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Hypoglycaemic and hypoketonaemic effects of single and repeated oral doses of methyl palmoxirate (methyl 2-tetradecylglycidate) in streptozotocin/alloxan-induced diabetic dogs

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1 The hypoglycaemic and hypoketonaemic effects of orally administered methyl palmoxirate were studied in streptozotocin/alloxan-induced diabetic dogs.

2 Single oral 50 mg doses ($\sim 7.5\,mg\,kg^{-1}$) of methyl palmoxirate produced statistically significant reductions of plasma glucose ($32 \pm 6\%$ maximum reduction from baseline) and ketones ($74 \pm 12\%$ maximum reduction from baseline), with the peak effect on plasma ketones (3.5 h) preceding that for plasma glucose (6.0 h).

3 Lower doses (0.7–2.0 $mg\,kg^{-1}$ daily) of methyl palmoxirate given repeatedly for seven days produced reductions of blood glucose and ketones equivalent to those produced with the higher single dose. Maximal reductions of plasma ketones were generally observed following the first dose of drug, whereas significant lowering of plasma glucose required several days of continuous dosing.

4 Repeated daily doses of methyl palmoxirate markedly reduced the overnight fasting ketone levels but not glucose levels of diabetic dogs.

5 In conclusion, administration of the fatty acid oxidation inhibitor methyl palmoxirate, in the absence of concomitant insulin therapy, was able to lower the plasma glucose and ketone levels of insulin-deficient streptozotocin/alloxan diabetic dogs. Only the plasma ketones were decreased to normal by this treatment.

Introduction

Methyl palmoxirate (Me-TDGA, methyl 2-tetradecylglycidate), is a potent, specific, irreversible inhibitor of the mitochondrial enzyme carnitine palmitoyltransferase (CPT-A) (Tutwiler & Ryzlak, 1980; Kiorpes *et al.*, 1984) and of long-chain fatty acid oxidation (Tutwiler *et al.*, 1979, 1981; Tutwiler & Dellevigne, 1979). Me-TDGA is an orally effective hypoglycaemic and hypoketonaemic agent in fasted nondiabetic and diabetic animals (Tutwiler *et al.*, 1978; 1979; 1981; 1983; Lee *et al.*, 1982) and in preliminary studies in diabetic patients (Mandarino *et al.*, 1984; Verhaegen *et al.*, 1984). In 48-h fasted nondiabetic rats, plasma ketones and liver mitochondrial CPT-A activity were previously shown to be significantly decreased following single oral doses of Me-TDGA (0.05–0.25 $mg\,kg^{-1}$) that were 10 to 25 fold less than those required for consistent inhibition of muscle CPT-A activity and lowering of blood glucose (Brentzel *et al.*, 1982; Tutwiler *et al.*, 1985). Furthermore, studies in nondiabetic rats showed that repeated daily dosing (3 days) with Me-TDGA produced greater hypoglycaemic efficacy than single doses (Tutwiler *et al.*, 1981). These studies were performed to compare the effects of single (7.5 $mg\,kg^{-1}$) versus multiple oral doses (0.1–2.0 $mg\,kg^{-1}$) of methyl palmoxirate in a diabetic animal model (streptozotocin/alloxan-induced diabetic dogs).

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Methods

Animals

Mongrel dogs (8–12 kg) were fed a high protein diet (34% protein, Hill's Science Diet) with water available *ad libitum*. Diabetes was induced by intravenous

injection of streptozotocin (20–30 mg kg^{-1}, Upjohn Co.) and alloxan (30–50 mg kg^{-1}, Sigma Chemical Co.) and dogs were stabilized for 3–4 weeks before use (Black *et al.*, 1980). Dogs fasted for 18 h were used for study.

Blood samples (5–10 ml), obtained from the jugular vein in heparinized Vacutainers at specified times after dosing, were centrifuged and the plasma removed. Plasma glucose concentrations were determined by the automated (Gilford Model 203 Clinical Analyzer) hexokinase method (Statzyme, Worthington Diagnostics, Inc.). Plasma ketones (β-hydroxybutyrate and acetoacetate) were measured on protein-free filtrates by use of a coupled enzymatic assay (enzymes purchased from Boehringer-Mannheim) described previously (Tutwiler *et al.*, 1978; 1979).

Experimental protocols

Single dose studies Blood samples were obtained from eight diabetic dogs immediately before dosing (−15 and 0 min), and again at 1, 2, 3, 4, 5, 6, 9 and 24 h after dosing for determination of plasma glucose and ketones (β-hydroxybutyrate and acetoacetate).

