

The Use Of 1,5-Anhydroglucitol (Glycomark) To Monitor New Classes Of Therapies For Managing Postmeal Glucose In Patients With Diabetes



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Abstract

Objective: To evaluate the use of 1,5-anhydroglucitol (1,5-AG) to monitor new therapies for PPG.
Methodology: Retrospective analysis of clinical drug studies utilizing 1,5-AG.
Results: 1,5-AG has recently been used in clinical studies with several new classes of therapies for managing postmeal glucose (amylin analogs, glucagon-like peptide-1 [GLP-1] derivatives, dipeptidyl peptidase-4 [DPP-4] inhibitors, alpha-glucosidase inhibitors). In the case of sitagliptin phosphates, a DPP-4 inhibitor, 1,5-AG increased by 4.45 ug/ml in the sitagliptin group (n=75) compared with a decrease of 0.33 ug/ml in the placebo (n=76), for a between-treatment group difference in 1,5-AG of 4.78 ug/ml (95% CI: 3.76, 5.80; p<0.001) over a 12-week period and consistent with improvement in PPG control. In a study with miglitol, an alpha-glucosidase inhibitor, comparing a placebo group (n=84) to a miglitol-treated group (n=158) over 12 weeks, 1,5-AG mean levels did not change significantly from baseline (4.62 ug/ml) to study end in the placebo group. In the miglitol-treated group, 1,5-AG increased from 4.79 ug/ml to 10.46 ug/ml from baseline to study end, consistent with changes in PPG control. After 4 weeks, the mean 1,5-AG was 9.15 (p<0.001 compared to baseline levels).
Discussion: A1C measurement is a critical component of diabetes management; however, a key limitation of A1C as a measure of glycemia is the lack of timeliness -- it does not detect underlying blood glucose excursion levels in moderately controlled diabetic patients (A1C < 8) as it is a measurement of mean glucose levels over the longer-term. In contrast, the 1,5-anhydroglucitol (1,5-AG) assay responds rapidly and sensitively to serum glucose levels above the renal threshold and has been demonstrated as a valid marker of postprandial hyperglycemia and short-term glycemic control (1,5-AG was recently included in the new International Diabetes Federation guideline for management of postmeal glucose as an emerging technology to measure PPG). Data from this retrospective analysis indicate that 1,5-AG revealed underlying treatment effects on postprandial glucose control which were not readily apparent by A1C measurements, confirming the role of 1,5-AG as a PPG marker.
Conclusion: 1,5-AG may be a useful complement to A1C to reflect PPG in diabetic patients treated with agents that target PPG.

Background

- Studies indicate that PPHG (postprandial hyperglycemia) is an independent risk factor for the development of macrovascular complications. Many well-controlled patients with diabetes have significant PPHG. 1,5-Anhydroglucitol (1,5-AG) is a naturally occurring dietary polyol that has been proposed as a marker for PPHG. During normoglycemia, 1,5-AG is maintained at constant steady-state levels due to a large body pool and lack of metabolism. Normally, 1,5-AG is filtered and completely reabsorbed in the kidneys. However, when serum glucose exceeds the renal threshold for glucosuria (generally above 180 mg/dL), serum 1,5-AG levels fall due to competitive inhibition of tubular reabsorption by glucose (Figure 1). Thus, 1,5-AG responds sensitively and rapidly (within a few days) to changes in serum glucose. 1,5-AG has been shown to reflect daily glycemic excursions in patients with A1Cs at or near goal. In contrast, A1C is a reflection of average glucoses over a much longer period of time (2-3 months), encompassing both hyperglycemic and hypoglycemic periods.
- In a recently reported study (Dungan, et al. Diabetes Care 2006; 29(6): 1214-1219), it was shown that 1,5-AG reflects glycemic excursions, often in the postprandial state, more robustly than A1C or fructosamine. It was also observed that the 1,5-AG assay was reflective of varying postmeal glucose levels despite similarities in A1Cs.
- Recent studies indicate that 1,5-AG revealed underlying treatment effects on postprandial glucose control which were not readily apparent by A1C measurements. Thus, 1,5-AG may be a useful complement to A1C to reflect PPG in diabetic patients treated with agents that target PPG.
- In this retrospective analysis, the use of 1,5-AG to monitor exenatide, pramlintide, sitagliptin, and biphasic insulin aspart therapies is examined.

