A pilot study of depot medroxyprogesterone acetate pharmacokinetics and weight gain in adolescent females

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Abstract

Objective—To explore the relationship between medroxyprogesterone acetate (MPA) pharmacokinetic (PK) parameter estimates and weight gain.

Study design—Prospective study of adolescents (N=40; age 12 – 21) initiating DMPA. PK parameters were calculated: maximum MPA concentration (C_{max}, ng/mL), time to C_{max} (T_{max}, days), and elimination rate constant (ng/mL/day). Optimal PK cut points were determined for predicting BMI increase 10%.

Results—C_{max} <2.88 ng/mL and elimination rate constant <0.021 ng/mL/day were associated (p<0.05) with BMI increase 10%. Elimination rate constant was most predictive of weight gain.

Conclusions—Pharmacokinetic evaluation may help identify adolescents at risk of excessive DMPA-associated weight gain.

Keywords

contraception; pharmacokinetics; adolescence; Depo Provera; weight

Introduction

Weight gain is highly variable among adolescents on depot medroxyprogesterone acetate (DMPA) [1–3]. Literature describing DMPA disposition reveals wide inter-individual variability in circulating medroxyprogesterone acetate (MPA) concentrations [4–7]. This wide variability has not been explained by number of prior DMPA injections, body mass index (BMI), or racial/ethnic background [5].

To our knowledge, the relationship between MPA pharmacokinetic (PK) measures and clinical side effects such as weight gain has not been examined. The objective of this pilot study was to explore the relationship between MPA PK parameter estimates and weight gain among adolescent females initiating DMPA.

Methods

Subjects consisted of healthy, post-menarcheal females, ages 12–21, initiating DMPA at two urban, outpatient Adolescent Medicine Clinics between December 2007 and September 2011. Exclusion criteria included: 1) DMPA use within the past 12 months; 2) pregnancy within the past 6 months; 3) other hormonal contraceptive use within the past 3 months; 4) chronic disease known to affect weight (e.g. diabetes); 5) use of medications known to affect weight (e.g. daily corticosteroids); and 6) need for confidential contraceptive care if <18 years.

Written informed consent was obtained from subjects 18 years and from a parent/legal guardian of subjects <18. Minor subjects provided written informed assent. The study protocol was approved by the Institutional Review Boards at participating institutions.

Study visits were conducted at baseline (within 1 week prior to the first DMPA injection); every 4 weeks during the first 12-week dosing interval; and at 12, 24, and 48 weeks at time of subsequent DMPA injections. Of 62 patients approached, 45 enrolled, and 40 had sufficient data for PK analyses. 39 and 31 returned at 24 and 48 weeks, respectively. No significant differences were found between study completers and non-completers. All patients received DMPA 150mg intramuscularly every 12 weeks.

Subject demographics and medical history were collected at baseline. Gynecologic age was calculated as the difference between chronologic and menarcheal age. Update interviews were conducted at subsequent visits to assess for changes in health or medications. At baseline, 12, 24, and 48 weeks, weight and height were measured. BMI was calculated as weight (kg)/height (m^2).

Blood was obtained at all study visits. In order to maximize available data for PK analyses and minimize number of blood draws, a sparse sampling strategy (population PK approach) was employed. Subjects were randomly assigned to one of four groups: blood draws at weeks 1, 5, and 9; blood draws at weeks 2, 6, and 10; blood draws at weeks 3, 7, and 11; or blood draws at weeks 4, 8, and 12. Serum samples were analyzed for MPA by liquid chromatography-mass spectrometry using Multiple Reaction Monitoring.

The main outcome measure was annualized percentage change in BMI dichotomized into two groups: 1) excessive weight gainers (BMI increase   10%); and 2) non-excessive weight gainers (BMI increase <10%). Patient demographics, weight measures, and PK parameter estimates were described for all subjects and by weight gain group.

A composite, population, time concentration curve was generated using all available MPA concentrations across the first 12-week interval. Individual PK parameter estimates (maximum MPA concentration (Cmax, ng/mL), time to Cmax (Tmax, days), and elimination rate constant (ng/mL/day)) were then calculated and compared across weight gain groups using Student's t-test. Optimal cut scores for individual PK parameter estimates were determined using Receiver Operating Characteristics (ROC) analysis. Backwards stepwise logistic regression was performed to investigate the independent relationship between individual PK parameter estimates and weight gain group. P-values are two-sided and unadjusted for multiple comparisons. Data analyses were performed using SAS (version 9.2, SAS Institute, Cary, NC).

Results

Fifteen subjects (37.5%) self-identified as white non-Hispanic, 14 (35.0%) as black non-Hispanic, and 11 (27.5%) as Hispanic. Mean chronologic and gynecologic age were 16.2 and 4.2 years, respectively. The majority of subjects had regular menstrual cycles (93.3%) and no prior pregnancy (91.1%). Excessive weight gain (BMI gain   10%) was observed in 11 (27.5%) subjects. Excessive and non-excessive weight gainers did not significantly differ at baseline with regards to mean chronologic/gynecologic age, race, or BMI.

