Balance'' (all rights reserved by the University of Cincinnati 2006) (Bhattacharya et al., 1995). The test procedure was non-invasive and required each child to undergo repeat trials of four static stationary standing tests and two semi-dynamic tests each lasting 30 s as per our previous publications (Bhattacharya et al., 1993, 1995). The tests were designed to indirectly eliminate and/or challenge all the afferents (vision, proprioception and vestibular systems) necessary for the maintenance of postural balance as per our previously published protocol (Bhattacharya et al., 1995). The static stationary standing tests were EO: standing on the force plate with eyes open; EC: standing on the force plate with eyes closed; FO: standing on a 4 in. high foam pad placed on the force plate with eyes open; FC: standing on a 4 in. high foam pad placed on the force plate with eyes closed. The semi-dynamic tests (Fig. 2) were: BO: standing on the force plate with eyes open for 12 s and then bending torso at the waist on verbal command, staying in that position for 5 s and then returning to upright position and staying in that position for the remainder of the 30 s test. This test provided a dynamic challenge to all the afferents relevant for postural balance. BC: same as BO except with eyes closed. The BC test provided a dynamic challenge to the proprioceptive and vestibular afferents relevant for postural

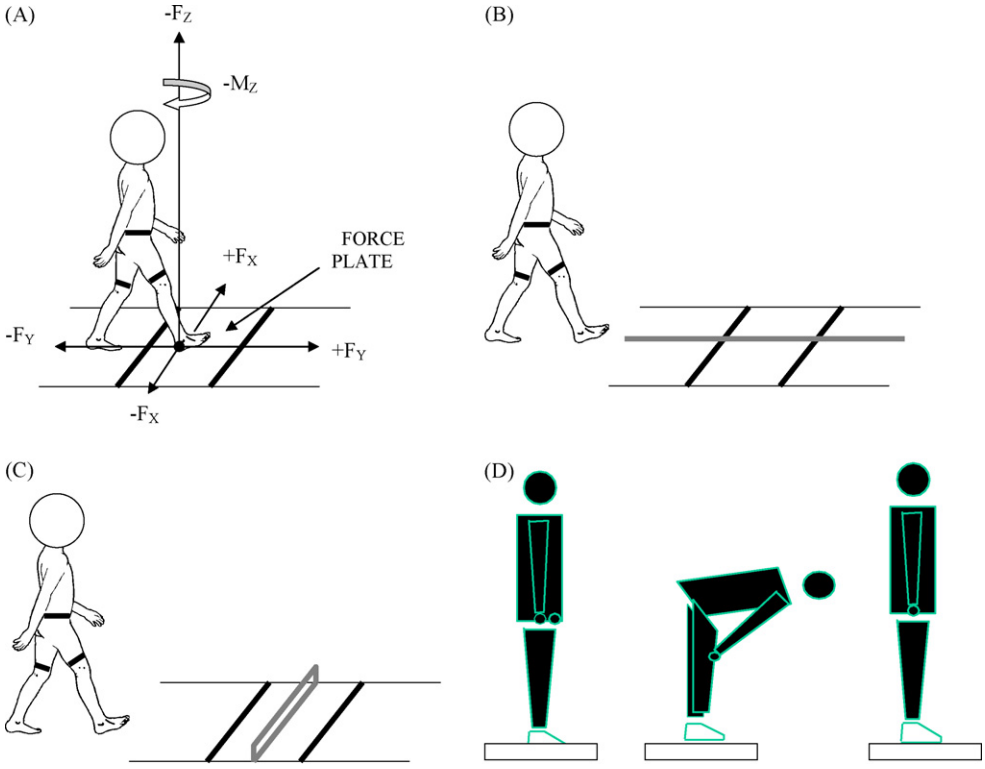

Fig. 2. Schematic of test conditions and nomenclature of gait forces and torques. (A) Normal walk test; (B) line walk test; (C) obstacle test; (D) bending test eyes open (BO) and eyes closed (BC) for postural balance evaluation. Nomenclature for gait variables are shown in (A) where the subject is stepping on the force plate during the single stance phase. $+F_Y$ = propulsive force; $-F_Y$ = braking force; $\pm F_X$ = medio-lateral (M-L) forces; $\pm M_Z$: vertical torques around the *Z*-axis, this torque is applied about the point of contact of the heel strike foot on the force plate. An increased $\pm M_Z$ is representative of higher effort by the body to bring the body's center of gravity to the middle of their base of support thereby maintaining adequate upright balance during single stance phase of walking.

balance. The postural balance was characterized by calculating two variables from three forces and three moments obtained from the force platform system. The variables were sway length (SL): total distance traversed by the body's center of pressure (CP) during the test period and sway area (SA): total area encompassed by the CP movement pattern in the x–y or horizontal plane (Bhattacharya et al., 1995).