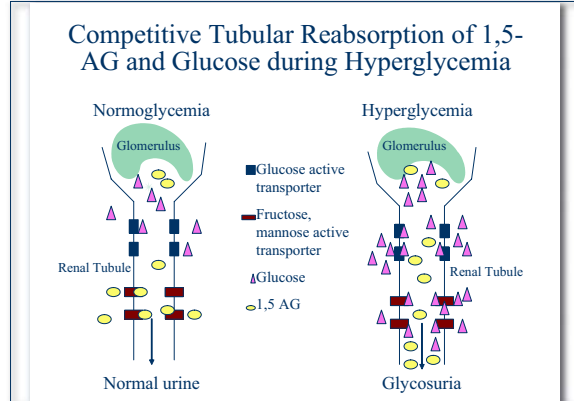


Figure 1: 1,5-AG is excreted through the glomerulus and 99.9% is reabsorbed through the fructose, mannose active transporter in the normoglycemic state. However, during glycemic excursions >180mg/dL, the glucose active transporter becomes saturated. Surplus glucose is then reabsorbed

Studies Showing Use of 1,5-AG to Reveal Underlying Treatment Effects

Exenatide Improves Postprandial Glucose (PPG) Control in Patients With Type 2 Diabetes as Measured by 1,5-Anhydroglucitol (GlycoMark)

Reference: Scientific Sessions of the American Diabetes Association – 2007 (David Kendall, et al.)

Results

Comparison of Changes in Values from Baseline to Study End

	Exenatide (5 ug)	Exenatide (10 ug)
1,5-AG	+2.7 +/- 0.6 ug/ml* 45.3 +/- 11.9 %	+2.9 +/- 0.6 ug/ml** 69.4 +/- 14.6 %
A1C	-0.5 +/- 0.1 %	-0.9 +/- 0.1 %**

*P < 0.05; ** P < 0.01

N = 144, Type 2 Diabetes
 Study Duration = 30 weeks
 Initial A1C levels = 8.2 +/- 1%
 Randomized to Exenatide (5 or 10 ug) or placebo

Interpretation

- Exenatide 5ug dosage showed no significant difference in A1C, while there was a significant change in 1,5-AG
- Exenatide 10 ug dosage showed significant differences in A1C and 1,5-AG
- 1,5-AG confirmed previously reported improvements in PPG in exenatide-treated patients

1,5-Anhydroglucitol (GlycoMark), a PPG Excursion Marker In Pramlintide-Treated Subjects

Reference: American Association of Clinical Endocrinologists 2007 Annual Meeting (Cameron Lush, et al.)

Results

Comparison of Changes in Values from Baseline to Study End

	Placebo (n=19)	Pramlintide (n=18)	Pramlintide vs. Placebo
2-hr PPG excursions	+6.5 +/- 7.6 mg/dL	-43.9 +/- 10.9 mg/dL	P < 0.001
Body Weight	+1.3 +/- 0.7 kg	-2.0 +/- 1.2 kg	P < 0.01
A1C	0.22 +/- 0.21 %	0.18 +/- 0.31 %	NS
1,5-AG	-0.65 +/- 0.41 ug/ml -9 +/- 8 %	+0.96 +/- 0.91 ug/ml +30 +/- 16 %	P < 0.05 P < 0.01

N = 37, Type 1 Diabetes
 Study Duration = 29 weeks
 Initial A1C levels = 7.2 to 8.0%

Interpretation

- Pramlintide, as an adjunct treatment for T1DM patients on intensive insulin therapy, led to improved PPG and significant reduction in body weight
- Despite similar reductions in A1C, the change in 1,5 AG levels was consistent with improvement in PPG control in pramlintide-treated subjects, as measured by SMBG
- 1,5-AG, as a complement to A1C, may be a useful marker of PPG control

Efficacy and Safety of Sitagliptin Monotherapy in Japanese Patients with Type 2 Diabetes

Reference: Diabetes Research and Clinical Practice 2008 (Kenji Noaka, et al.)

