

Influence of megestrol acetate on nutrition and inflammation in dialysis patients – preliminary results[★]

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Malnutrition is a common clinical problem in dialysis patients. So far the management of malnutrition in this population has not been fully successful. The aim of the study was to evaluate the efficacy and safety of use of megestrol acetate suspension in malnourished dialysis patients. Twenty-six hypoalbuminemic (albumin ≤ 3.8 g/dl) dialysis patients took 160 mg of megestrol acetate daily for a period of two months. Anthropometry (dry weight, body mass index) and biochemical measurements of nutrition (serum albumin, triglycerides, total cholesterol) and inflammation (hsCRP, IL-1 β , IL-6) were performed on a monthly basis. The treatment led to a statistically significant increase ($P < 0.05$) in anthropometry and albumin concentration, with no statistically significant changes in total cholesterol, triglycerides and indices of inflammation. Side effects included overhydration, diarrhoea and hyperglycaemia. Thus, megestrol acetate may be an effective therapeutic agent in improving the nutritional status of carefully selected dialysis patients, while it might not mitigate inflammation. Because of the prevalent side effects it must be monitored closely.

Keywords: malnutrition, megestrol acetate, proinflammatory cytokines

INTRODUCTION

The number of end-stage renal disease (ESRD) patients is constantly increasing, including the number of patients who require chronic renal replacement therapy. Despite the huge headway that has been made in dialysis techniques and equipment, the symptom burden faced by maintenance dialysis

patients remains unacceptably high. Among the most common problems experienced by dialysis patients are anorexia and malnutrition/wasting (Murtagh *et al.*, 2007). Their prevalence varies, depending on the study between 10% and 75%. Not only is malnutrition a problem because of its negative impact on the quality of life (Dwyer *et al.*, 2002) and the number of comorbidities and hospitalizations but, what is most

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Abbreviations: AIDS, acquired immunodeficiency syndrome; BMI, body mass index; CPD, continuous peritoneal dialysis; ESRD, end-stage renal disease; hsCRP, high-sensitivity C-reactive protein; IL-1, interleukin 1; IL-6, interleukin 6; Kt/V, urea clearance over time related to the volume of urea distribution; MHD, maintenance haemodialysis; MIA, malnutrition-inflammation-atherosclerosis; SGA, subjective global assessment; TNF- α , tumour necrosis factor alpha.

important, its enormous influence on cardiovascular and all-cause mortality (Kalantar-Zadeh *et al.*, 2001). Therefore, successful management of malnutrition could ameliorate the cardiovascular epidemic and poor outcome in dialysis patients (Kalantar-Zadeh *et al.*, 2003; 2005).

The aetiology of malnutrition in ESRD is complex and may include many underlying factors. Hence, its treatment is difficult. Protein-energy malnutrition often overlaps with inflammation and atherosclerosis leading to malnutrition-inflammation-atherosclerosis (MIA) syndrome (Rashid Qureshi *et al.*, 2002; Kalantar-Zadeh *et al.*, 2003). The key role in all these events is played by proinflammatory cytokines such as IL-1, IL-6, and TNF- α . That is why, when conventional nutritional and metabolic interventions do not provide satisfactory results, treatment aimed at eliminating or reducing inflammation becomes a necessity. Several new strategies, including the use of megestrol acetate, are under investigation.

Megestrol acetate is a synthetic progestagen that has been demonstrated to increase appetite and weight in patients with cancer or AIDS (Lopez *et al.*, 2004) and is believed to act by down-regulating the proinflammatory cytokines IL-1, IL-6, and TNF- α (Mantovani *et al.*, 1998a; 1998b). Therefore not only could it improve the nutritional status, but also reverse the cytokine-dependent inflammatory process.

So far, only a limited number of studies has been published evaluating the use of megestrol acetate in dialysis patients (Lien & Ruffenach, 1996; Burrowes *et al.*, 1999; Boccanfuso *et al.*, 2000; Costero *et al.*, 2004; Rammohan *et al.*, 2005; Monfared *et al.*, 2009). These limited but promising studies with variable results, and the successful use of megestrol acetate in cancer and AIDS patients, together with the lack of data regarding the influence of megestrol acetate on inflammation in ESRD patients, support the rationale for conducting a study aimed at evaluating the use of megestrol acetate in dialysis patients. Therefore, the goal of this study was to examine the influence of megestrol acetate (160 mg daily) on nutrition and inflammation in dialysis patients over a period of two months. The dose of 160 mg was chosen as it was reported to be safe, yet efficient.