2.3. Locomotion or gait tests

The locomotion or gait tests were carried out in our gait research facility consisting of 20 feet of walkway fitted with a microprocessor-based force platform in the center of the walkway (Fig. 2). These tests were designed to examine the normal walking patterns and the functional gait (line walk and obstacle crossing) patterns which challenged various neuromotor control systems necessary for maintaining upright balance and at the same time keeping dynamic control of body segments during progression of gait. All subjects underwent four trials each of: (1) normal walking which was used as the baseline performance of their gait, (2) walking on a line drawn on the gait walkway which challenges the subject's ability to maintain balance in the frontal plane and (3) negotiating an obstacle consisting of crossing a styrofoam bar placed at the mid-patellar height of the subject while walking which challenges the subject's visual-spatial abilities while maintaining balance in the sagittal and the frontal planes. During the test the subject was required to step on the force platform during the performance of the above-mentioned three tests.

2.4. Bruininks–Oseretsky test of motor proficiency (BOTMP)

The Bruininks–Oseretsky test of motor proficiency (Bruininks, 1978), a comprehensive and standardized assessment of gross- and fine-motor functioning, was administered on the same day when postural balance was assessed. Gross motor skills for subjects were assessed with the subtests for agility, balance, bilateral coordination, and strength, while fine motor skills were indexed by the subtests of response speed, visual-motor control, and upper-limb speed and dexterity. The examination yields standard scores for all subtests, a gross motor composite, fine motor composite, and battery composite.

2.5. Statistical analysis methods

SL and SA variables were transformed to their natural logarithm for the analysis as this helped to normalize each variable which is a requirement for ANCOVA. The ANCOVA after controlling for co-factors was used. Based on our previous publication (Bhattacharya et al., 1995) covariates included for the analysis of postural balance data were: age, weight–height ratio, parent's IQ, foot area, race, sex and hours slept before the tests. For the gait data analysis, in addition to the above mentioned co-variates, additional co-factors used were cadence (steps/s), average stride width (both right and left in cm), average stride length (both right and left in cm), and walking speed (steps/s). The final model was obtained by a backward stepwise elimination procedure allowing only those variables to stay in the model which showed a significance level of $p \leq 0.05$. Comparison of treated and placebo groups following the ANCOVA, was done based on covariate-adjusted least square means of the treatment groups and their associated standard errors.

3. Results

Table 1 provides data on demographics, and co-factors. Fig. 1 provides mean PbB levels of both groups recorded during the study period. In the following, results from the postural

Table 1
Demographics and candidate co-factors examined (mean ± S.D.)

Variable	Succimer group ($N = 77$)	Placebo group ($N = 80$)
Age (month)	67.5 ± 5.0	67.5 ± 4.8
Height (in.)	44.3 ± 2.8	44.6 ± 2.4
Weight (lb)	45.1 ± 7.6	47.7 ± 12.1
Hours slept before test	9.87 ± 1.2 ($N = 68$)	9.88 ± 1.8 ($N = 66$)
Parents' IQ	81.5 ± 12.0 ($N = 73$)	79.4 ± 10.5 ($N = 78$)
Foot area	131.9 ± 16.5	136.4 ± 17.8
Race		
Black no. (%)	48 (62.3)	54 (67.5)
Sex		
Female no. (%)	35 (45.5)	33 (41.3)
Cadence for line walk (steps/s)	2.26 ± 0.34 ($N = 74$)	2.22 ± 0.28 ($N = 76$)
Cadence for normal walk (steps/s)	2.31 ± 0.34 ($N = 76$)	2.26 ± 0.34 ($N = 74$)
Cadence for obstacle walk (steps/s)	2.09 ± 0.26 ($N = 74$)	2.036 ± 0.21 ($N = 76$)
Average stride length (right and left foot, cm)	38.24 ± 4.43 ($N = 76$)	38.18 ± 5.25 ($N = 76$)
Average stride width (right and left foot, cm)	18.78 ± 2.84 ($N = 72$)	18.33 ± 3.33 ($N = 76$)
Walking speed for line walk (cm/s)	98.93 ± 17.27 ($N = 72$)	96.12 ± 15.82 ($N = 73$)
Walking speed for normal walk (cm/s)	106.33 ± 18.51 ($N = 72$)	101.9 ± 16.16 ($N = 74$)
Walking speed for obstacle walk (cm/s)	93.3 ± 13.2 ($N = 72$)	91.85 ± 12.12 ($N = 74$)

t-Test showed no difference between the succimer and placebo groups ($p > 0.05$).

balance and gait tests are given. Fig. 2 shows schematics of various test conditions used in this study.