Repeat dose studies Two experimental protocols were used. Because the diabetic state was variable among dogs, a placebo–drug–placebo experimental design was used.

Protocol I Diabetic dogs ($n = 5$) were dosed orally with placebo on day 1 followed by Me-TDGA (5·0 mg total dose) given once-a-day for seven consecutive days (day 2 through day 8). After seven treatment days, all dogs were given placebo for eight additional days. On days 1, 2, 3, 5, 8 and 16, blood samples were obtained before dosing (−15 and 0 min) and at 2, 4 and 6 h after dosing for determination of plasma levels of glucose and β-hydroxybutyrate (β-hydroxybutyrate represented >90% of the total plasma ketones measured in single dose studies). Dogs were schedule-fed for 2 h after the 6 h bleeding with remaining food removed at the end of the feeding period. Thus, all dogs were fasted for 18 h before obtaining baseline blood samples on the next day.

Protocol II Diabetic dogs were dosed orally with hard gelatin capsules containing either vehicle or Me-TDGA so that an equivalent dose on a mg kg^{-1} body weight basis could be administered. Me-TDGA delivered in hard gelatin capsules was shown in pilot studies to produce hypoglycaemic activity equivalent to that produced by the drug in soft gelatin capsules. After two days of placebo treatment, dogs received doses of Me-TDGA with each dose given for seven consecutive days, progressing from 0.1 mg kg^{-1} daily to a maximum dose of 2.0 mg kg^{-1} daily followed by placebo treatment for an additional 7 to 14 days. In three other dogs, after placebo treatment for two days, Me-TDGA was administered at 0.8 and 2.0 mg kg^{-1} daily for seven consecutive days at each dose, followed by placebo treatment for eight days. During placebo treatment and on days 1, 3 and 7 of drug-treatment, blood samples were obtained prior to dosing (−15 and 0 min) and at 3 and 6 h after dosing. On days 2, 4 and 6 of each treatment period, only morning baseline fasting blood samples were obtained (i.e., 24 h after the preceding day's dose).

Drug preparation

Methyl 2-tetradecylglycidate (Me-TDGA; generic name: methyl palmoxirate), synthesized as previously described (Tutwiler *et al.*, 1981), was given as soft gelatin capsules containing either 5 mg or 50 mg of Me-TDGA formulated in 180 mg neutral oil + 600 mg Tween 80 as vehicle (prepared by R.P. Scherer Co.). In one repeat dose study (Protocol II), hard gelatin capsules containing the desired amount of the drug on a mg kg^{-1} body weight basis were prepared using the Scherer vehicle. Me-TDGA has been shown to be stable under these conditions of formulation. Capsules containing vehicle were used as placebo. The actual dose of Me-TDGA delivered (mg kg^{-1}) was calculated for each dog using the pretest body weight.

Statistics

Data are presented as mean (±s.e. mean) concentrations (mg dl^{-1} and mM for glucose and ketones, respectively) and as the percentage lowering from daily baseline. The maximum percentage reduction from daily baseline was calculated for each dog and averaged to yield mean maximum percentage reductions from baseline (±s.e. mean). Data were statistically analyzed using Dunnett's t test for multiple comparisons after one-way analysis of variance or, where appropriate, by the paired Student's t test. A P value of 0.05 or less was considered to be statistically significant.

Results

Single dose studies

A single oral dose of Me-TDGA (mean of 7.5 mg kg^{-1}, range of 5 to 10 mg kg^{-1}) produced statistically significant reductions of plasma glucose and ketones (Table 1), with mean maximum % reductions from baseline of 32 ± 6% and 74 ± 12%,

Table 1 Effects of a single oral dose of methyl palmoxirate (Me-TDGA)[a] on plasma glucose and ketone levels of fasted diabetic dogs

Parameter	*Hours after oral administration*									*Mean maximum % reduction from baseline*[d]
	0[b]	1	2	3	4	5	6	9	24	
Plasma glucose ($mg\,dl^{-1}$)	168 ± 26[c]	178 ± 28	171 ± 28	152 ± 28	147 ± 27*	134 ± 28**	133 ± 27**	133 ± 28*	160 ± 27	32 ± 6
Plasma ketones (mM)	1.70 ± 0.67	1.17 ± 0.57	0.20 ± 0.06*	0.12 ± 0.02*	0.13 ± 0.01*	0.16 ± 0.02*	0.16 ± 0.02*	0.21 ± 0.03*	1.18 ± 0.37	74 ± 12

[a] Each soft gelatin capsule (described in Methods) contained 50 mg of Me-TDGA; the mean ± s.e. mean body weight of the dogs was 6.6 ± 0.2 kg, yielding an average dose of 7.5 $mg\,kg^{-1}$ (range 5.3–10.0 $mg\,kg^{-1}$).