Results

Comparison of Changes in Values from Baseline to Study End

	Placebo		Sitagliptin 100mg		Between Group Comparison	
	LS	95% CI	LS	95% CI	LS Difference	95% CI
A1C	0.41	(0.26, 0.5)	-0.65	(-0.80, 0.50)	-1.05*	(-1.27, -0.84)
1,5-AG	-0.33	(-1.05, 0.38)	4.45	(3.73, 5.17)	4.78*	(3.76, 5.80)

*P value < 0.001

Change in Postmeal Glucose Compared to A1C and 1,5-AG % Changes (Baseline to Study End)

	Absolute Change in 2 hour postmeal glucose (mg/dL)	A1C Absolute % change	1,5-AG Absolute % change
Sitagliptin 100mg	-69.2	-8.6%	83%
Placebo	11.7	5.2%	-7.3%

N = 151, Type 2 Diabetes
 Study Duration = 12 weeks
 Initial A1C levels = 6.5 to 10.0%

Interpretation

- Although 2-hour postprandial glucose decreased by 69.2 mg/dL in the sitagliptin group, A1C changed only 8.6% in absolute % change. This is compared to a % change of 83% for 1,5-AG
- The substantial increase in 1,5-AG was consistent with marked decrease in postprandial excursion observed during meal tolerance tests

Does serum 1,5-AG establish a relationship between improvements in HbA1c and postprandial glucose excursions? Supportive evidence utilizing the differential effects between biphasic insulin aspart 30 and insulin glargine.

Reference: Diabetic Medicine 2008 (Alan Moses, et al.)

Results

Comparison of Changes in Values from Baseline to Study End

Type 2 Diabetes Study Duration = 28 weeks		BIAsp 70/30 + Met	Glargine + Met	p-value
1,5-AG (ug/mL) (mean ± SD)	Baseline	4.9 ± 3.5 (N=113)	4.3 ± 2.6 (N=114)	0.2651
	Week 28	13.4 ± 5.7 (N=92)	11.1 ± 6.0 (N=101)	0.0050
A1C (%)	Baseline	9.7 ± 1.5 (N=117)	9.8 ± 1.4 (N=114)	0.4782
	Week 28	6.8 ± 0.9 (N=99)	7.3 ± 1.2 (N=110)	0.0003

Interpretation

- The greater reductions in postprandial excursion achieved with BIAsp 30 compared with glargine were associated with greater increases in 1,5-AG.
- Even moderate elevations in A1C substantially lower 1,5-AG, suggesting that it can be most discriminating in identifying patients with excessive postprandial glucose excursions at A1C levels that are in the moderate range.

Summary – Managing Postmeal Glucose Studies

Comparison of % Changes in Values from Baseline to Study End – Treated Populations

	1,5-AG (Absolute % Change)	A1C (Absolute % Change)
Exenatide 5 ug (30 weeks)	+ 45.3%	-6.1%
Pramlintide (29 weeks)	+30.0%	-2.4%
Sitagliptin (12 weeks)	+83.1%	-8.6%
BIAsp 70/30 (28 weeks)	+273.5%	-29.9%

Conclusions

- 1,5-AG reflected changes in PPG more dynamically than A1C in moderately controlled patients treated by exenatide, pramlintide, sitagliptin, and biphasic insulin aspart.
- Several clinical studies using 1,5-AG are ongoing; including once-weekly exenatide and lispro mixture (DURABLE trial).
- 1,5-AG may be a useful complement to A1C to reflect PPG in diabetic patients treated with agents that target PPG.
- An algorithm utilizing 1,5-AG to reach glycemic goals is proposed.