3.1. Effect of succimer therapy on postural balance

Succimer therapy was associated with a reduction in postural SL (i.e. improvement in postural balance) in six out of six static and semi-dynamic tests but a statistically significant difference was obtained in only one of the dynamic bending tests of postural balance. For this dynamic bending eyes closed test (BC), Fig. 3A and B show representative stabilograms [*x*–*y* plot of subjects' CP movement during the postural sway test] from two children: one from the succimer treated group and the other from the placebo group. As noted by the SA and SL responses in Fig. 3, the succimer treated subject showed significantly lower SL and SA levels compared to that of placebo subject implying an improved postural balance. Similar response differences between the groups were also found for all subjects. The ANCOVA (using generalized linear modeling) after controlling for co-factors showed that the dynamic postural sway test (BC) response for the succimer group was significantly ($p = 0.04$) lower (6.6%) than the placebo group implying improved postural balance in the treated group (Fig. 4). The SA response also showed improvement in the succimer group compared to that in the placebo group but was not statistically significant.

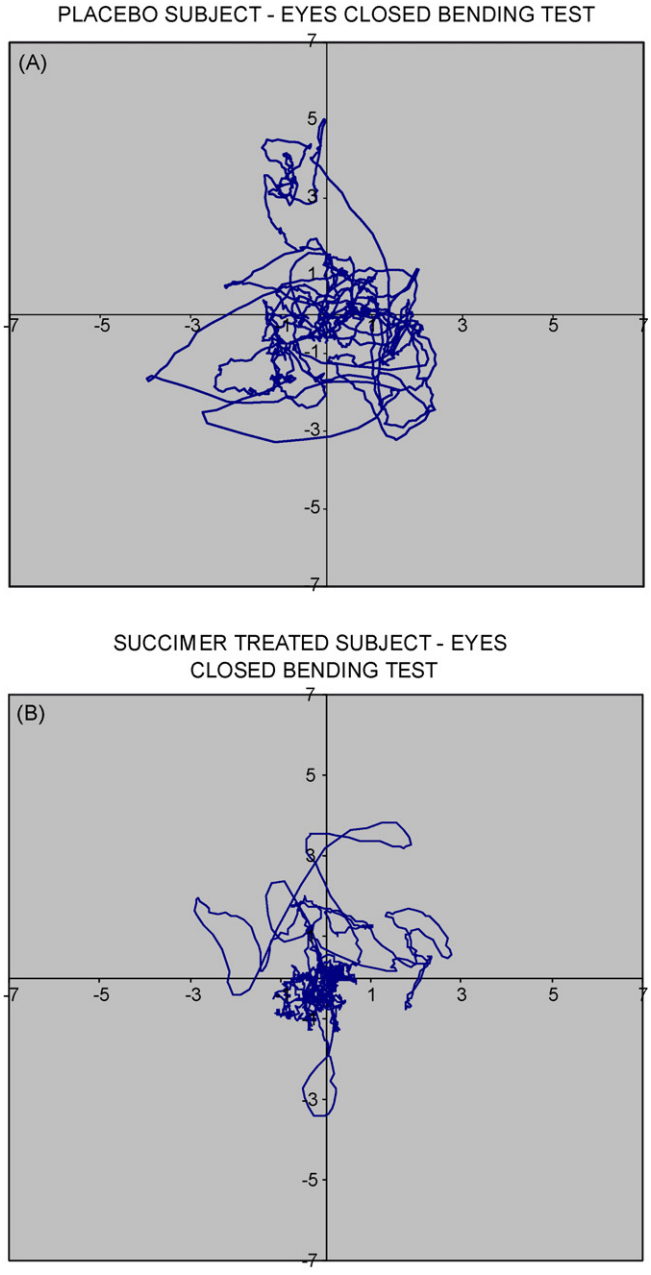

Fig. 3. (A) Illustrative example of a stabilogram from a placebo group subject [age: 64 months; PbB (μg/dL) levels at: 1 week before treatment begins = 25.8 and 14 weeks after treatment begins = 19.8; sway length = 176 cm; sway area = 24.4 cm^2]. (B) Illustrative example of a stabilogram from a succimer group subject [age: 64 months; PbB (μg/dL) levels at: 1 week before treatment begins = 21.8 and 14 weeks after treatment begins = 12.2; sway length = 142.8 cm; sway area = 15.13 cm^2].

