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ScienceDirect
Metabolism Clinical and Experimental 59 (2010) 763 – 765
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Letters to the Editor

Comments on a pilot study to test the effect of pulsatile insulin infusion on type 1 diabetes mellitus patients with proteinuria

To the Editor:

Outpatient intravenous insulin infusion (OVIT) given weekly in a pulsatile fashion added to a regimen of subcutaneous multiple daily insulin (MDI) injections has been touted by a select number of authors as superior to MDI alone for the treatment of type 1 diabetes mellitus. Weinrauch and colleagues have published apparently supportive data in this journal, and I wish to take exception to one publication in particular.

In this article [1], Weinrauch et al report a pilot study of 18 patients that represents a subset of a larger study from 2000 [2]. They report that OVIT led to preservation of renal function and was associated with improvement in the efficiency of fuel oxidation, although it was not associated with other parameters they hypothesized might mediate the benefits of this therapy [1].

There are multiple, glaring problems with this report and conclusions. The baseline characteristics of the control and OVIT group were not the same. Initial mean hemoglobin A_{1c} was 9.8% for controls and 9.1% for the treatment group; and mean arterial pressure (MAP) was 103.8 vs 96.2 mm Hg, respectively. They state that "blood pressures were not significantly different at baseline and 12 months"; but this is misleading because the important point is that MAP started out notably higher, and remained notably higher, in the control group over 12 months. Given the known effects of blood pressure on progression of renal disease in diabetic nephropathy, this finding alone invalidates any conclusions about "preservation of renal function." It is possible that, when concluding there was preservation of renal function, they were referring to the larger trial [2]. However, these are not the data they presented; and the larger trial had a number of issues as well (a 46% dropout rate, lack of statistical significance at 12 months but comparison of the 18-month group to the 12-month cohort, differences in glucose control, etc) [3].

Some of the reported results do not make sense. For example, they report that 83% of controls developed edema; but the control number of 8 makes that not possible (even if they were counting individual legs). There are 2 results reported for baseline respiratory quotient (0.854 and 0.826).

The authors make no mention of the fact that the control group ended up with a *better* A_{1c} than the treatment group. A major premise of the OVIT hypothesis is that glycemic control is *better* with OVIT added to MDI than with MDI alone [4]. Hence, this part of the hypothesis is contradicted by their data; and no conclusions in this context can be made from their data. They may be attempting to get around this by describing "glycemic control" as the increase in the RQ seen in the OVIT group. However, RQ was not even measured in the control group: for all we know, it improved even more (because A_{1c} was lower at end of study). Statements implying a connection between increased fuel utilization, preservation of renal function, and OVIT in this study are completely unwarranted.

In summary, I believe they present no credible data that OVIT is associated with preservation of renal function, presentation of some of the data are misleading, and the speculations offered are wholly unwarranted.

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doi:10.1016/j.metabol.2010.01.020

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What have trials of pulsatile intravenous insulin taught us?

To the Editor:

Dr Leinung expresses concern about a multicenter publication published a decade ago [1]. Recruitment began in 1992, at which time the Diabetes Control and Complications Trial and captopril studies had established that the preferred approach to therapy was multiple insulin injections plus angiotensin-converting enzyme (ACE) inhibitors. Baseline blood pressure and glycohemoglobin A_{1c} in this randomized study were not significantly different between study groups. Control vs pulsatile insulin infusion patients who were not treated with ACE inhibitors (9 of 34 controls, 17 of 37 infusions) had nearly identical slopes of creatinine clearance decline at −5.3 vs −5.2 mL/(min y) ($P = .98$) at 52 weeks and at −5.9 vs −5.5 mL/(min y) ($P = .91$) at 78 weeks. Control vs infusion patients treated with ACE inhibitors had slopes of −7.1 vs −0.96 at 52 weeks ($P = .11$) and −8.86 vs −0.60 at 78 weeks ($P = .016$). Thus, the infusion group with a lower percentage treated with ACE inhibition still had statistically significantly slower declines in creatinine clearance due to very different results in those treated with ACE inhibitors. As shown in the figure in that publication, there was no difference in the slope of the decline for patients in the original 52-week protocol vs those who elected to stay on for an additional 26 weeks. Dr Leinung refers to this as "dropout." We see this as electing not to continue after having completed one's agreed commitment.

Because ACE inhibition may have effects through both the angiotensin receptor signal (such as hyperkalemia) and extrareceptor pathways (such as the inflammation cascade) that might have a measurable impact on one individual and not another in a randomized population, we reviewed results at both extremes of loss of creatinine clearance. Ambulatory blood pressure recordings from 10 patients in both the control and the infusion groups with the highest slope of decline in creatinine clearance returned mean arterial pressures (MAPs) of 93.1 ± 2.3 mm Hg for controls vs 91.8 ± 2.0 mm Hg for the infusion group (P = not significant). The MAP results for 10 patients in the groups with the lowest slope of decline in creatinine clearance were 103.1 ± 3.0 mm Hg for controls vs 100.7 ± 3.0 mm Hg for infusion patients (P = not significant). Clearly, these associations questioned the concept that blood pressure alone controls renal function. One year after the final patient was enrolled at the Joslin Clinic, a study was published from the University of California at Davis: control and infusion patients who were studied in a crossover design, either by starting from control, proceeding to infusion, and back to control or by starting as infusion, moving to control, and back to infusion, were found to require significantly less antihypertensive medication during the infusion phases [2].

From observations on preservation of renal function in relationship to blood pressure control, we can summarize:

1. Pulsatile insulin infusion was associated with lower blood pressure in short-term observations.
2. Pulsatile insulin infusion had an added effect on preservation of renal function when ACE inhibition was used and did not have an added effect in the absence of ACE inhibition.
3. Level of blood pressure may not be the most important factor in preservation of renal function in type 1 diabetes mellitus patients with nephropathy treated with insulin and antihypertensive medications.

Dr Leinung claims our hypothesis to be that glycemic control is better with pulsatile insulin infusion than with multiple daily insulin doses alone. However, in the article criticized [3], we stated our hypothesis to be quite different from that related to insulin delivery systems and glycemia control. We analyzed potential roles of cardiac autonomic and hemostatic function in progression of renal disease among patients using 2 different methods of insulin delivery. Dr Leinung states that the statistically nonsignificant difference in baseline blood pressures favors the infusion group. In this connection, factors that were also not significantly different between infusion and controls, but "favored" the control group, included plasma fibrinogen, factor VII, fibrinolytic activity, as well as both platelet adhesion and aggregation. None of these test results were different to a statistically significant degree between groups during the course of the study; this was also the case for day/night MAP and autonomic function. Our hypothesis that autonomic and prothrombotic factors may have provided an explanation for renal function differences could not be confirmed in this small pilot study [3]. Dr. Leinung correctly identifies a typographical error in Table 1 regarding edema.

In prior studies from our group, we noted that improvement in glycohemoglobin and advanced glycemic end-products was associated with significant decreases in left ventricular mass and septal thickness despite similar blood pressures when compared with patients whose A_{1c} rose over 1 year [4]. We have also recorded statistically significant improvement in cardiac parasympathetic function [5] when glycohemoglobin improved as well as in plasma fibrinogen and factor VII [6] when advanced glycated end-product concentrations fell significantly. Dr Leinung also questions the benefits of pulsatile insulin infusion on glycemia, in that the control group glycohemoglobin A_{1c}