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Oral ghrelin receptor agonist MK-0677 increases serum insulin-like growth factor 1 in hemodialysis patients: a randomized blinded study*

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*This study is registered with ClinicalTrials.gov (NCT00395291; 1 November 2006).

ABSTRACT

Background. Protein-energy wasting (PEW) in end-stage renal disease (ESRD) patients is associated with increased morbidity and mortality, but options for treatment are limited. Growth hormone (GH) increases insulin-like growth factor 1 (IGF-1), with improved nutritional parameters, but must be given subcutaneously and does not provide normal GH secretion patterns. MK-0677, an oral ghrelin receptor agonist (GRA), maintains normal GH secretion and increases lean body mass in normal subjects; it has not been studied in dialysis patients, an essential step in assessing efficacy and safety prior to clinical trials.

Methods. We performed a randomized crossover double-blind study in assessing the effect of MK-0677 versus placebo on IGF-1 levels, the primary outcome, in hemodialysis patients. In total, 26 subjects enrolled and 22 completed the 3-month crossover study.

Results. The geometric mean IGF-1 was 1.07-fold greater [95% confidence interval (CI) 0.89–1.27; $P = 0.718$] after placebo. In patients receiving MK-0677, the geometric mean IGF-1 were 1.76-fold greater (95% CI 1.48–2.10; $P < 0.001$) following MK-0677. When the data were adjusted for preintervention IGF-1 concentration, the ratio of geometric means (MK-0677 relative to placebo) for the pre- versus postintervention change in the IGF-1 was 1.65 (95% CI 1.33–2.04; $P < 0.001$). These data demonstrate a 65% greater increase (95% CI 33–104%) in IGF-1 in MK-0677-dosed subjects compared with placebo. There were no serious adverse effects attributable to MK-0677.

Conclusions. MK-0677 increased serum IGF-1 levels with minimal adverse effects in hemodialysis subjects. Studies are needed to evaluate whether long-term therapy with MK-0677 improves PEW, lean body mass, physical strength, quality of life and survival in CKD/ESRD patients.

Keywords: ESRD, ghrelin, growth hormone, IGF-1, protein-energy wasting

INTRODUCTION

Protein-energy wasting (PEW) is a common finding in end-stage renal disease (ESRD) patients and begins in chronic kidney disease (CKD). Half of patients with CKD have PEW, and this increases with ESRD [1–3]. Decreased albumin has been linked with future morbidity and mortality in ESRD patients [4–11]; prealbumin [12] and body mass index [13] have also been linked to adverse outcomes in ESRD. The etiologies of PEW in ESRD are diverse, including anorexia, uremic factors such as metabolic acidosis and increased levels of cytokines leading to increased catabolism as well as insulin resistance [14–19].

Current options for PEW intervention in ESRD have met with limited success. Options such as dietary counseling, appetite stimulants and dietary supplements often are insufficient to improve PEW. To date, the only intervention with data to suggest improvement is intradialytic parenteral nutrition [20]. Recent studies have assessed hormonal treatment of PEW in ESRD using either anabolic steroids or interventions on the growth hormone (GH)–insulin-like growth factor 1 (IGF-1)

axis. These suggest that stimulation of the GH–IGF-1 axis can potentially improve PEW.

Ghrelin is an endogenous hormone that decreases acute and chronic inflammation, enhances the immune system, stimulates appetite and causes physiologic pulsatile release of GH. MK-0677 was developed by Merck as a high-affinity, long-acting, orally active GH secretagogue (GHS) [21]. MK-0677 was then used as a tool to clone its receptor, then known as the GH secretagogue receptor. This receptor was then used to identify its endogenous ligand, which resulted in the discovery of ghrelin [22]. This receptor has been renamed the ghrelin receptor and is the only known mechanism of action for both ghrelin and MK-0677. Studies have demonstrated that MK-0677, and also ghrelin, enhance the amplitude of endogenous pulses of GH secretion, resulting in increased levels of circulating IGF-1 [23]. MK-0677, an orally active ghrelin receptor agonist (GRA), is a GHS. It has been shown to increase pulsatile GH secretion in elderly patients [13, 24]. MK-0677 has not been previously assessed in an ESRD patient population. Endogenous GH secretion, unlike exogenous GH administration, is pulsatile and therefore time-of-draw dependent, while IGF-1 levels provide a constant indicator of GH secretion [23]. We hypothesized that this GRA would increase IGF-1 in ESRD patients on hemodialysis and could possibly improve their nutritional status. While MK-0677 has shown efficacy in normal subjects, it has not been shown to be efficacious or safe in dialysis patients. It is necessary to demonstrate efficacy and safety for a new agent in the vulnerable ESRD population before it can be assessed in long-term trials. We report here successful achievement of our primary goal of an increase in IGF-1 in response to GRA MK-0677, with minimal adverse effects.