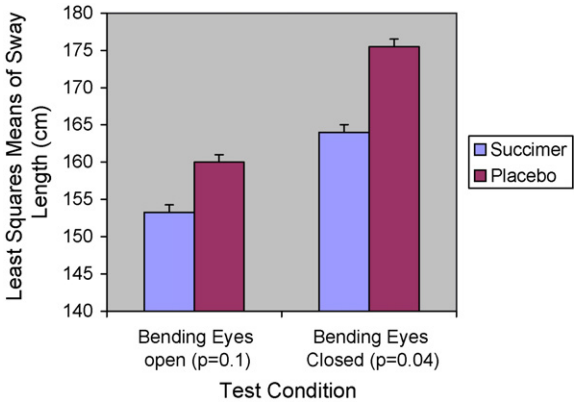

Fig. 4. Least squares mean postural sway length (S.E.M.) responses of placebo and succimer groups under dynamic postural balance test conditions: bending eyes open and bending eyes closed.

3.2. Effect of succimer therapy on functional locomotion or gait performance

During the obstacle crossing test, the succimer treated group showed significantly lower (19%) medio-lateral postural sway compared to the placebo group implying improved balance (in the frontal plane) in children on succimer therapy (Fig. 5A). During the obstacle-crossing test, the maximum propulsive force in the placebo group was significantly larger (10.3%) than the treated group implying that the untreated group was moving faster and that may jeopardize their stability in the anterior–posterior direction (Fig. 5B). During the normal walking test, four out of eight dependent variables showed significant differences between the treated and untreated groups. These variables are: maximum braking force with and without normalized with body weight, maximum propulsive force, maximum medial force and maximum negative torque. Similar to the obstacle crossing test, during the normal walk test the placebo group also had a significantly higher (6.1%) maximum propulsive force than the treated group (Fig. 6A). Similarly, maximum braking force was significantly higher (16.3%) for the placebo group than the treated group for the normal walking

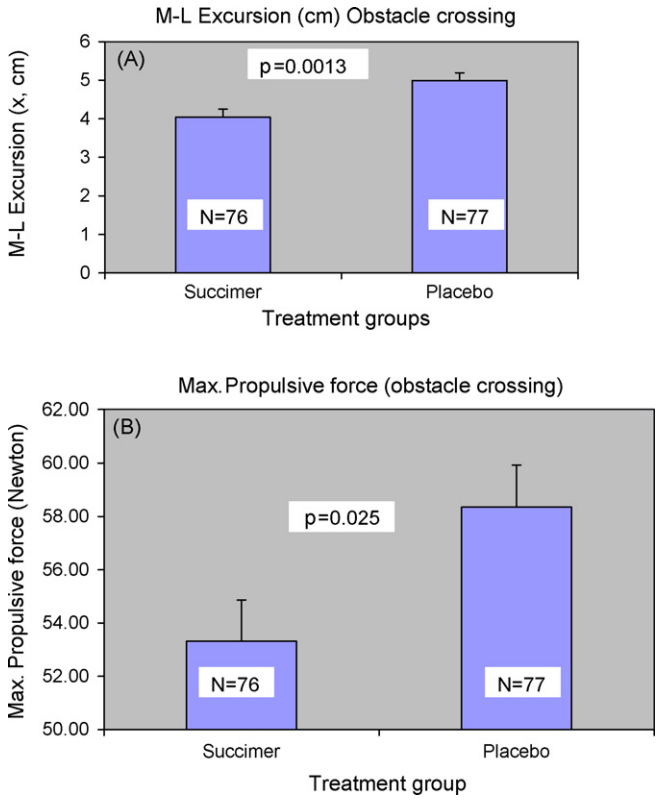

Fig. 5. (A) Least square mean (S.E.M.) medial-lateral (M-L) excursion responses of center of pressure during obstacle crossing test in succimer and placebo groups. (B) Least square mean (S.E.M.) max. propulsive force responses during obstacle crossing test in succimer and placebo groups.

