



Pioglitazone and Insulin: effects on tight glycaemic control assessed by the continuous glucose monitoring system (CGMS)

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Abstract:

Background and aims: There is clear evidence that HbA_{1c} is the best parameter for assessing the quality of long-term glycaemic control. Furthermore, postprandial hyperglycaemia is recognized as a significant risk factor for vascular complications generating additional information on the individual risk status. Pioglitazone (PIO), a PPAR γ -Agonist provides sustained and durable glycaemic control. Insulin therapy (INS) applied with multiple daily injections is believed to be the most potent regimen achieving best possible glycaemic control. This study is aiming to compare both treatment options with regard to the prevalence of hypo- and hyperglycaemic episodes. **Material and Methods:** Monocentric, parallel-cohort study. 30 well-controlled (HbA_{1c} \leq 7%) patients with type-2-diabetes (T2DM) were monitored for 72h using the CGMS (Medtronic), thereof 15 on PIO (30 mg od. in combination with a mean dose of 1,700 mg metformin, MET) and 15 on INS. Results were analysed descriptively. **Results:** Mean INS dose was 59.6 U/d. Both groups were comparable for risk factors and comorbidities.

Parameter (Median)	PIO, n = 15	INS, n = 15
HbA _{1c} (%) / FBG (mg/dl)	5.9 / 120	6.4 / 131
Number of glucose values	844	837
Hyperglycaemic episodes:	7 / 4.6	16 / 11
> 160 mg/dl; number/time (h)		
Patients with episodes < 60 mg/dl	3	7
Glucose values 60 – 160 mg/dl (%)	92	78

Mean duration of hypoglycaemic episodes were 1.9h (INS) and 0.4h (PIO), respectively. Baseline (BL) HbA_{1c} does not correlate with the frequency and duration of hyperglycaemic events whereas a correlation for hypoglycaemic episodes exists for BL HbA_{1c} as well as insulin dose. **Conclusions:** even well-controlled patients with T2DM show a remarkable variability of glucose excursions. PIO/MET compared to INS offers benefits in terms of a lower prevalence of hypo- and hyperglycaemic episodes.

Background:

There is clear evidence that HbA_{1c} is the best parameter for assessing the quality of long-term glycaemic control in type 2 diabetic patients (T2DM). The observation that patients develop microvascular disease despite acceptable HbA_{1c} levels raised the possibility that other features of glycaemic control, not reflected in the HbA_{1c}, might contribute to the risk complications¹. Meanwhile, postprandial hyperglycaemia is recognized as a significant risk factor for vascular complications generating additional information on the individual risk status^{3,6}. Hyperglycaemia is also an important factor that limits the ability to achieve tight glycaemic control, especially in patients taking insulin¹.

Pioglitazone (PIO), a PPAR γ -Agonist provides sustained and durable glycaemic control. Insulin therapy (INS) applied with multiple daily injections is believed to be the most potent regimen achieving best possible glycaemic control.

The Medtronic Minimed® Continuous Glucose Monitoring System (CGMS) is the first commercially available which allows the performance of interstitial glucose monitoring and a determination of the prevalence of hypo- and hyperglycaemia. It provides a continuous glucose profile by taking samples from the subcutaneous interstitial fluid every 5 min^{7,8}.

Aim:

This study is aiming to compare both treatment options (PIO and INS) in type 2 diabetic patients apparently well-controlled according their low HbA_{1c} with regard to the prevalence of hypo- and hyperglycaemic episodes.

Methods:

In this monocentric, parallel-cohort study, patients with type-2-diabetes were recruited if their HbA_{1c} was \leq 7%. A total of thirty patients were each monitored for 72h using the Continuous Glucose Monitoring System CGMS.

Fifteen T2DM patients (7 men, 8 women), mean age 58.7 years with a HbA_{1c} of 5.9 % were on Pioglitazone, PIO (30 mg od. in combination with a mean dose of 1,700 mg metformin, MET) and fifteen T2DM patients (8 men, 7 women), mean age 63.5 years with a HbA_{1c} of 6.4% were on a basis/bolus Insulin regimen, INS. Results were analysed descriptively.

Results:

Mean INS dose was 59.6 U/d. Both groups were comparable for risk factors and comorbidities.

Table 1. Baseline Characteristics

	Patients on OAD therapy	Patients on INS therapy
Mean Age [years]	58,7	63,5
Mean BMI	32,7	31,5
LDL-cholesterol [mg/dl]	120	98
HDL-cholesterol [mg/dl]	54	49
Gamma-GT [U/L]	22	38