ORIGINAL ARTICLE

MATERIALS AND METHODS

Design

This was a randomized crossover double-blind study. The protocol was reviewed by the General Clinic Research Center and the Institutional Review Board at the University of Virginia and was compliant with the Helsinki Accord. The trial is registered at ClinicalTrials.gov (identification number NCT 00395291; 1 November 2006). The trial design is provided in the Supplementary data. Enrolled patients gave written consent to participate in the study. Matching placebo and MK-0677 were provided by Merck Research Laboratories. Patients received 25 mg of MK-0677 daily or placebo. The study design was a 3-month crossover treatment. Subjects were randomized to receive MK-0677 either in month 1 or 3. After a 1-month washout period, patients were switched to the alternate regimen. The primary outcome was IGF-1 levels. Compliance was assessed by pill counts. Care providers and the study team were blinded to randomization. Subjects were seen, examined and queried for adverse events (AEs) at the beginning and end of each month. In addition to evaluation for AEs at each visit, subjects were queried by telephone interviews for AEs at the midpoint of each month and 2 weeks after the third period. A per-protocol analysis was performed (see details below).

Power analysis

This study was designed to have at least 0.80 statistical power $(1-\beta)$ to detect a MK-0677 versus placebo IGF-1 geometric mean ratio of 1.48 with 22 individuals (11 individuals randomly assigned to receive placebo initially and 11 individuals randomly assigned to receive MK-0677 initially). Details related to the power analysis are provided in the Supplemental data.

Recruitment

Approximately 250 charts from three University of Virginia dialysis clinics were preliminarily reviewed for study criteria over a 14-month period. In total, 49 subjects met preliminary criteria and were consented. These subjects were screened by history and physical exam, initial chart review and laboratory testing to assess for the presence of preexisting conditions or underlying disease that would exclude the individual's participation. Inclusion requirements were that subjects received long-term regular dialysis thrice weekly. Incident dialysis patients and those with dialysis vintage <3 months were not enrolled. Exclusion criteria are listed in Table 1. In total, 26 patients were enrolled.

Randomization

The study biostatistician (J.P.) generated the randomization list prior to the onset of patient enrollment. In traditional two-period crossover design fashion, the sequential order of the treatments assigned to the first and second periods of the crossover design was randomly permuted. For 50% of the treatment assignment sequences (i.e. $n = 13$), placebo was assigned to the first crossover period and MK-0677 was assigned to the second crossover period, while for the remaining 50% of the treatment assignment sequences MK-0677 was assigned to the first crossover period and placebo assigned to the second crossover period.

In order to maintain treatment sequence balance with patient dropout, 10 replacement treatment sequence assignments were generated *a priori*. Patients who were designated as replacement patients for patients who withdrew from the study were assigned to the same treatment sequence as the patient they replaced.

Blinding

Placebo and MK-0677 provided by Merck Research Laboratories included a randomization identification number and masked treatment assignment (A or B) to which only Merck and the study biostatistician were unblinded. Patients as well as study personnel (i.e. principal investigator, co-investigators, clinical trial coordinator and laboratory technicians) were blind to the pill bottle contents.

Drug disbursement

Drug was released by a study pharmacist and dispensed by the study coordinator. Study compliance was assessed with pill counts (see Supplementary data).