[b] Represents means of predose values at −15 min and immediately prior to dosing.

[c] Each value is the mean ± s.e. mean for eight dogs. Total ketones = β-hydroxybutyrate + acetoacetate.

[d] Maximum % reduction calculated relative to baseline value (0 min) for each dog and then averaged (mean ± s.e. mean).

Statistical significance of changes versus baseline were determined by the paired Student's *t* test: * $P < 0.05$; ** $P < 0.02$.

respectively. Maximal reductions of plasma ketones (mean time of 3.5 ± 0.3 h) preceded the maximal reductions of plasma glucose (mean time of 6.0 ± 1.0 h). Plasma ketone levels were in the normal range by 2 h post-dosing and were maintained during at least 9 h post-dosing. Although not statistically significant, plasma ketones were still reduced by 31% at 24 h after dosing, whereas fasting plasma glucose had returned to baseline levels.

Repeat dose studies

Protocol I Lower oral doses of Me-TDGA given repeatedly to diabetic dogs for seven days (mean dose of $0.7\,mg\,kg^{-1}$ daily for 7 days) produced significant reductions of plasma glucose and β-hydroxybutyrate levels (Table 2). Following the first dose (day 2) of Me-TDGA, plasma β-hydroxybutyrate levels were markedly decreased and these reductions from daily baseline were maintained with continued dosing. In contrast, the mean plasma glucose levels were only modestly decreased ($9 \pm 3\%$) following the first dose of Me-TDGA (Table 2). With continued dosing however, the magnitude of the plasma glucose reduction progressively increased, with a mean maximal reduction of $30 \pm 5\%$ achieved following the seventh dose of drug (day 8). Continued Me-TDGA treatment qualitatively improved glycosuria and ketonuria, which returned to predrug levels after eight days of placebo treatment (data not shown).

The drug effect on plasma glucose did not carryover to the next day, since the daily baseline fasting glucose level (i.e., 24 h after the previous dose) was not significantly different from that on the previous day nor was there a trend for improvement of overnight fasting plasma glucose with continued dosing (Table 2). Repeated daily dosing with Me-TDGA did, however, markedly lower (76% reduction, day 8 vs day 1) the overnight fasting plasma β-hydroxybutyrate levels (Table 2), which returned to predrug levels following eight consecutive days of placebo treatment.

Protocol II The antiketonaemic and hypoglycaemic effects of lower repeated doses of Me-TDGA,

Table 2 Effects of repeated low oral doses of methyl palmoxirate (Me-TDGA) on plasma glucose (G) and β-hydroxybutyrate levels of fasted diabetic dogs

Treatment[a]	*Day of treatment*	*Avg. daily dose*[b] ($mg\,kg^{-1}$)	*Plasma glucose and ketones at hours after dosing* 0	2	4	6	*Mean maximum % reduction from daily baseline*[c]
Plasma glucose ($mg\,dl^{-1}$)							
Placebo	1	0.0	164 ± 32[c]	191 ± 40	160 ± 31	162 ± 28	3 ± 2
Me-TDGA	2	0.7	171 ± 36	175 ± 35	160 ± 31	152 ± 29	9 ± 3
Me-TDGA	3	0.7	171 ± 34	164 ± 30	151 ± 22	141 ± 18	14 ± 6
Me-TDGA	5	0.7	162 ± 26	157 ± 26	127 ± 18*	123 ± 16*	25 ± 5§
Me-TDGA	8	0.7	172 ± 35	152 ± 30*	129 ± 23*	117 ± 18*	30 ± 5§
Placebo	16[d]	0.0	163 ± 28	156 ± 28	155 ± 29	153 ± 28	7 ± 2
Plasma β-hydroxybutyrate (mM)							
Placebo	1	0.0	1.25 ± 0.77	1.25 ± 0.75	1.38 ± 0.78	1.34 ± 0.75	-6 ± 5
Me-TDGA	2	0.7	1.08 ± 0.74	1.01 ± 0.72	0.23 ± 0.16	0.12 ± 0.06	55 ± 15§
Me-TDGA	3	0.7	0.64 ± 0.53	0.09 ± 0.04	0.07 ± 0.02	0.09 ± 0.04	57 ± 13§
Me-TDGA	5	0.7	0.80 ± 0.53	0.12 ± 0.03	0.08 ± 0.02	0.11 ± 0.04	61 ± 14§
Me-TDGA	8	0.7	0.30 ± 0.17	0.05 ± 0.01	0.05 ± 0.01	0.07 ± 0.02	56 ± 14§
Placebo	16[d]	0.0	1.20 ± 0.80	1.39 ± 0.87	1.42 ± 0.87	1.62 ± 0.96	-20 ± 5