PATIENTS AND METHODS

Subject recruitment and study design. A multicenter, prospective study design was used. The study protocol was approved by the Bioethics Committee of the Medical University of Gdańsk (registration number NKEBN/5/2006, issued 24.02.2006).

All procedures were performed in accordance with the Helsinki Declaration.

Between June 2006 and March 2007 maintenance hemodialysis patients (MHD) and chronic peritoneal dialysis (CPD) patients from six hemodialysis facilities (381 patients) and two peritoneal dialysis centres (89 patients) were screened for eligibility. Inclusion criteria were: (1) MHD or CPD for at least 3 months, (2) serum albumin concentration ≤ 3.8 g/dl (Bromocresol Green), while exclusion criteria were (1) concurrent use of glucocorticoids and (2) inadequate dialysis as defined by Kt/V of < 1.2 for MHD and < 2.0 for CPD patients. HIV/AIDS or malignancy were not exclusion criteria. Before enrolment, patients received detailed written and verbal information regarding the aims and protocol of the study. Written informed consent was obtained from all study patients.

At baseline and at monthly intervals anthropometric measurements and biochemical analyses were performed.

Patients were provided with megestrol acetate solution (Megalia, Vipfarm) after the baseline measurements and instructed to take 4 ml (160 mg) daily.

Anthropometric indices. These included height, dry weight and body mass index (BMI). BMI was calculated using the following equation: dry weight (kg) : height squared (m^2).

Biochemical analysis (nutritional and inflammatory indices). Blood sample were drawn from peripheral vein (CPD patients) or from artero-venous fistula or catheter before commencing dialysis (MHD patients). Serum was separated < 30 min after drawing and stored at -70°C until needed for analysis. Standard laboratory techniques were used for the determination of serum albumin, triglycerides and total cholesterol concentrations (Abbott Clinical Chemistry). HsCRP and cytokine (IL-1 β and IL-6) concentrations were measured by commercial, high-sensitivity sandwich enzyme-linked immunosorbent assay (ELISA) kits (DRG and BenderMed Systems, respectively).

Statistics. All analyses were performed using Statistica 7.1 (StatSoft) software. Data are presented as mean \pm S.D., unless otherwise indicated. $P < 0.05$ was considered to be significant. To assess the normalcy of the distributions we used the Kolmogorov-Smirnov test. Spearman's or where appropriate Pearson's rank order correlation coefficient was used to explore the relationship between nutritional and inflammatory indices at baseline. To assess the significance of changes of the repeated measures of investigated variables either One Way ANOVA or nonparametric Friedman's ANOVA and Least Significant Differences tests (post hoc comparisons) were used, when appropriate.

RESULTS

Baseline characteristics of patients

Forty-nine MHD and nineteen CPD of the total 381 MHD and 89 CPD patients were found to be eligible for the study. Thirty-four MHD and eleven CPD patients consented to participation and were enrolled in the study. Thirteen patients dropped out before the study started or within the first four weeks of the study. Nine of those subjects withdrew their consent without giving an explanation (as they were entitled to do), two underwent renal transplantation, one person died in the fourth week of the study of reasons unrelated to the study (cholangitis leading to sepsis) and one was excluded from the study because of noncompliance. Their data were not included in the analysis. The analysis presented below regards 26 patients (18 MHD and 8 CPD; 13 male and 13 female) who had completed two months of megestrol acetate treatment by the end of February 2007. Mean age of the studied patients was 68.54 ± 11.22 years (range 38–85). The causes of ESRD were: diabetic nephropathy (9), glomerulonephritis (6), polycystic kidney disease (2) and other (9).

Before the initiation of the megestrol acetate treatment we found no statistically significant cor-

relation between laboratory indices of nutrition and inflammation.