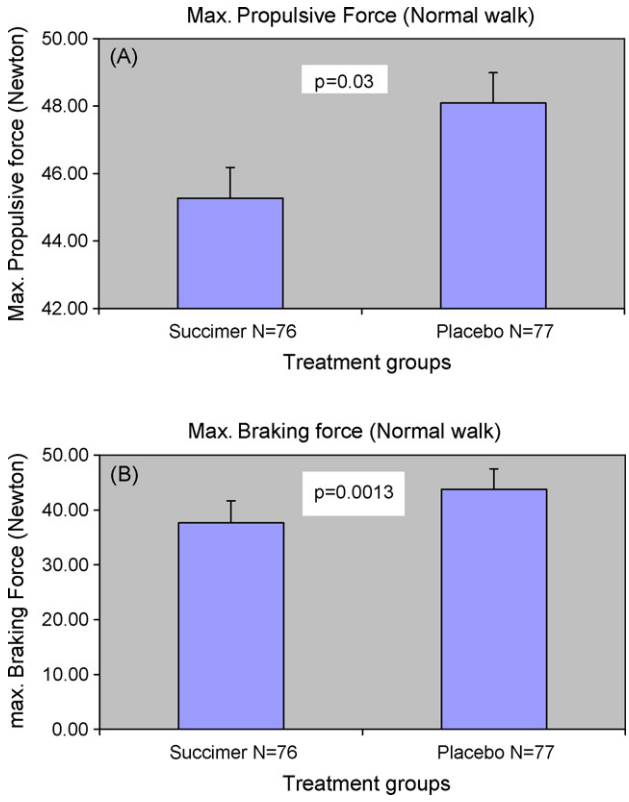

Fig. 6. (A) Least square mean (S.E.M.) max. propulsive force responses during normal walk test in succimer and placebo groups. (B) Least square mean (S.E.M.) max. braking force responses during normal walk test in succimer and placebo groups.

test (Fig. 6B). For the normal walk and line walk, the maximum negative torque (around the vertical axis parallel to the spinal column) as well as maximum medial force were significantly higher (16.7% for torque and 14.4% for medial force) in the placebo group than the succimer group, implying that the non-treated group rotated their body in the medial direction harder to keep their center of gravity (CG) within the base of support for maintaining postural stability in the frontal plane (Fig. 7A and B).

3.3. Effect of succimer therapy on the Bruininks–Oseretsky (BOTMP) performance

The effect of succimer therapy was associated with improvement in neuromotor performance in seven out of eight BOTMP subtests standard scores but statistical significance was not attained. These seven tests were balance (score of 11.84 for succimer versus 11.5 for placebo group), bilateral coordination (score of 14.3 for succimer versus 13.1for placebo group), strength (score of 19.51 for succimer versus 17.7 for placebo group), upper limb coordination (score of 14.31 for succimer versus 12.92 for placebo group), visual motor control (score of 10.11 for succimer group versus 10.00 for placebo group), upper limb speed (score of 13.79 for succimer versus 13.4 for placebo group) and fine motor (score of 34.67 for succimer versus 34.03 for placebo group).

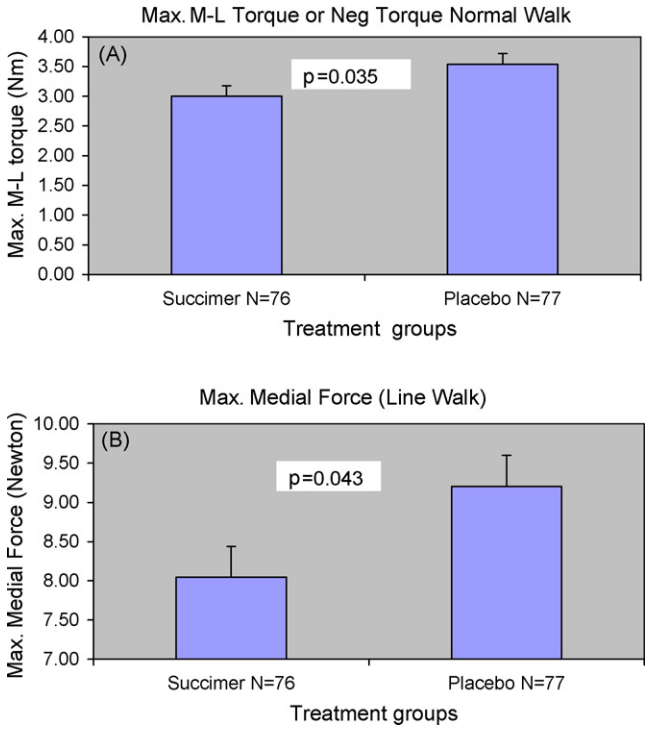

Fig. 7. (A) Least square mean (S.E.M.) max. medial-lateral (M-L) torque responses during normal walk test in succimer and placebo groups. (B) Least square mean (S.E.M.) max. medial force responses during line walk test in succimer and placebo groups.