Outcome measures

Laboratory values were collected at multiple points during the study (see Supplementary data for study procedures

Table 1. Exclusion criteria

- Body mass index ≥35 or morbid obesity
- Uncontrolled hyperthyroidism, defined as a Thyroid Stimulating Hormone (TSH) less than the lower limit of normal and an elevated free T4 when tested at screening
- Hemoglobin ≤10 g/dL
- Elevated serum transaminases (≥2 times the upper limit of normal at screening)
- Diabetes with one or more of the following:
  - Poorly controlled diabetes as defined by a hemoglobin $A1_C$ >7.0% at screening
  - Proliferative diabetic retinopathy. (To participate in this study, diabetic patients were required to have had a dilated ophthalmology exam within 12 months of enrollment. Individuals who already had extensive background retinopathy had to have a dilated ophthalmology examination with 3 months of enrollment. Patients with preproliferative or proliferative retinopathy were excluded.)
  - Unwilling or unable to check blood glucose at home at least daily
- Currently receiving a systemic corticosteroid dose ≥10 mg prednisone (or equivalent) or patient has received for a duration ≥30 days in the previous 6 months (i.e. prior to signing the informed consent form) a systemic corticosteroid dose ≥10 mg prednisone (or equivalent). (The previous use or current use of a topical or inhaled corticosteroid was allowed.)
- Currently taking or previously on an anabolic steroid or growth hormone at any dose or for any duration during the 12 months prior to study entry
- Significant end-organ disease other than kidney disease that in the opinion of the investigator might pose an added risk to the patient, confound the study results or impair the patient's ability to complete the trial
- Any of the following disorders within 6 months prior to baseline:
  - Acute coronary syndrome (e.g. myocardial infarction or unstable angina)
  - Coronary artery intervention (e.g. coronary bypass graft, percutaneous transluminal coronary angioplasty)
  - Stroke or transient ischemic neurological disorder (e.g. transient ischemic attack)
- New or worsening signs or symptoms of coronary heart disease within the 3 months prior to baseline
- New York Heart Association class III or IV congestive heart failure
- Uncontrolled hypertension when checked at the screening visit: as evidenced by ≥160 mmHg systolic and/or 100 mmHg diastolic blood pressure (measured in dominant or nondialysis access arm after at least 5 min sitting)
- Cancer or diagnosis of malignancy within the last 5 years, except for adequately treated basal or squamous cell skin cancer or adequately treated *in situ* cervical cancer
- Active carpal tunnel syndrome
- Patient was, in the opinion of the investigator, mentally or legally incapacitated such that informed consent could not be obtained or such that adherence to the study procedures and dosing regimens was questionable
- Patient was, at study entry, a regular user (including 'recreational use') of illicit drugs or had a recent history (within the last 5 years) of drug or alcohol abuse
- Patient plans to relocate or change to a different dialysis center during the study, rendering follow-up per protocol impractical
- Patient was participating in or had participated in another study with an investigational drug within 30 days prior to signing the informed consent form
- If female, patient must not be pregnant or nursing. Patient must be postmenopausal, surgically sterilized or willing to take adequate contraceptive precautions (i.e. use double barrier methods)
- HIV positive (medical history review and patient report)
- Patient was on potent CYP3A4 inhibitor drugs within 1 week of starting the study drug

schedule details). As part of the prestudy screening, a comprehensive metabolic panel (CMP), hemoglobin A1c and complete blood count (CBC) were obtained in addition to other screening labs. At the monthly study visits and the post-study follow-up (visit 4), the following studies were obtained: interleukin 1β (IL-1β), tumor necrosis factor α (TNF-α), IL-6, IL-10, high-sensitivity C-reactive protein (hsCRP), GH, IGF-1, insulin, leptin, ghrelin, esterase, adiponectin, CBC, comprehensive metabolic profile, albumin, prealbumin and metabolic chemistry (sodium, potassium, chloride bicarbonate, glucose, urea nitrogen). Thyroid function tests and liver function tests were performed in the Clinical Laboratory at the University of Virginia. Other studies were performed as described below. Blood and vital signs, including weight, were obtained immediately before the initiation of regularly scheduled treatments. Since subjects from all dialysis shifts participated, it was not possible to obtain fasting blood samples. Each cycle (placebo, washout and MK-0677) was coordinated with these blood draws (i.e. begun after the blood was obtained).

