Original Article

Long- term Efficacy and Safety of Vanadium in the Treatment of Type 1 Diabetes

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Abstract

Background: Vanadium compounds are able to reduce blood glucose in experimentally- induced diabetic rats and type 2 diabetic patients, but data about their long- term safety and efficacy in diabetic patients are scarce.

Methods: Fourteen type 1 diabetic patients received oral vanadyl sulfate (50 – 100 mg TID) for a period of 30 months. Fasting blood sugar (FBS), lipid levels, hematologic, and biochemical parameters were measured before and periodically during the treatment.

Results: The daily doses of insulin decreased from 37.2 ± 5.5 to 25.8 ± 17.3 units/day and at the same time the mean FBS decreased from 238 ± 71 to 152 ± 42 mg/dL. Meanwhile, there was a decrease in plasma total cholesterol without any change in triglyceride level. No significant clinical or paraclinical side effects, with the exception for mild diarrhea at the beginning of treatment, were observed during 30 months therapy.

Conclusion: Vanadium is effective and safe for long- term use in type 1 diabetic patients.

Keywords: Diabetes mellitus, insulin, type 1, vanadium

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Introduction

It is strongly believed that vanadium salts might be a valuable supplement to insulin in the treatment of diabetes mellitus.[1,2] Studies performed by us and others have demonstrated that oral administration of vanadium to streptozotocin- induced diabetic rats,[3–7] or genetically inherited diabetic animals,[8,9] ameliorated hyperglycemia.

Extensive studies have been carried out to elucidate the mechanism by which vanadium acts in cellular regulation of glucose metabolism. These mechanisms are increased hepatic glycogenesis and inhibition of glucose output from the liver,[10] and activation of glucose transport into tissues such as adipocytes,[11] and skeletal muscle.[12] Although the exact mechanism of these actions are not yet well understood, there are evidences pointing to the fact that vanadium diminishes the requirement of diabetic animals for insulin and relieves diabetes.[4,6,13]

Another phenomenon which is extensively investigated shows that vanadium influences pancreatic beta cells. In streptozotocin-induced diabetic rats, vanadium increased the number of beta cells,[14,15] and had protective effect on them.[5,16] Works done in our center have shown the hyperplastic and hypertrophic actions of vanadium on the beta cells of streptozotocin- induced diabetic rats.[17] Finally, recent reports have indicated that vanadium salts present in tea have produced remarkable hypoglycemic effects and restoration of cardiac function.[2] However, the use of oral vanadium in the treatment of diabetes deserves intense investigation about its long- term accumulation in the organs of the body. As with any new agent there have been concerns over the long- term safety and effectiveness of vanadium in man prior to its use as a conventional therapy for diabetic complications.[18] To resolve the question of safety and efficacy of vanadium, we undertook this study in 1993, continued for two and a half years with six years follow-up.

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Patients and Methods

The details of the study were approved by the Ethical Committee of Shiraz University of Medical Sciences and complied with Helsinki Declaration. Fourteen type 1 diabetic patients (seven males and seven females) were selected from those under care of the Motahari Polyclinic, affiliated to Shiraz University of Medical Sciences, Shiraz, Iran. Patients with hematologic, renal, hepatic, and respiratory abnormalities were excluded. They were in good general health, did not suffer from retinopathy, nephropathy, cardiovascular disease, except having uncontrolled blood sugar despite insulin therapy. They were taking neutral protamine of Hagedorn (NPH) and regular insulin once or twice per day and had poor glucose control.

The females were not married. Patients' characteristics before participation in the study are presented in Table 1. The patients' mean age was 18.3 ± 7.4 (eight to 36 years) with the average body mass index (BMI) of 17.6 ± 2.3 kg/m^2 and the mean body weight of 40.0 ± 12.5 kg. The mean duration of diabetes mellitus was 3.1 ± 39 years (one month to 12 years). The patients were taking NPH and regular insulin once or twice per day and had poor blood glucose control. During the initial run-in period of two months each patient had an extensive physical examination; baseline complete blood count and hemoglobin (CBC, Hb; Table 2); liver function tests (LFT; Table 3); and blood chemistry such as blood urea nitrogen (BUN), creatinine, electrolytes, calcium, phosphate, serum pH, and bicarbonate (Table 4). Triglyceride (TG) and total choles-