Figure 1. Concomitant medication

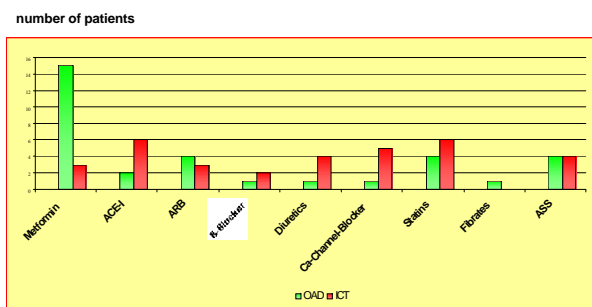


Figure 2. Co-morbid conditions

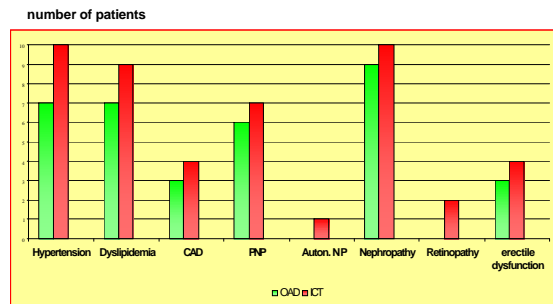


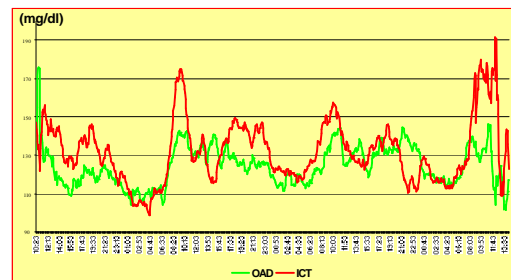
Table 2. Effect of PIO and INS on the number and duration of hypo- and hyperglycaemic episodes

Parameter (Median)	PIO, n = 15	INS, n = 15
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Glucose values 60 – 160 mg/dl (%)	92	78

The number of measured glucose values was 844 in the PIO arm and 837 in the INS arm. The incidence of hyperglycaemic (>160 mg/dl) and hypoglycaemic (<60 mg/dl) episodes was determined.

The mean glucose values were 120 mg/dl in the PIO arm and 131 mg/dl in the INS group. Seven hyperglycaemic episodes (with a duration of 4.6 hours) occurred in the PIO/MET group and 3 patients (20%) experienced hypoglycaemic episodes. The corresponding numbers in the INS group were 16 hyperglycaemic episodes (duration 11 hours) and 7 patients (46%) with hypoglycaemic events. Mean duration of hypoglycaemic episodes were 1.9h (INS) and 0.4h (PIO), respectively.

Figure 3. Mean blood glucose values determined by CGMS in patients under PIO/MET and INS-therapy



Baseline (BL) HbA_{1c} does not correlate with the frequency and duration of hyperglycaemic events whereas a correlation for hypoglycaemic episodes exists for BL HbA_{1c} as well as insulin dose.

Conclusions:

Even well-controlled patients with T2DM show a remarkable variability of daily glucose excursions that are neither clinically obvious nor identified by current monitoring techniques. PIO/MET compared to INS offers benefits in terms of a lower prevalence of hypo- and hyperglycaemic episodes. Particularly with regard to the postprandial episodes, an advantage of PIO in preventing the under INS treatment existent hyperglycaemic peaks becomes obvious. Thus, the continued therapy with PIO offers advantages in terms of a better control of postprandial glycaemic episodes and should therefore be maintained as long as possible.

References

1. The Diabetes Control and Complications Trial (DCCT) Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-986
2. Ceriello, A.: The emerging role of post-prandial hyperglycaemic spikes in the pathogenesis of diabetic complications. Diabet. Med. 1998;15:188-193.
3. I.M. Stratton, A.I. Adler, H. A. W Neil, D.R. Matthews, S.E. Manley, C.A. Cull, D. Hadden, R.C. Turner, and R.R. Holman: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35); prospective observational study, BMJ, Aug 2000; 321: 405 - 412.
4. E.J. Bastyr, C.A. Stuart, R.G. Brodows, S. Schwartz, C.J. Graf, A. Zagar, and K.E. Robertson: Therapy focused on lowering postprandial glucose, not fasting glucose, may be superior for lowering HbA_{1c}. IOEZ Study Group, Diabetes Care, Sep 2000; 23: 1236 - 1241.
5. J.E. Shaw, AM Hodge, M de Courten, P Chitson, and PZ Zimmet : Isolated post-challenge hyperglycaemia confirmed as a risk factor for mortality. Diabetologia, Sep 1999; 42(9): 1050-4.
6. P.J. Lefebvre, A.J. Scheen : The postprandial state and risk of cardiovascular disease. Diabet. Med. 1998; 15 Suppl 4:S63-8.
7. R. Amin, K. Ross, C.L. Acerini, J.A. Edge, J. Warner, D. B. Dunger: Hypoglycemia Prevalence in Prepubertal Children With Type 1 Diabetes on Standard Insulin Regimen: Use of Continuous Glucose Monitoring System. Diabetes Care, Mar 2003; 26: 662 - 667.
8. B. Aussetat, M. Dupire-Angel, R. Gifford, J. C. Klein, G. S. Wilson, and G. Reach: Interstitial glucose concentration and glycaemia: implications for continuous subcutaneous glucose monitoring. Am J Physiol Endocrinol Metab, Apr 2000; 278: 716 – 728
9. F. Kaufman, L.C. Gibson, M. Halvorson, S. Carpenter, L.K. Fisher, and P. Pitukcheewanont: A Pilot Study of the Continuous Glucose Monitoring System: Clinical decisions and glycaemic control after its use in pediatric type 1 diabetic subjects. Diabetes Care, Dec 2001; 24: 2030 - 2034.