Composite serum concentration time curves, constructed from MPA values during the first 12-week interval, support a relationship between weight gain and PK parameter estimates (Figure 1). Subjects with excessive weight gain demonstrated a lower Cmax and a flatter concentration curve than subjects with non-excessive weight gain.

In unadjusted, bivariate analyses, significant ($p<0.05$) associations were found between weight gain group and two PK parameter estimate cut points (Table 1). Cmax <2.88 ng/mL had a sensitivity of 0.73 and a 1-specificity of 0.38 for identifying subjects with excessive weight gain. Elimination rate constant <0.021 ng/mL/day had a sensitivity of 1.00 and a 1-specificity of 0.64 for identifying subjects with excessive weight gain. Although not significant, excessive weight gainers had, on average, a longer Tmax (38.9 vs. 30.4 days, respectively). In backwards stepwise logistic regression (data not shown), only elimination rate constant <0.021 ng/mL/day remained a significant predictor (p=0.05) of an annualized BMI increase   10%.

Discussion

We found that flatter MPA concentration time curves, i.e. those with lower Cmax and more gradual slope, were related to higher BMI gains. Lower Cmax coupled with slower elimination rate likely results in increased area under the curve (AUC), a surrogate marker for drug exposure. Higher AUC and correspondingly higher MPA exposure might explain greater weight gain.

Interpretation of our data is limited by small sample size. Our sparse sampling strategy (employed to improve recruitment and compliance in adolescents) limited our ability to fully characterize each subject's concentration time curve. Although given intramuscularly, DMPA injection site (gluteal or deltoid) was not standardized.

Despite these limitations, the current study provides a new framework for evaluating DMPA-associated side effects as prior studies found inconsistent relationships between clinical characteristics and weight gain [2,3,8,9]. Our data suggest that PK evaluation may assist in the identification of patients at risk of excessive weight gain. Future studies with larger sample sizes or standard PK methods should be conducted to determine optimal PK predictors of DMPA-associated side effects and to better characterize the etiology of MPA PK variability.

Acknowledgments

References

1. Bonny AE, Ziegler J, Harvey R, Debanne SM, Secic M, Cromer BA. Weight gain in obese and nonobese adolescent girls initiating depot medroxyprogesterone, oral contraceptive pills, or no hormonal contraceptive method. Arch Pediatr Adolesc Med. 2006; 160:40–5. [PubMed: 16389209]

2. Risser WL, Gefter LR, Barratt MS, Risser JM. Weight change in adolescents who used hormonal contraception. J Adolesc Health. 1999; 24:433–6. [PubMed: 10401972]

3. Mangan SA, Larsen PG, Hudson S. Overweight teens at increased risk for weight gain while using depot medroxyprogesterone acetate. J Pediatr Adolesc Gynecol. 2002; 15:79–82. [PubMed: 12057528]

4. Ortiz A, Hirol M, Stanczyk FZ, Goebelsmann U, Mishell DR. Serum medroxyprogesterone acetate (MPA) concentrations and ovarian function following intramuscular injection of depo-MPA. J Clin Endocrinol Metab. 1977; 44:32–8. [PubMed: 833262]

5. Smit J, Botha J, McFadyen L, Beksinska M. Serum medroxyprogesterone acetate levels in new and repeat users of depot medroxyprogesterone acetate at the end of the dosing interval. Contraception. 2004; 69:3–7. [PubMed: 14720612]

6. Koetsawang S, Shrimanker K, Fotherby K. Blood levels of medroxyprogesterone acetate after multiple injections of depoprovera or cycloprovera. Contraception. 1979; 20:1–4. [PubMed: 477312]

7. Jeppsson S, Johansson. Medroxyprogesterone acetate, estradiol, FSH and LH in peripheral blood after intramuscular administration of Depo-ProveraR to women. Contraception. 1976; 14:461–69. [PubMed: 975831]

8. Polaneczky M, Liblanc M. Long-term depot medroxyprogesterone acetate (Depo Provera) use in inner-city adolescents. J Adolesc Health. 1998; 23:81–8. [PubMed: 9714170]