Hormone and cytokine assays

Determination of GH, IGF-1, insulin, hsCRP, IL-6, IL-10 and TNF-α are provided in the Supplementary data.

Assays for ghrelin and butyrylcholinesterase

We used two separate two-site sandwich assays, one specific for acyl ghrelin (AG) and one for des-acyl ghrelin (DG). These assays do not measure ghrelin fragments and have demonstrated superior specificity for AG and DG determination relative to single site assays [25, 26]. Total ghrelin was the sum of AG and DG. Butyrylcholinesterase (BuChE), which degrades ghrelin, was measured as described [25]. Details are provided in the Supplementary data.

Outcome data

The outcome data that were utilized in the statistical analyses represented the pre- to postintervention change in the outcome variable. With the exception of the data for body weight (kg), all of the outcome data were transformed to the natural logarithmic scale prior to computing the pre- to postintervention change. The logarithmic transformations were conducted as a consequence of exploratory analyses, which showed the logarithmic change to be more symmetrically distributed. The data for each outcome were analyzed via a conventional two-period crossover linear mixed model. The model specification details are provided in the Supplementary data.

Hypothesis testing

With regard to hypothesis testing, a linear contrast of means was constructed to formally test whether the mean pre- to post-intervention change in the outcome was equal to zero. Similarly, a linear contrast of means was constructed to test whether the mean pre- to postintervention change in the outcome was the same regardless of the intervention (MK-0677 or placebo). Each hypothesis was evaluated using a two-sided test and a $P \leq 0.05$ decision rule.

CI construction

CI construction was based on the Student's *t* distribution. For those variables that were analyzed on the natural logarithmic scale, the lower and upper limits of the CI were exponentiated to obtain a 95% CI for the ratio of geometric means.

Table 2. Baseline characteristics of those 22 patients who completed the trial prior to first admission

Baseline variables	Summary
Gender (male)	16 (72.7)
Age (years)	53.0 (47.7–71.5)
Race (African American)	17 (77.3)
Body weight (kg)	77.7 (66.7–87.7)
Vintage (years)	4.5 (1.3–7.8)
IGF-1 (ng/mL)	117.5 (75.0–185.5)
GH (ng/mL)	1.5 (0.8–3.6)
Leptin (ng/mL)	4.2 (0.9–17.9)
Acyl ghrelin (pg/mL)	38.4 (12.1–118.2)
Des-acyl ghrelin (pg/mL)	210.9 (65.5–298.4)
Total ghrelin (pg/mL)	321.0 (109.7–348.4)
Adiponectin (ng/mL)	18 310.7 (11 968.1–28 805.3)
Insulin (mIU)	16.4 (10.5–23.1)
hsCRP (mg/dL)	5.1 (2.1–9.0)
IL-1β (pg/mL)	0.25 (0.13–0.50)
IL-6 (pg/mL)	5.1 (2.9–8.0)
IL-10 (pg/mL)	1.8 (1.2–3.2)
TNF-α (pg/ml)	3.9 (2.9–4.6)
Esterase (U/mL)	40.3 (353–47.5)

Categorical variables presented as *n* (%). Continuous variables presented as median (interquartile range) of the empirical distribution.

RESULTS

Details of the results of the laboratory studies and AEs are presented in the Supplementary data, as well as individual dialysis vintage, diagnoses and compliance. The baseline characteristics of the patients are provided in Table 2. Of 49 subjects screened, 26 were enrolled from June 2008 to January 2009. Two males and two females dropped out. Twenty-two subjects completed the study, for a dropout rate of 15.4%. There were 17 African American and 5 Caucasian subjects. There was a wide range of ages enrolled in the study. The size of the study population precluded meaningful subgroup analysis. Ninety-five percent of subjects were receiving an erythropoietic agent, antihypertensive and vitamin D, while 91% were on phosphate binders, 86% on dietary supplements and 77% were receiving various medications for gastrointestinal symptoms. Other medications for other symptoms were used less frequently. The primary and secondary diagnoses for ESRD included hypertension in all 22, focal segmental glomerular sclerosis in 3, diabetes in 3, membranoproliferative glomerulonephritis in 1 and chronic interstitial nephritis in 1.