Table 1. Patients' characteristics, daily insulin requirements, and fasting blood sugar before and during 30 months continuous vanadyl therapy*

Name	Sex	Age (years)	AD (years)	BW (kg)	BMI (kg/m²)	Vanadyl (mg/kg/day)	INS (u/day)		FBS (mg/dL)	
							Before	During	Before	During
F-R	F	10	9	26	14.5	5.77	22	10	282	182
M-K	M	15	14	44	17.3	4.11	50	20	280	200
R-CH	M	10	9	34	16.2	4.12	24	24	275	161
A-M	M	12	11	34	15.0	4.12	17	14	216	70
F-K	F	25	25	47	18.5	3.19	22	14	267	222
S-P	M	15	14	40	17.3	5.63	70	55	195	170
Z-S	F	8	5	18	13.8	8.33	14	12	144	124
H-B	M	19	14	61	21.1	3.69	60	60	300	185
L-H	F	16	11	42	20.0	3.57	42	5	170	135
H-AN	F	23	16	54	19.7	4.17	25	17	147	132
M-Z	M	24	12	67	21.1	3.36	80	50	151	105
M-SJ	F	23	21	44	17.3	6.82	30	30	265	168
M-B	M	22	22	48	17.1	6.25	35	25	391	105
Z-ZL	F	17	16	42	16.4	7.14	30	25	250	168
Mean ± SD		**17.1 ± 5.7**	**14.2 ± 3.4**	**42.9 ± 12.9**	**17.5 ± 2.3**	**5.02 ± 1.6**	**37.2 ± 20.5**	**25.8 ± 17.3**	**238 ± 71**	**152 ± 42**
P-value							**0.003**		**0.001**	

*-Data are presented as mean ± SD; AD: Age at diagnosis; BW: Body weight; BMI: Body mass index; INS: Insulin dose; FBS: Fasting blood sugar.

Table 2. Hematologic survey before and during 14, 24, and 30 months vanadyl therapy*

White blood cell differential counts	Before	Treatment			
		14 months	24 months	30 months	P-value
Hb (g/dL)	13.0 ± 0.8	12.9 ± 0.5	12.8 ± 0.4	12.9 ± 0.4	0.446
WBCx10³/µL	6589 ± 490	6964 ± 355	7007 ± 263	6744 ± 659	0.079
LYMPH/µL	2260 ± 134	2349 ± 82	2300 ± 116	2312 ± 111	0.058
PMNs/µL	2346 ± 102	2453 ± 106	2361 ± 117	2441 ± 111	0.868
EOS/µL	235 ± 21	233 ± 22	240 ± 18	234 ± 27	0.868
MONO/µL	420 ± 42	430 ± 40	439 ± 44	435 ± 55	0.712
PLTx10³/µL	2373 ± 348	2247 ± 275	2515 ± 270	2394 ± 283	0.137

*-Data are presented as mean ± SD; N = 14.

terol (TCHL) were measured consequently. Fasting blood sugar (FBS) and afternoon blood sugar (ABS) were measured six times weekly and the average was considered as baseline.

Each patient received information about vanadium therapy and the study (as required by the Ethical Committee of the university) and a written consent was obtained. Each patient started with two capsules of 40 – 60 mg vanadyl (vanadyl sulfate Penta hydrate, Merck, equivalent to 0.6 mg elemental vanadium/kg/day) as a minimum daily dose for two to five weeks. After adaptation, this dose gradually increased to 225 – 300 mg/day vanadyl (three capsules of 75 – 100 mg vanadyl; equivalent to 1.5 mg elemental vanadium/kg/day) and continued for 30 months. The patients were instructed to keep their lifestyle, diet, and physical activity as before. For the first two months, the patients received their medicines and asked to have weekly visits or whenever they got any adverse effect. In each visit, they had a full check- up and reported any problem to the physician who was in charge. FBS and ABS were checked in each visit and if hypoglycemia was observed the dosage of insulin was decreased to obtain a reasonable level of blood sugar. Insulin dosage was not changed unless hypoglycemia was observed. The patients´ compliance was checked by capsule count. After two months or when the patients' blood sugar levels became stable, they had monthly visits.