[a] Methyl palmoxirate (5 mg total dose) or vehicle (placebo days) was administered orally as soft gelatin capsules (Sherer formulation) using repeat dose protocol I.
[b] The average daily dose was $0.7\,mg\,kg^{-1}$ ($0.5–0.9\,mg\,kg^{-1}$) based on the mean daily body weight (kg) of the five dogs.
[c] Each value is the mean ± s.e. mean for five dogs.
[d] Day 16 response to vehicle was determined following eight consecutive days on placebo capsules.
[e] Maximum % reduction was calculated relative to the daily baseline value (zero hours) for each dog and then averaged (mean ± s.e. mean).
* Statistical significance of changes versus baseline were determined by the paired Student's t test: $P < 0.05$.
§ Statistical significance vs. placebo Day 1 by analysis of variance and Dunnett's two-tailed t test: $P < 0.05$.

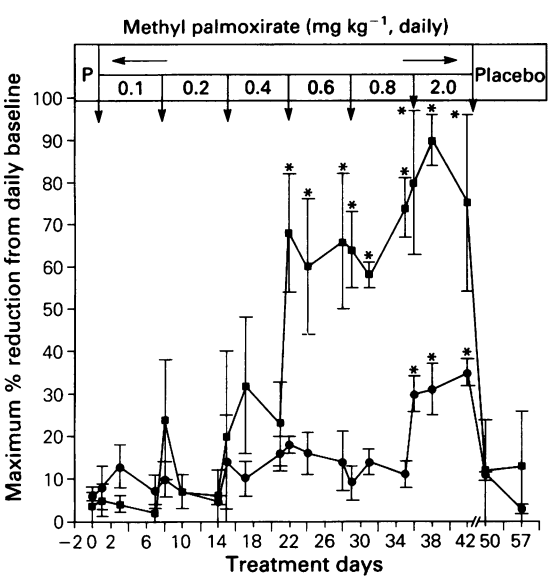

Figure 1 Effects of repeated lower oral doses of methyl palmoxirate (Me-TDGA) on plasma glucose (●) and total plasma ketone (■) levels of fasted diabetic dogs. Studies were performed as described in Methods, Protocol II. Dogs had fasting plasma glucose levels of 170–280 mg dl^{-1} and plasma ketones of 2.70–4.19 mM during the initial two days of placebo treatment. Data are presented as the mean maximum % reduction from the daily baseline for three diabetic dogs; s.e. mean shown by vertical lines. Statistical significance of changes on each treatment day compared to placebo treatment (Day 0) were determined by analysis of variance and Dunnett's t test: * $P < 0.05$.

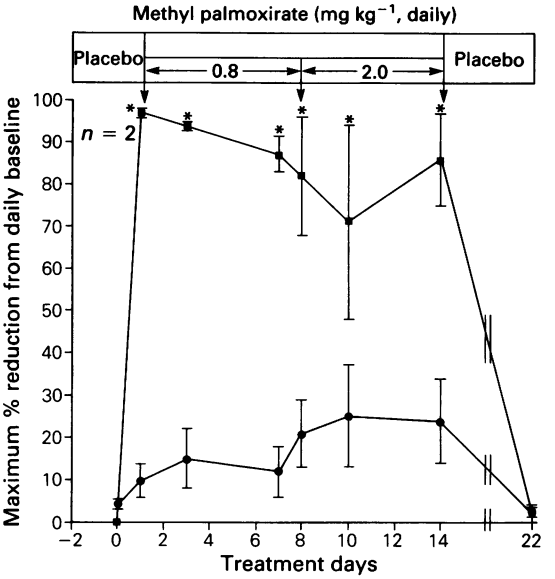

Figure 2 Effects of repeated oral doses of methyl palmoxirate (Me-TDGA) on plasma glucose (●) and total plasma ketone (■) levels of fasted diabetic dogs. Studies were performed as described in Methods, Protocol II. Dogs had fasting plasma glucose levels of 303–327 mg dl^{-1} and total plasma ketones of 5.48 to 7.41 mM during the initial day of placebo treatment. Data are presented as the mean maximum % reduction from the daily baseline for three diabetic dogs: s.e. mean shown by vertical lines. Statistical significance of changes on each treatment day were compared to placebo changes (day 0) by analysis of variance and Dunnett's t test: * $P < 0.05$.