GH and IGF-1

The geometric mean for IGF-1 concentration was 1.07-fold greater (95% CI 0.89–1.27; $P = 0.718$) following placebo dosing than before receiving placebo. In subjects receiving MK-0677, the geometric mean for IGF-1 concentration was 1.76-fold greater (95% CI 1.48–2.10; $P < 0.001$) following MK-0677 intervention (Figure 1A). When the data were adjusted for preintervention IGF-1 concentration, the ratio of geometric means (MK-0677 relative to placebo) for the pre- versus postintervention change in IGF-1 was 1.65 (95% CI 1.33–2.04;

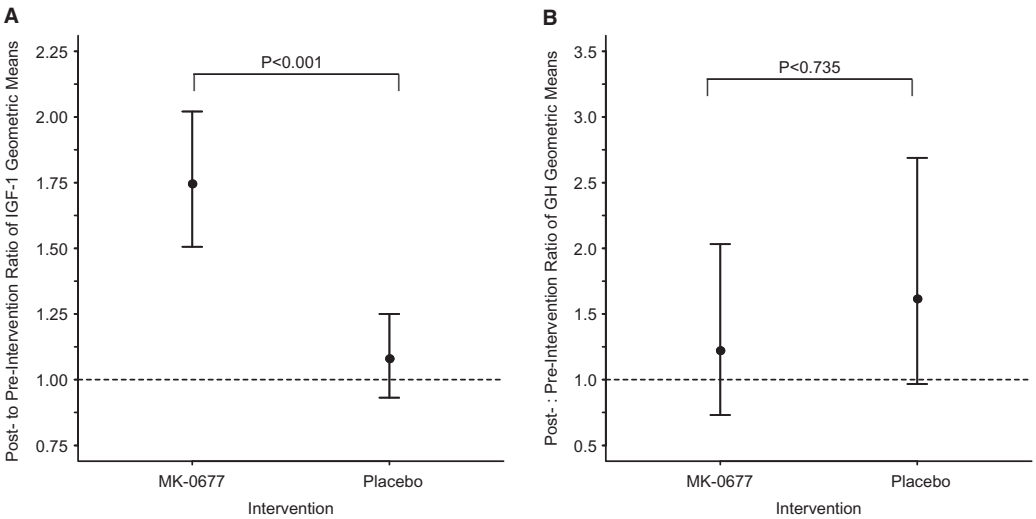

FIGURE 1: Postintervention:preintervention ratio of IGF-1 and GH geometric means. Circles identify the geometric mean ratio and the vertical lines identify the 95% CIs for the geometric mean ratio. Hatch lines denote the reference line for a geometric mean ratio equal to 1. P-values correspond to the test of the null hypothesis that the ratio of geometric means is the same irrespective of the intervention.

$P < 0.001$). These data demonstrate a 65% greater increase (95% CI 33–104%) in IGF-1 concentration in the MK-0677-dosed subjects at 30 days compared with placebo.

GH did not show a statistically significant change with either placebo or MK-0677. Neither the postintervention geometric mean for GH in the MK-0677 group nor the postintervention geometric mean for GH in the placebo group differed from the preintervention geometric mean ($P = 0.437$ and $P = 0.066$, respectively) . The ratios of post- to preintervention GH levels were 1.22 (95% CI 0.73, 2.03) and 1.61 (95% CI 0.97–2.69), respectively, for MK-0677 and placebo ($P = 0.735$; Figure 1B).

Blood glucose

Pre- to postintervention change in blood glucose differed between the MK-0677 and placebo interventions ($P = 0.048$). The geometric mean blood glucose increased by 31% (95% CI 11, 55; $P = 0.003$) while on MK-0677 compared with 0% (95% CI −15, 19; $P = 0.977$) while on placebo. However, the results may have been skewed by the inclusion of three type 2 diabetic patients (subjects 3, sulfonylurea; 5, diet control and 20, insulin). These individuals had increases of random blood glucose of 164, 246 and 301 mg/dL. A *post hoc* analysis excluding the three diabetic patients demonstrated that the pre- to postintervention change in blood glucose differed only marginally between the MK-0677 and placebo interventions ($P = 0.068$). For this subset of patients, geometric mean blood glucose increased by 12% (95% CI 2, 23; $P = 0.020$) while on MK-0677 compared with −3% (95% CI −12, 7; $P = 0.564$) while on placebo.