Statistical analysis

All values are expressed as mean ± SD. The statistical analysis was performed with SPSS 18. Wilcoxon-signed rank test was used to evaluate the differences among the daily doses of insulin and FBS levels before therapy and 30 months after vanadyl treatment, and also data presented in Tables 2 – 4. Exact P-values are presented for each parameter, and a $P < 0.05$ was considered as statistically significant.

Results

The only side effects of the drug were diarrhea and abdominal pain (in 30% of the cases) during the first two to four weeks of the treatment, and greenish-blue discoloration of stool. Diarrhea and abdominal pain disappeared after decreasing the initial dosage of vanadium and then gradually increasing it to the desired level. There was no dropout due to complication. The hematologic surveys did not show any significant change among the mean values of the measured parameters after 14, 20, and 30 months of vanadyl consumption (Table 2). The results of liver function test (LFT) indicated that long- term vanadyl consumption did not disturb the normal hepatic functions (Table 3). The renal function tests, serum bicarbonate, and pH were in normal range (Tables 3, 4). During 30 months of vanadyl therapy, the mean body mass index (BMI) increased from 17.5 ± 2.4 to 19.7 ± 2.3 kg/m² ($P = 0.001$).

Effects on insulin dosage and FBS

The insulin requirement of the patients decreased by 30% from an initial dose of 37.2 ± 5.5 u/day to 25.8 ± 4.6 u/day ($P = 0.003$) with a concomitant 30% decrease in FBS from 238 ± 19 mg/dL to 152 ± 11 mg/dL ($P = 0.001$).

The ABS also decreased from 250 ± 25 mg/dL to186 ± 20 mg/dL ($P < 0.03$). In two patients the daily insulin requirement decreased to less than 10 u and in one patient BS stayed normal for up to 10 days after insulin withdrawal. In five patients (35%) it

Table 3. Liver function test (LFT) analysis before and during 14, 24 and 30 months vanadyl therapy*

LFT	Before	Treatment			
		14 months	24 months	30 months	P-value
SGOT(AST) (u/L)	31 ± 5	29 ± 5	31 ± 4	27 ± 3	0.172
SGPT(ALT) (u/L)	35 ± 4	33 ± 2	33 ± 4	34 ± 6	0.518
ALK Ph (u/L)	217 ± 36	225 ± 17	235 ± 20	213 ± 34	0.193
Albumin (g/dL)	4.1 ± 0.2	4.5 ± 0.4	4.4 ± 0.4	4.2 ± 0.3	0.061
Globulin (g/dL)	2.3 ± 0.3	2.2 ± 0.3	2.3 ± 0.4	2.6 ± 0.1	0.995

*-Data are presented as mean±SD; N=14.

Table 4. Renal functions, serum pH, and bicarbonate concentrations [$HCO3^-$] before and during 14, 24, and 30 months vanadyl therapy*

Blood chemistry	Before	Treatment			
		14 months	24 months	30 months	P-value
BUN (mg/dL)	15.1 ± 3.3	16.8 ± 2.0	17.5 ± 2.1	15.3 ± 3.2	0.079
Creatinine (mg/dL)	0.8 ± 0.1	0.9 ± 0.2	0.9 ± 0.2	0.8 ± 0.1	0.345
Uric acid (mg/dL)	4.6 ± 0.3	4.8 ± 0.5	4.5 ± 0.5	4.6 ± 0.4	0.250
K (mEq/L)	4.5 ± 0.4	4.4 ± 0.5	4.4 ± 0.4	4.3 ± 0.3	0.406
Na (mEq/L)	136 ± 2	135 ± 2	136 ± 2	137 ± 1	0.139
Ca (mg/dL)	9.5 ± 0.3	9.5 ± 0.1	9.5 ± 0.2	9.7 ± 0.3	0.100
P (mg/dL)	3.3 ± 0.2	3.3 ± 0.3	3.3 ± 0.3	3.3 ± 0.2	0.991
pH	7.379 ± 0.035	-----	-----	7.386 ± 0.029	0.278
[$HCO3^-$] (mEq/L)	23.5 ± 0.6	-----	-----	23.9 ± 0.7	0.208

*-Data are presented as mean±SD; N=14.

was possible to decrease the daily insulin injection to once a day. Most of the changes in insulin requirement and improvement of glucose control occurred during the first three months of the treatment and then it remained stable throughout the study.