4. Discussion

The major aim of this study was to investigate the intent to treat effects on postural balance and gait/locomotion. Succimer therapy was associated with improvements in some of the outcomes of postural balance tests and also in functional gait performance. The implications of these findings are discussed in the following.

4.1. Implications of succimer therapy on postural balance

In comparison to the placebo group, the average SL response was lower among subjects on succimer for all six tests (EO, EC, FO, FC, BO and BC), but was statistically significant only for the BC test. A decrease in SL implies improved postural balance. The amount of decrease (range 4.2–6.6%) in SL response observed with succimer therapy is comparable (in terms of magnitude of response) to those reported by us in our previous publication (Bhattacharya et al., 1995) showing Pb exposure associated detrimental changes in postural sway. Unlike the findings from the present study the results from our case study (Bhattacharya et al., 1998) of an adolescent Pb intoxicated patient undergoing a combination of CaEDTA and succimer therapy showed a much higher (26–50% decrease in SL after therapy for EO, EC and FO tests) improvement in postural balance. However, with FC test that provides relatively more challenge to the vestibular system, the SL and SA responses for this teenager actually became somewhat worse (increased by about 4%) after the combined CaEDTA-succimer therapy.

The mean SA response from the present study did not show any statistically significant improvement in the succimer group and for most of the tests SA response was either similar or somewhat higher than that of placebo group's mean response. This finding is consistent with the results of our case study (Bhattacharya et al., 1998) of an adolescent Pb intoxicated patient.

The differences in mean response patterns of SL and SA observed above may provide some insight into how different afferent systems relevant for postural balance were influenced by the succimer therapy. A previous study (Yasuda et al., 1999) of patients with known neurological disorders have shown that SL (or the velocity of sway which is significantly correlated with SL) and SA responses imply different physiological controls of human equilibrium. They reported that patients with primarily vestibular disorders respond with a higher SA than normal subjects. On the other hand, patients with primarily proprioceptive disorders show a higher SL response than normal subjects. Keeping this in mind, in the present study the SA response pattern implies that the succimer therapy was not able to produce beneficial changes in the vestibular system's contribution to postural balance. This finding is consistent with the results of our case study (Bhattacharya et al., 1998) of an adolescent Pb intoxicated patient whose postural balance showed no improvement or worsening with succimer therapy for the test (eyes closed on foam) which indirectly challenged the vestibular system. In the BC test, the subject's postural balance is intentionally or voluntarily perturbed by the subject and balance control is primarily maintained by the vestibular and the proprioception systems (as the eyes are closed during the test) which have been implicated to be influenced by Pb exposure (Bhattacharya et al., 1995). Since in the present study the mean SA response to BC did not show statistically significant improvements in postural balance (even though there was an absolute decrease in SA value in the succimer group), one could imply that vestibular functionality was not improved with succimer therapy.

On the other hand, in the BC test, a significantly lower SL response in the treated group than the placebo group implies that the proprioception system was assisted by succimer therapy. However the SL responses in BO test did not show significant improvement (although the absolute values of SL were lower in children on succimer) implying that availability of vision actually minimized the differences in the SL responses between the groups. In other words availability of vision was sufficient to offset the potential Pb-associated problems in the functionality of the proprioception and vestibular systems during the BO test.

A recent study by Cecil et al. (2005) presents new evidence that early exposure to Pb is associated with gray matter loss in the cerebellum, providing additional support to the postural balance responses observed in the present study. Since the cerebellum is known to play a significant role in the control of postural balance, it is worthwhile discussing how Pb-associated damage to the cerebellum relates to the results of the present study. Three areas of the cerebellum have significant contributions for coordination of movement and postural balance. They are the flocculonodular lobe, vermis and intermediate hemispheres and lateral hemispheres. The flocculonodular lobe receives information from visual and vestibular systems and outputs go to the vestibular nuclei for postural balance control (Shambes et al., 1978; Shumway-Cook and Woollacott, 2001). Vermis and intermediate hemispheres receive inputs from proprioceptive and cutaneous receptors via spinocerebellar tracts and corresponding responses control execution of movement and muscle tone. The lateral hemispheres of the cerebellum appear to contribute to both motor and non-motor skills, including preparation of movement as previous studies showed that, when subjects were asked to simply imagine making a movement, their cerebral blood flow and cerebellar activities increased (Decety et al., 1990; Middleton and Strick, 1994, 1996, 2001; Shumway-Cook and Woollacott, 2001). Middleton and Strick's neuroanatomical experiments have shown projections from the lateral dentate nucleus of the cerebellum into frontal association areas (Middleton and Strick, 1994, 2001).