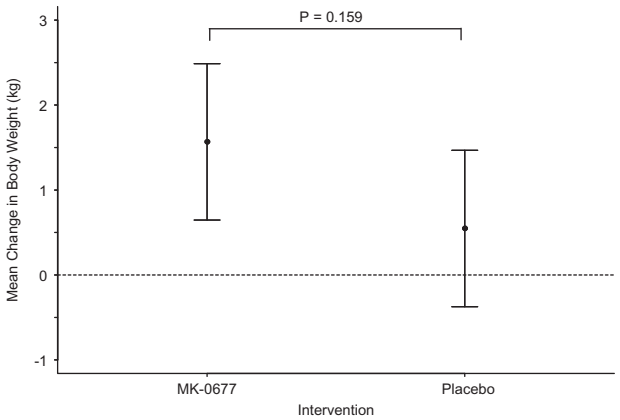

FIGURE 2: Change in body weight from pre- to postintervention. Circles identify the mean change in body weight and the vertical lines identify the 95% CI for the mean change. Hatch lines denote the reference line for a mean change equal to 0. The P-value corresponds to the test of the null hypothesis that the mean change in body weight (kg) is the same irrespective of the intervention.

Other hormone and cytokine studies

The remainder of assessed hormones and cytokines did not demonstrate a statistically significant change after placebo or MK-0677 (Table 3).

Body weight

There was an increase in weight with both MK-0677 and placebo. Weight increased by 1.6 kg with MK-0677 (95% CI 0.6, 2.5; $P = 0.001$) and 0.5 kg with placebo (95% CI −0.4–1.5; $P = 0.237$). However, there was not a statistically significant difference in weight change between MK-0677 and placebo ($P = 0.159$).

AEs

There were no serious AEs attributable to MK-0677. However, there were few subjects and the treatment time was short. See the Supplementary data for details of adverse events.

DISCUSSION

Resistance to the GH–IGF-1 axis has been documented in uremia and is consequent to multiple etiologies [27, 28, 29]. Various studies have examined the use of recombinant GH in ESRD patients and its effects on secondary markers of nutrition [30]. These have shown an increase in albumin and lean body mass and a decrease in protein catabolic rate. In addition, GH is used to increase growth in uremic children. A drawback to these

Table 3. Ratio of post- to preintervention geometric means for the secondary outcome variables

	MK-0677		Placebo		
Variable	Geometric mean ratio (95% CI)	P-value[†]	Geometric mean ratio (95% CI)	P-value[†]	P-value[‡]
AG	0.61 (0.40–0.92)	0.020	0.95 (0.63–1.44)	0.813	0.169
DG	1.07 (0.75–1.52)	0.718	0.95 (0.67–1.35)	0.733	0.782
Total ghrelin	0.92 (0.72–1.18)	0.512	0.92 (0.72–1.18)	0.485	0.900
GH	1.22 (0.73–2.03)	0.437	1.63 (0.97–2.69)	0.066	0.735
Adiponectin	1.05 (0.96–1.16)	0.262	1.01 (0.92–1.11)	0.876	0.545
Insulin	1.22 (0.94–1.59)	0.131	0.93 (0.72–1.21)	0.597	0.075
hsCRP	0.95 (0.59–1.53)	0.841	0.99 (0.61–1.59)	0.949	0.929
IL-1β	1.09 (0.81–1.46)	0.557	0.95 (0.71–1.28)	0.736	0.905
IL-6	1.40 (1.00–1.95)	0.049	1.08 (0.77–1.51)	0.651	0.233
IL-10	0.96 (0.73–1.25)	0.734	1.20 (0.92–1.58)	0.177	0.277
TNF-α	1.12 (0.82–1.53)	0.450	1.04 (0.76–1.43)	0.780	0.385
Esterase	0.95 (0.83–1.07)	0.388	0.97 (0.86–1.10)	0.668	0.875