Effect on TG and CHL: There was a significant (22%) decrease in total CHL from 232 ± 30 to 180 ± 22 mg/dL (P = 0.02) without a significant change in TG.

Effect of vanadium withdrawal: At the end of the study, vanadium was discontinued. The patients´ blood sugar and insulin requirements remained stable for about one month. Afterward, it was necessary to increase the daily insulin dosage to keep blood sugar level the same as before. After three months, the mean daily requirement of insulin rose from the initial 25.8 ± 17.3 u to 42.5 ± 15.4 u (P = 0.001). After the study, all the patients were followed up as usual and none of them developed any systemic disease.

Discussion

We studied the glucose lowering property and side effects of vanadyl in man over a period of two and a half years. This seems to be the longest human trial with vanadyl therapy. Goldfine, et al. studied the effects of vanadium on five type 1 and five type 2 diabetic patients over two weeks period and showed lower insulin requirement in type 1 and improved glucose metabolism in type 2 diabetics.[19] Halberstam, et al. reported the effects of different doses of vanadium on seven patients with type 2 diabetes and six normal subjects over two weeks period and concluded that vanadium improves the defect in insulin signaling.[20] The safety and the effectiveness of vanadyl therapy were reported in type 2 diabetic patients treated for six weeks by Goldfine and colleagues.[21] The results of our study indicated the safety and efficacy of oral vanadyl sulfate during 30 months period in type 1 diabetic patients. This will hopefully pave the way for further long- term human trials of other vanadium compounds prior to their use as conventional therapy in diabetes. Our study also revealed that the hypoglycemic effect of vanadium persisted for about one month after withdrawal. This phenomenon is similar to animal studies and it has been attributed to the gradual release of vanadium from tissue storage sites or restored insulin secretion.[22]

The toxicity and long- term accumulation of vanadium is a big concern about its therapeutic use in diabetic patients. High doses of vanadium used in animals was associated with diarrhea, decreased food intake, weight loss, hepatotoxicity, and nephrotoxicity.[23] However, many studies have failed to show any detectable histologic changes in tissues such as stomach, heart, lung,[24] and functional changes in the liver and kidney of vanadium- treated animals.[25] Despite earlier concerns about vanadium toxicity, later studies showed that vanadium had an antitumor activity.[26] In our long- term study, as in other short-term human trials[20,21,27,28] there was not any obvious liver and kidney functional changes during two and a half years vanadyl therapy and six years follow-ups. In contrast to animal studies, our patients had a significant increase in BMI which was attributed to better metabolic control. Nausea and diarrhea, the only detected side effects seen during the first or two weeks of vanadyl therapy in some patient, were corrected by temporarily reducing the daily dose of vanadyl, and then gradually increasing it to the desired therapeutic levels.

Although we could not measure the level of vanadyl in the plasma, urine, and stool, but through the greenish-blue discoloration of patients´ stools, the cause of initial diarrhea was the remained significant proportion of vanadium remained in the digestive tract as was the case in experimental animals treated with high doses of vanadium.[29]. Therefore, reduction of daily oral dose of vanadium could be achieved by increasing absorption rate of new products from digestive tract, and retain the therapeutic level of plasma concentration of vanadium. Thus the decreased gastrointestinal side effects of oral vanadium will improve the overall efficacy of vanadium compounds as seen in animal studies.[30,31] Organic vanadium compounds produced for this purpose showed to have a better absorption rate, lower toxicity with promising antidiabetic activity, and no diarrhea in animals.[32]

Limitations of our study: At the time of the study, we could not measure HbA_{1c} and c-peptide to overcome the problems and we had to rely on the repeated measurements of blood sugar.

Long- term use of vanadium is safe and effective. It decreases insulin need and blood sugar. Further studies on the use of vanadium compounds with better absorption and their effects on insulin and c-peptide levels are recommended.

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