Studies have shown that damage to the cerebellum causes problems with postural balance such as increased muscle response to a perturbation resulting in an increased postural sway amplitude; possibly implicating functional decrements of the vestibular system (Horak et al., 1990; Shumway-Cook and Woollacott, 2001). In the present study, since SA response did not show a significant decrease with succimer therapy, it possibly implicates potential Pb associated damage to

cerebellum reported by Cecil et al. (2005). Studies by Mushiake and Strick and Sanes et al. showed that certain neurons in the dentate nucleus of the cerebellum utilize the visual system to control movement patterns (Mushiake and Strick, 1993; Sanes et al., 1988). Sanes et al. (1988) showed that patients with cerebellar damage actually have better motor performance in the eyes closed condition and caused cerebellar tremor under the eyes open condition. This could be the reason that in the present study the SL response (which captures postural muscle tremor) under the eyes open condition for the BO test was not able to statistically discriminate the beneficial effect of succimer.

4.2. Implications of succimer therapy on locomotion (gait)

The results from gait evaluations indicated different gait patterns in the succimer therapy group compared to those in the placebo group. The gait evaluations consisted of normal walking or baseline and functional gait tests where the associated neuromotor controls were challenged. The functional gait tests were line walking and obstacle crossing (Fig. 2).

During the normal walking test, the placebo group applied significantly more braking force than the succimer group implying that the placebo group had to apply more braking force to slow down their body motion during the gait cycle. This phenomenon also implies poorer neuromuscular control in the non-treated group. During the gait cycle it is common for subjects to apply medio-lateral (M-L) torque (toward the midline of the torso; also known as negative M-L torque) to keep their body's CG within the base of support to help maintain safe upright balance (Winter et al., 1993). In this study, the placebo group had a significantly higher M-L torque than the succimer group, implying that the placebo group had to work harder to keep their CG within the base of support. This finding is consistent with results of Bagchee and Bhattacharya (1994) who reported that children with higher Pb exposure produced a much higher M-L torque compared to those with lower Pb exposure.

During the obstacle crossing task, there are three types of important controls needed: visuomotor coordination, body stability, and control of the crossing limb when going over the obstacle (Law and Webb, 2005). In the present study, the BOTMP battery (Bruininks, 1978) was carried out to obtain performance scores in the areas of visuomotor coordination and bilateral coordination. While the BOTMP results were not statistically significant, they showed slight improvements in scores of visuomotor coordination and bilateral coordination. A combination of improved (not statistically significant) visuomotor coordination and bilateral coordination potentially helped with the obstacle crossing task in the succimer group which showed a significantly smaller M-L sway compared to the placebo group. Therefore, it appears that slight improvements in visuomotor coordination and bilateral coordination were sufficient to reduce the M-L sway in the succimer group during the obstacle crossing task without the need to have an increased M-L torque for keeping the body's CG within the base of support. A comparison of M-L excursion response during gait between the succimer and the placebo groups indicated that the treated group had a significantly better postural balance in the frontal plane during obstacle crossing task. However, during the obstacle-crossing test the placebo group showed a significantly higher propulsive force than the succimer group implying that the placebo group hurried over the obstacle. A higher propulsive force in the placebo group may also contribute to poorer balance in the frontal plane as documented by the higher value of M-L postural sway or excursion in this group.

During the line walk test, subjects had to maintain their postural balance by keeping their CG within the base of support while walking on a straight line. This requires a significant amount of visuomotor and bilateral coordination, but unlike the obstacle-crossing task, it did not require the need to maintain postural balance during the single stance for prolonged periods. During this task the succimer group showed significantly better or smaller M-L sway, and it was accomplished with a significantly lower M-L force than that of the placebo group.

There were no statistically significant differences in the variables of cadence, and walking speed, describing the gait temporal patterns between the succimer group and the placebo group. However, the placebo group showed more of a cautious gait pattern compared to those of succimer group. The cautious gait pattern among the placebo children was characterized by slower cadence (steps/s) and slower walking speed (cm/s). However, these differences were not statistically significant (Table 1). In comparison to normal, unexposed children (for a 5 year old the cadence is 2.5 steps/s or 150 steps/min), the cadence levels in both groups were slower implying a more cautious gait pattern (Hausdorff et al., 1999; Sutherland, 1997). Decreased speed of gait in the placebo group implies that these children are using more time to process the visuomotor information, especially in the more challenging gait tasks of line walk and obstacle crossing. In a previous study from our group we observed that children with higher PbB levels showed decreased gait speed (Bagchee and Bhattacharya, 1994). Cerebral palsy patients also show slower cadence and gait speed (Sutherland, 1978).