Nutritional indices

All patients reported improved appetite, which was accompanied by a substantial increase in the daily energy intake. There was a concurrent increase in mean body weight and BMI after two months of treatment to 64.79 ± 12 kg from the baseline of 63.59 ± 12.38 kg and to 23.68 ± 3.63 kg/m² from the baseline of 23.06 ± 3.26 kg/m², respectively. Both changes were statistically significant ($P < 0.05$). An increase in serum albumin concentration over the intervention period from 3.51 ± 0.33 g/l to 3.659 ± 0.449 g/dl was observed, and this was also statistically significant ($P = 0.023$ after one month and $P = 0.004$ after two months). The concentrations of total cholesterol and triglycerides decreased after two months of megestrol acetate treatment from 173.96 ± 57.66 mg/dl to 165.27 ± 57.46 and from 146.13 ± 75.21 mg/dl to 131.71 ± 59.52 mg/dl, respectively. These changes were insignificant (Table 1).

Inflammatory indices

There was an increase in hsCRP concentration from 7.4 ± 5.68 to 9.99 ± 7.16 mg/l of borderline signif-

Table 1. Nutritional and inflammatory indices before and after 1 and 2 months of megestrol acetate administration (n=26)

Variable	Baseline (mean \pm S.D.; median; interquartile range)	1 month (mean \pm S.D.; median; interquartile range)	2 month (mean \pm S.D.; median; interquartile range)	P value
Weight (kg)	63.59 ± 12.38 63.9 20.4	64.22 ± 12.1 63.75 18.3	64.79 ± 12 66.65 20.0	*0.049
BMI (kg/m ²)	23.06 ± 3.26 22.97 4.74	23.34 ± 3.3 22.89 5.2	23.68 ± 3.63 23.08 4.75	*0.01
Albumin (g/dl)	3.51 ± 0.33 3.6 0.32	3.72 ± 0.403 3.8 0.3	3.659 ± 0.449 3.75 0.3	*0.023 **0.004
Total cholesterol (mg/dl)	173.96 ± 57.66 164.0 70.0	168.42 ± 51.85 152.0 55.0	165.27 ± 57.46 153.5 49.0	NS
Triglycerides (mg/dl)	146.13 ± 75.21 130.5 93.0	140.29 ± 59.72 127.5 86.0	131.71 ± 59.52 123.0 87.0	NS
HsCRP (mg/l)	7.4 ± 5.68 4.8 7.7	6.99 ± 5.74 4.8 8.5	9.99 ± 7.16 13.05 14.9	*0.052
IL-1 β (pg/ml)	2.33 ± 4.58 0.0 3.0	1.91 ± 3.18 0.8 2.2	1.5 ± 1.6 1.0 2.3	NS
IL-6 (pg/ml)	32.8 ± 7.47 26.8 28.0	39.96 ± 8.72 20.4 33.5	32.26 ± 9.21 13.8 42.2	NS

*baseline versus at 2 months; **baseline versus at 1 month

icance. However, we did not observe any significant changes in the other biochemical markers of inflammation – IL-1 β or IL-6 (Table 1).

Side-effects

Side-effects were common. Overhydration of varying severity or excessive fluid gain (>4 kg interdialytic weight gain and/or overhydration causing pulmonary congestion and dyspnoea) between haemodialysis sessions were a problem in 9 patients, and dose reduction was required in all subjects. Excessive weight gain (>5% of initial body weight within four weeks) appeared in 6 subjects and in 4 of them dose reduction was necessary, while the two other patients decided to withdraw from the study. One of the diabetics required dose reduction because of hyperglycaemia, which was difficult to control with increased insulin dosage. Diarrhoea in 2 patients and nausea and vomiting in 3 subjects led to discontinuation of the megestrol acetate treatment.

DISCUSSION

Even though malnutrition is a common clinical problem and a strong predictor of cardiovascular and all-cause mortality in dialysis patients, there is still no single test that could be considered an indicator of protein-energy malnutrition. Therefore, correct assessment of nutritional status in dialysis patients is difficult. We decided to apply the most commonly used, simple and inexpensive marker of malnutrition, which is serum albumin concentration ≤ 3.8 g/dl.

The main drawback of our study is the lack of a control group. This was due to a very limited number of patients eligible for the study who consented to participate (26 patients out of 490 patients screened). This suggests that the actual prevalence of malnutrition among dialysis patients may have been reduced or confirms that serum albumin concentration is not a perfect malnutrition assessment tool. The former possibility is consistent with the recently published results by de Mutsert *et al.* (2008). In that study, three months after the start of chronic hemodialysis treatment only 10% of patients were diagnosed as being malnourished. In our study one of the inclusion criteria was maintenance dialysis treatment for at least 3 months.