were evaluated in diabetic dogs which began treatment either at 0.1 mg kg^{-1} or at 0.8 mg kg^{-1} daily and progressed to a maximum dose of 2.0 mg kg^{-1} daily for seven days (Figures 1 and 2 respectively). At repeated doses of 0.1 to 0.4 mg kg^{-1} daily, Me-TDGA produced small, statistically nonsignificant reductions of plasma glucose and ketones from daily baseline (Figure 1). At higher doses of 0.6 to 2.0 mg kg^{-1} daily, Me-TDGA effectively lowered plasma ketone levels (Figures 1 and 2); however, statistically significant reductions of plasma glucose were only achieved at the 2.0 mg kg^{-1} daily dose in one study (Figure 1). At doses of 0.8 and 2.0 mg kg^{-1} daily, the mean fasting plasma ketone level measured 24 h after the previous day's dose was significantly lowered (6.45 ± 0.97 to 1.81 ± 0.47 mM, $n = 3$, $P < 0.05$), whereas the mean fasting plasma glucose level was unchanged with continued dosing. After placebo treatment for one to two weeks, fasting plasma ketones returned to predrug levels (5.80 ± 0.67 mM).

Discussion

The hypoglycaemic and hypoketonaemic effects of the fatty acid oxidation inhibitor Me-TDGA were studied in an insulin-deficient diabetic dog model following either oral administration of repeated lower doses (0.1–2.0 mg kg^{-1} daily) or a higher single dose (7.5 mg kg^{-1}).

We have shown that repeated administration of lower doses (0.7 to 2.0 mg kg^{-1} daily for seven days) of Me-TDGA to diabetic dogs produced reductions of blood glucose and ketones that were quantitatively similar to those produced by a higher single dose (7.5 mg kg^{-1}). Whereas significant reductions of plasma ketones were observed following the first dose of drug, in general, slightly higher doses or longer periods of continuous dosing were required for significant reductions of plasma glucose.

Why higher doses of Me-TDGA or longer periods of lower doses are required to reduce blood glucose significantly cannot be determined from these

studies. However, these results are in agreement with the previously reported observation that blood glucose levels of fasted nondiabetic rats given a single low dose (0.05 to 0.25 mg kg^{-1}) of Me-TDGA were not reduced under conditions where hepatic CPT-A activity was significantly inhibited and plasma ketones were lowered by greater than 90% (Tutwiler *et al.*, 1985). Our current belief is that the blood glucose reduction observed in fasted nondiabetic rats following oral administration of single higher doses (> 2.5 mg kg^{-1}) of Me-TDGA is due to the ability of the drug to stimulate peripheral glucose utilization (Tutwiler *et al.*, 1981; Tuman *et al.*, 1987) and, that the ability of Me-TDGA to inhibit hepatic gluconeogenesis is not, by itself, sufficient to contribute significantly to glucose reduction. This idea is further supported by the observation in nondiabetic rats that peripheral skeletal muscle mitochondrial CPT-A activity was significantly inhibited only with acute oral doses of Me-TDGA greater than 2.5 mg kg^{-1} (Tutwiler *et al.*, 1985). Furthermore, isotopic glucose studies in diabetic dogs suggest that repeated low oral doses of Me-TDGA (2–3 mg kg^{-1}) lower fasting plasma glucose both by enhancing peripheral tissue glucose clearance and by decreasing hepatic glucose production, with the latter activity being important only in dogs having elevated hepatic glucose output (unpublished data). It is probable that in these diabetic dogs, as in nondiabetic rats, peripheral muscle CPT-A activity is not sufficiently inhibited by low oral doses (0.1–0.6 mg kg^{-1} daily) of Me-TDGA, and only after repeated administration of higher doses (0.7–2.0 mg kg^{-1}, daily) of this irreversible inhibitor is muscle CPT-A activity sufficiently inhibited and peripheral glucose utilization sufficiently stimulated to impact circulating blood glucose levels. Thus, the irreversible nature of the inhibition may produce a sustained block of peripheral CPT-A enzyme activity and long-chain fatty acid oxidation which could result in progressively greater blood glucose reduction with continued dosing. This hypothesis will have to be tested in further studies, since peripheral CPT-A activity and peripheral glucose utilization were not determined in these dogs.

An alternative possibility is that the reduction in blood glucose observed following multiple low doses was produced by an accumulation of drug with continued dosing. We cannot exclude this possibility since an adequate analytical method to determine blood levels of Me-TDGA is not available.

In summary, Me-TDGA was shown to be an orally effective hypoglycaemic and hypoketonaemic agent in insulin-deficient diabetic dogs. The therapeutic significance of this activity has been demonstrated in preliminary studies in diabetic patients (Mandarino *et al.*, 1984; Verhaegen *et al.*, 1984).

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