[†]P-value for the test of the null hypothesis that the ratio of the postintervention to preintervention geometric mean (post: pre) is equal to 1.
[‡]P-value for the test of the null hypothesis that the MK-0677 geometric mean ratio is equal to the placebo geometric mean ratio.

studies includes the short time frame and small number of patients. In addition, GH replacement must be administered by subcutaneous injection, resulting in poor patient compliance, and it produces a single pharmacologic pulse in 24 h versus the normal physiologic pattern of 20–25 pulses in 24 h [31;32]. MK-0677 is not the same as GH. As a GRA, it induces secretion of GH and also preserves the physiological pattern of GH secretion, unlike exogenously administered GH [23].

Ghrelin is a peptide that affects appetite and has anti-inflammatory properties. Ghrelin exists in two forms, acylated and des-acyl ghrelin. AG stimulates appetite and antagonizes leptin, which has a negative effect on appetite [33, 34]. DG has been reported to delay gastric emptying and causes a decrease in food intake [33, 35]. Ghrelin levels, specifically DG, are elevated in ESRD patients [36]. Ghrelin has been linked with anorexia of ESRD, which has been suggested to be due to the negative effects of DG [33, 34, 37], which can be removed by dialysis [38, 39].

The GRA MK-0677 has previously been shown to increase IGF-1 level in healthy and elderly patients with intact renal function [23, 40]. It binds to the ghrelin receptor GH secretagogue receptor and mimics the effect of AG. We have now documented the same effect in subjects with ESRD receiving traditional hemodialysis thrice weekly. Given this finding, it is possible that other primary and secondary outcomes assessed in studies on MK-0677 could be applied to the hemodialysis patient population as well.

Previous work on GH has suggested that supplementation of GH can have numerous effects on markers of PEW, bone disease, and lipid metabolism. Markers that have been specifically assessed include an increase in albumin, body mass and transferrin. GH has also been shown to reduce protein catabolic rate. Although our study was not designed to show these effects, demonstration that MK-0667 can increase IGF-1 levels would suggest that in an expanded study it may provide these same effects. This is also suggested by the increase in blood glucose with MK-0677 in the present study, consistent with a GH effect. Larger studies will be needed to assess any detrimental effects of MK-0677 on glucose.

Ghrelin also has effects not related to GH activities. The GRA activity of MK-0677 might thus provide similar results for ESRD patients. In several small studies, administration of ghrelin to ESRD patients with PEW increased food intake [24, 41]. Ghrelin also increases fat stores compared with GH, which is lipolytic. This is important to consider given data that increased fat stores improve outcomes in ESRD [42]. Previous studies of MK-0677 in elderly patients documented an increase in limb fat [23]. Ghrelin also has potent anti-inflammatory properties, promotes lymphocyte development in bone marrow and thymus and decreases age-related thymic involution [43]. These properties are especially relevant in the CKD/ESRD population. Finally, low IGF-1 levels are associated with increased mortality in dialysis patients independent of biomarkers of PEW [44]. MK-0677 increases IGF-1 levels. While GH treatment did not improve survival in ESRD subjects in previous studies, these may have been underpowered [45].

The relationship between AG and DG in ESRD patients is important to consider. No effect was seen on either hormone in this study with placebo or MK-0677. The actions of MK-0677 as a GRA suggest its actions in ESRD patients are consistent with AG. The effects of increasing appetite and antagonizing leptin could be beneficial in ESRD patients with PEW. No effect was seen on leptin concentrations in this study, but an antagonistic effect on leptin could benefit malnourished and anorexic ESRD patients.

Our study has limitations. Its duration was short and the sample was small, limiting assessment of safety in this population. The population was heavily weighted to African American men. There could have been a carryover effect when the MK-0677 group crossed over to placebo. However, the plasma half-life of MK-0677 is only 6–13 h (investigators brochure). We also saw no evidence of a biologic carryover effect (Supplementary data). Finally, we previously reported that IGF-1 levels returned to pretreatment levels within 1 month after having received MK-0677 for a year [23].