4.2.1. Potential role of lead in affecting mechanoreceptors of the locomotor system

The above mentioned findings of higher braking force, propulsive force and medio-lateral torque among the placebo group during normal walk and obstacle crossing tasks (compared to succimer group) suggest a potential role of Pb in affecting load receptors found in locomotor systems associated with muscles and tendons (Dietz, 1997; Law and Webb, 2005; Sorensen et al., 2002). The performance of smooth and coordinated motor tasks such as normal walking and obstacle crossing is controlled by two mechanoreceptors: (1) muscle spindle and (2) golgi tendon. Previous studies have implicated that during gait the load receptors within the muscles (muscle spindles and golgi tendons) play an important role in the placement of feet within the base of support that is

necessary for maintaining safe upright balance. Collectively, muscle spindle and golgi tendon regulate muscle stiffness, i.e. muscle force (by golgi tendon) per unit muscle length (by muscle spindle) (Gordon and Ghez, 1991). Since obstacle crossing requires postural balance during single stance, a potential mechanism as to how higher Pb burden in the placebo group might interfere with locomotion is discussed below.

Based on study by Sorensen et al. (2002), primary endings of ankle muscle spindles play a major role in describing the motion of center of mass or CG with respect to single stance support foot thereby assisting in the control of posture and balance during walking over an obstacle. Stretching of muscle spindles causes distortion of intrafusal fibers (inside the muscle spindle) thereby initiating depolarization of the terminal and creating a receptor potential which then gives rise to an action potential (Burt, 1993). Since Pb has been shown to compete with calcium (Ca) (i.e., inhibition of Ca which is important for normal nervous system function) at the neuromuscular junction and impede the generation of the action potentials at the muscle end-plate, it (Pb) may decrease (or modify) the sensitivity of load receptors (golgi tendons and muscle spindle) (Cooper and Manalis, 1983; Cooper and Steinberg, 1977; Cooper et al., 1984). Therefore, placebo group subjects may produce increased M-L force and increased M-L torque to keep their CG (by placing their feet) within their base of support for safe maintenance of postural balance during walking (Bagchee and Bhattacharya, 1994). On the other hand, during obstacle crossing, the visual information is informing the subject that his/her balance will be threatened when crossing the obstacle. Therefore, he/she may have to move faster during the propulsive phase of gait (i.e., tried to hurriedly go over the obstacle). This finding is consistent with that of our previous study (Bagchee and Bhattacharya, 1994). In summary, postural balance and functional locomotion (gait) tests provided objective quantifiable outcomes for evaluating the potential benefits of succimer therapy on neuromotor function. Based on these results, it appears that SL responses showed some improvement in the postural balance implying beneficial effects of succimer therapy to the proprioceptive system which are known to be detrimentally influenced by Pb (Bhattacharya et al., 1995, 2006). Since the mean response of SA of the group on succimer were either the same or higher than the placebo group, it appears that succimer therapy is not effective in improving vestibular functionality consistent with the findings from our case study (Bhattacharya et al., 1998). The results of succimer therapy on the performance in locomotion or gait tests showed that the treated group's performances were better than the placebo group. However, both groups showed cautious gait characterized by decreased speed of gait and reduced cadence. While some beneficial neuromotor effects of succimer therapy were observed in the present study, there remains several unanswered questions such as how long these effects will persist and how succimer impacts cerebellar function with respect to postural balance and functional locomotion. The findings reported here are correlational and therefore has limitations; caution should be exercised when interpreting the result.

In its most recent guidelines for the management of lead-exposed children, the CDC has omitted any recommendation for the chelation of children with PbB levels under 45 μg/dL (USCDC, 2002). Succimer is labeled only for children with higher PbB levels. The findings of this study, nor those that involved the entire TLC sample (Dietrich et al., 2004; Rogan et al., 2001) do not provide strong support for any changes to current practice. However, even in the absence of a recommended medical treatment at these levels, high-risk children should still be screened for Pb exposure. This is principally because such screening can trigger environmental controls that can limit further exposure. More effective public health policies to assist parents with such environmental interventions are also needed. The elimination of childhood Pb poisoning by the year 2010 remains a worthwhile goal and progress in this direction can only be assessed if screening continues. Our efforts, however, should go beyond mere screening for cases. Indeed, the first line of defense against this avoidable environmental disease should be the screening of homes with potentially hazardous sources of exposure. By the time a child is identified as Pb poisoned the damage may have already been done with possibly irreversible consequences.

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