9. O'Dell CM, Forke CM, Polaneczky MM, Sondheimer SJ, Slap GB. Depot medroxyprogesterone acetate or oral contraception in postpartum adolescents. Obstet Gynecol. 1998; 91:609–14. [PubMed: 9540951]
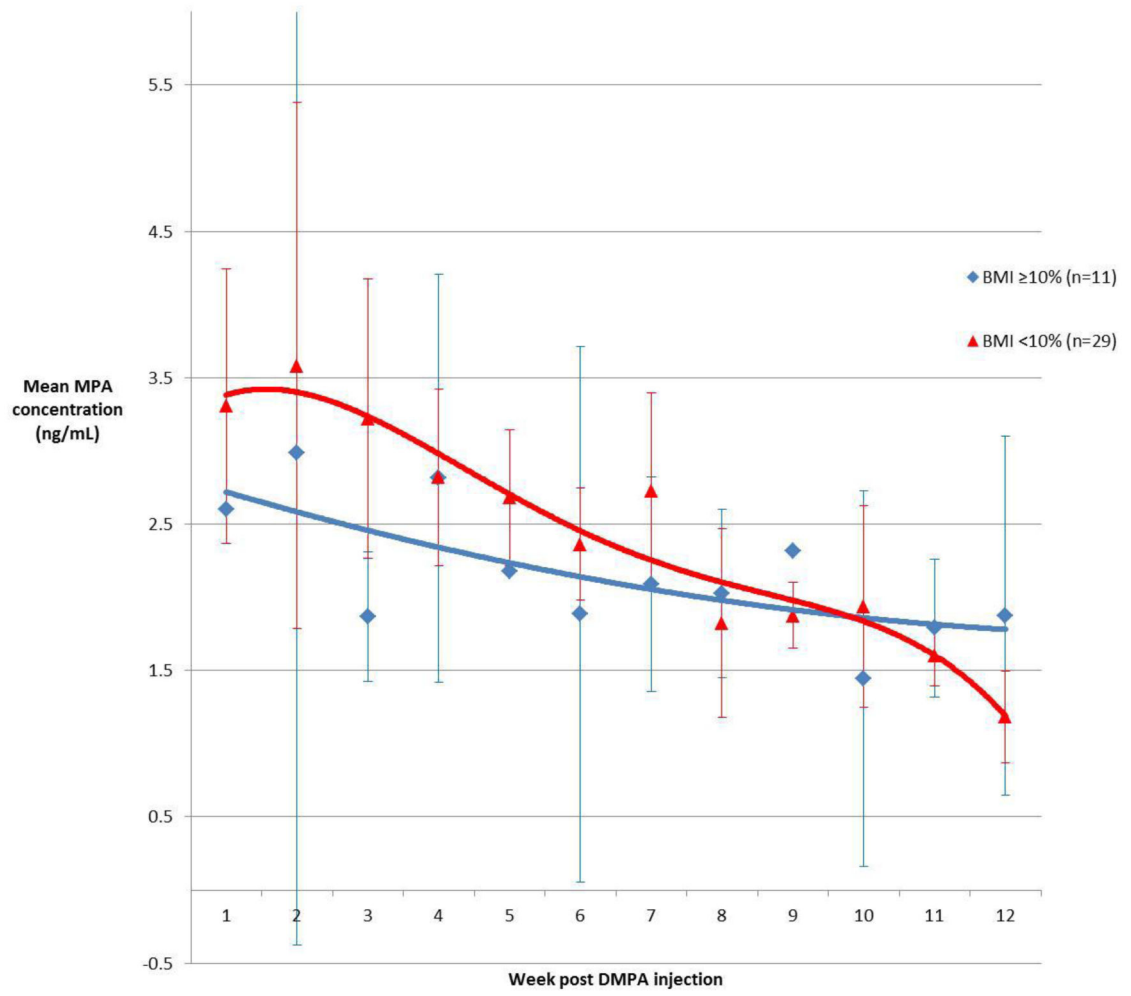
Figure 1.
Composite MPA concentration time curves (95% confidence intervals)

Table 1

Medroxyprogesterone acetate pharmacokinetic parameters estimates by annualized percentage increase in body mass index

Pharmacokinetic Parameter Estimate	BMI gain ≥10% (n=11)	BMI gain <10% (n=29)	p-value[a]
Cmax[b]			0.145
Mean (SD)	2.61 (1.04)	3.23 (1.21)	
Median	2.52	2.92	
Min - Max	1.27 – 4.70	1.57 – 6.12	
Cmax <2.88			0.049
n(%)	8 (72.7)	11 (37.9)	
Elimination Rate Constant[c,d]			0.196
Mean (SD)	0.011 (0.006)	0.019 (0.017)	
Median	0.009	0.016	
Min - Max	0.003 – 0.021	0.002 – 0.076	
Elimination Rate Constant <0.021			0.047
n(%)	8 (100.0)	18 (64.3)	
Tmax[e]			0.320
Mean (SD)	38.9 (28.81)	30.4 (21.88)	
Median	28	27	
Min - Max	7 – 87	6 – 87	

[a] Unadjusted Student's t-test analyses p-value

[b] Maximum serum medroxyprogesterone acetate concentration (ng/mL)

[c] Natural logarithm medroxyprogesterone acetate elimination rate constant (ng/mL/day)

[d] Three subjects with BMI gain ≥10% and one subject with BMI gain <10% had no post-peak concentration data and were missing from the elimination rate constant determination

[e] Time to Cmax (days)