This was a 'proof-of-concept' study to assess the effects of MK-0677 on the IGF-1 axis and examine short-term safety in ESRD patients. It showed that an oral GRA can increase serum IGF-1 levels in ESRD patients on hemodialysis thrice weekly. GH is known to be diabetogenic. We observed in this study, as expected and previously observed in other studies, that diabetic patients may need additional treatment to control their blood glucose while on MK-0677. Only the known diabetic patients had significant worsening of their random blood glucoses. The other subjects had a modest increase in blood glucose. No effect of MK-0677 on acyl, des-acyl and total ghrelin levels was observed. However, the samples were only drawn once pre- and once posttreatment and were not fasting, which is not ideal.

CONCLUSIONS

This study demonstrates a positive effect on IGF-1 by the GRA MK-0677. Stimulation of ghrelin receptors effected by MK-0677 has the potential for significant benefit for CKD/ESRD patients with PEW, where our treatment options are limited. Since MK-0677 is an oral agent, compliance is likely to be greater compared with subcutaneous injections required for GH or GH releasing factors such as AKL-0707 [46]. No toxicity was observed in our study, in contrast to the oral anabolic steroid oxymetholone, despite its positive anabolic effects [47]. Further studies will need to be conducted to determine the clinical effects of MK-0677 in CKD/ESRD.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

At the time of the study none of the authors had any competing financial interests. Since the performance of the study, one author (M.O.T.) founded Ammonett Pharma, which is now developing MK-0677.

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ORIGINAL ARTICLE

Prediction equation for calculating residual kidney urea clearance using urine collections for different hemodialysis treatment frequencies and interdialytic intervals

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ABSTRACT

Background. The purpose of the study was to explore the precision of an equation designed to estimate residual kidney urea clearance (K_{RU}) from interdialytic urine collection data and pre-hemodialysis (HD) serum urea nitrogen (SUN) in different hemodialysis treatment schedules.

Methods. The generalizability of the proposed equation was tested in 32 731 HD treatments where urine was collected prior to a dialysis session, mostly for 24 h but sometimes longer, in patients being dialyzed 1–4 times/week.

Results. The residual kidney urea clearance estimating equation predicted a K_{RU} that matched the one computed by formal modeling within 5% in >98% of sessions analyzed. The errors in estimated versus modeled K_{RU} for interdialytic intervals (IDIs) of 2, 3, 4 and 7 days, were $1.6 \pm 1.5\%$, $-0.4 \pm 1.6\%$, $0.9 \pm 1.6\%$, and $1.5 \pm 1.2\%$, respectively. Percent errors were similar for schedules of 1–4/week with the exception of urine collection during the 2-day interval of a 2:5-day twice-weekly schedule; here error averaged $5.0 \pm 1.2\%$. Use of the average of the SUN values at the start and end of the collection period overestimated modeled K_{RU} by $11.3 \pm 4.5\%$, whereas an equation suggested by others underestimated modeled K_{RU} by $-9.9 \pm 3.4\%$.

Conclusions. The equation tested predicts values for K_{RU} that are similar to those obtained from formal urea kinetic modeling, with percent errors that only rarely exceed 5%. It gives relatively precise results for a wide range of HD treatment schedules, IDIs and urine collection periods.

Keywords: chronic hemodialysis, clearance, guidelines, hemodialysis, predialysis

INTRODUCTION

There is increased interest in measuring, monitoring and preserving residual kidney function in maintenance hemodialysis (HD) therapy [1], as well as in the use of residual kidney urea clearance (K_{RU}) in predicting mortality risk [2] and guiding prescription of incremental HD [3]. K_{RU} commonly is measured by collecting urine for 24–68 h prior to a dialysis session, calculating the per-minute urinary urea nitrogen (UN) excretion rate, and then dividing this by the estimated time-averaged serum (theoretically, plasma) water urea concentration during the collection interval. The latter concentration is not easy to estimate in the absence of a computer program that generates a weekly interdialytic serum urea nitrogen (SUN) profile. Usually, the only serum sample used in the calculation is that taken at the end of the urine collection period, i.e. at the start of