So far, only six studies evaluating the use of megestrol acetate in dialysis patients have been published. Burrowes *et al.* (1999) published a case study of a haemodialysis patient placed on 320 mg/day of megestrol acetate for 24 weeks. The patient reported an improvement in appetite, and his fat mass in-

creased by 163%, whereas his lean mass decreased by 10.6%. Lien *et al.* (1996) placed 12 chronic peritoneal dialysis (CPD) and four maintenance hemodialysis (MHD) hypoalbuminemic patients (<3.5 g/dl for two consecutive months) on 20 mg twice daily of megestrol acetate. An increase in serum albumin was seen in 75% of the patients. One patient stopped megestrol because of vaginal bleeding from leiomyoma. Boccanfuso *et al.* (2000) evaluated the effect of megestrol acetate suspension in 17 MHD patients with serum albumin <3.5 g/dl for 2 consecutive months. Four hundred milligram orally twice daily was prescribed for up to 6 months. At the end of the third month only 53% of those patients were still in the study, whereas only three of them were able to take the studied medicine for 5 to 6 months. Each of these three patients showed a positive change in nutritional status measured by subjective global assessment (SGA), appetite and caloric intake and an increase in dry weight. Side effects that led to dropout were common and included diarrhoea, confusion, headache and hyperglycaemia. Costero *et al.* (2004) treated 32 CPD patients with 160 mg of megestrol acetate daily for 1–23 months and observed an increase in appetite in most patients, as well as significant weight gain with a nonsignificant increase in serum albumin. No side-effects were observed. Rammohan *et al.* (2005) assessed the efficacy of 400 mg of megestrol acetate daily used for 16 weeks in nine MHD and one CPD patient. Appetite, daily energy intake, weight and serum albumin increased significantly. There was also a decrease of serum CRP of borderline significance. Quality of life was reported to be improved as well. No major side-effects were observed. Recently, Monfared *et al.* (2009) published results of a randomized controlled trial in a group of hypoalbuminemic haemodialysis patients. Eleven patients assigned to the experimental group were treated with 40 mg of megestrol acetate twice daily over a period of two months, while 11 patients in the control group received their current treatment. There was a statistically significant increase in albumin concentration with concurrent changes in CRP level in the treatment group and there were no significant changes in the control group. However, the authors reported no changes in the total pre- and postdialysis weight of patients.

Our results show that administering 160 mg of megestrol acetate suspension in hypoalbuminemic dialysis patients for a period of two months improved body weight and BMI, with a significant increase in serum albumin concentration. These findings are consistent with the results published by Rammohan *et al.* (2005) and partly with the results of Monfared's group (2009). Surprisingly, we observed a trend towards a decrease in total cholesterol and triglyceride levels. Costero *et al.* (2004) did

not find any significant changes of cholesterol level, while Rammohan *et al.* (2005) showed only a statistically insignificant 1% increase.

The exact mechanisms by which megestrol acetate exerts its orexigenic effect remains unknown. It is suggested that it is likely due to down-regulation of the synthesis and secretion of proinflammatory cytokines. Hence, it was assumed that possessing both appetite-stimulating and anti-inflammatory properties would make it an optimal tool in the treatment of malnutrition or even of the MIA syndrome. However, we only observed an increase of borderline significance in hsCRP level and did not observe any significant changes in IL-1 β or IL-6 concentrations after megestrol acetate treatment. Similar results regarding IL-6 were observed by Jatoi *et al.* (2002) in a group of 85 patients with cancer-associated anorexia or weight loss.

Another issue that should be raised is the high prevalence of significant side effects resulting in the necessity to reduce the dose or to end the planned treatment prematurely. This was especially surprising as the 160 mg dose we decided to use has been described to be safe and associated with no adverse events (Costero *et al.*, 2004). It is even more difficult to explain the lack of side-effects when using higher doses of megestrol acetate (Rammohan *et al.*, 2005).

In conclusion, megestrol acetate may be an effective therapeutic agent in reversing poor appetite in carefully selected maintenance dialysis patients. Our limited experience suggests that it might not mitigate inflammation or improve the quality of life, but our ongoing study should clarify this issue. Because of the prevalent side effects its use must be monitored closely. Perhaps tailoring the dosage according to individual response would solve some megestrol-related problems. Further studies are needed to learn whether benefits of megestrol acetate would outweigh the side effects.

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