Effects of Vanadyl Sulfate on Carbohydrate and Lipid Metabolism in Patients With Non–Insulin-Dependent Diabetes Mellitus

Guenther Boden, Xinhua Chen, Jose Ruiz, George D.V. van Rossum, and Salvatore Turco

The safety and efficacy of vanadyl sulfate (VS) was tested in a single-blind, placebo-controlled study. Eight patients (four men and four women) with non–insulin-dependent diabetes mellitus (NIDDM) received VS (50 mg twice daily orally) for 4 weeks. Six of these patients (four men and two women) continued in the study and were given a placebo for an additional 4 weeks. Euglycemic-hyperinsulinemic clamps were performed before and after the VS and placebo phases. VS was associated with gastrointestinal side effects in six of eight patients during the first week, but was well tolerated after that. VS administration was associated with a 20% decrease in fasting glucose concentration (from 9.3 ± 1.8 to 7.4 ± 1.4 mmol/L, $P < .05$) and a decrease in hepatic glucose output (HGO) during hyperinsulinemia (from 5.0 ± 1.0 pre-VS to 3.1 ± 0.9 μmol/kg · min post-VS, $P < .02$). The improvement in fasting plasma glucose and HGO that occurred during VS treatment was maintained during the placebo phase. VS had no significant effects on rates of total-body glucose uptake, glycogen synthesis, glycolysis, carbohydrate (CHO) oxidation, or lipolysis during euglycemic-hyperinsulinemic clamps. We conclude that VS at the dose used was well tolerated and resulted in modest reductions of fasting plasma glucose and hepatic insulin resistance. However, the safety of larger doses and use of vanadium salts for longer periods remains uncertain.

VANADIUM is a trace element occurring in most mammalian cells in concentrations ranging from 0.1 to 1.0 μmol/L.[1] The main source of vanadium intake is food. In humans, daily intake is estimated to range from 0.2 to 1.4 μmol.[2] The physiological role of vanadium in humans is not known, although it seems to be needed for normal growth and development.[3,4] In recent years, vanadium salts have attracted considerable interest since it was discovered that they exerted insulin-like activities, including stimulation of hexose transport and oxidation, glycogen formation, and lipogenesis in rat skeletal muscle and adipocytes and inhibition of lipolysis in rat adipocytes.[5-8] Of great interest was the observation by Heyliger et al[9] that orthovanadate added to drinking water normalized plasma glucose concentrations in streptozotocin (STZ)-diabetic rats within 4 days without increasing the low plasma insulin concentrations. These results were subsequently confirmed by others.[10] Thus, in vivo animal data suggested that oral administration of vanadate could restore normoglycemia, decrease insulin resistance, and convert a catabolic state into an anabolic state in severely insulin-deficient STZ-diabetic rats without signs of toxicity.[9,10]

The precise mechanisms by which vanadium salts exert these insulin-like activities remained uncertain. Some of the improvement in STZ-diabetic rats appeared to be due to improved β-cell function.[11,12] On the other hand, many in vitro studies have demonstrated that vanadium salts have insulin-like activities of their own.[5-8] However, it has remained controversial as to whether vanadium affects the initial steps in the chain of events leading to insulin action, ie, insulin receptor autophosphorylation and receptor kinase activity, perhaps by inhibiting tyrosine kinase phosphatase activity.[13,14] Other studies have suggested that vanadium salts act via insulin-independent pathways (reviewed in Shechter[13]). In any case, therapeutic use of vanadium salts may be of clinical interest. Vanadium salts, by bypassing some initial dysfunctional steps in the insulin pathway, may be more effective than insulin in treating insulin-resistant diabetic patients. Moreover, the possibility of using vanadium as an "oral insulin" is attractive.

Presently, the literature contains only a limited amount of information with respect to the use of vanadium salts in human diabetes. More than 100 years ago, Lyonnet et al[15] reported a decrease in urinary glucose excretion in two of three diabetic patients given 4 to 5 mg/d sodium vanadate. While this report was in preparation, Goldfine et al[16] reported that Na metavanadate (125 mg/d) improved insulin-stimulated glucose disposal in five patients with non–insulin-dependent diabetes mellitus (NIDDM)[16] and Cohen et al[17] reported that oral use of vanadyl sulfate ([VS] 100 mg/d) improved insulin action on hepatic and peripheral carbohydrate (CHO) metabolism in six patients with NIDDM.

It was the objective of the present study (1) to investigate whether VS orally at a dosage of 100 mg/d improves hepatic and peripheral insulin sensitivity and decreases blood glucose in patients with NIDDM, and (2) to examine its safety. We chose VS because it has been reported to be less toxic than but equally as effective as sodium vanadate.[18]

SUBJECTS AND METHODS

Subjects

Clinical characteristics of eight NIDDM patients who received VS for 4 weeks are shown in Table 1. These characteristics were not significantly different in the group of eight and the subgroup of six subjects (four men and two women) who continued with the study for an additional 4 weeks during which they received placebo.

From the Division of Endocrinology/Diabetes/Metabolism and the General Clinical Research Center, Temple University Schools of Medicine and Pharmacy, Philadelphia, PA.

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Address reprint requests to Guenther Boden, MD, Temple University Hospital, 3401 N Broad St, Philadelphia, PA 19140.

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Table 1. Subject Characteristics

Sex (M/F)	4/4
Age (yr)	53.5 ± 2.6*
Weight (kg)	88.8 ± 8.8*
Height (cm)	168.5 ± 5*
Body mass index (kg/m^2)	31.5 ± 2.0*
Mean NIDDM duration, yr (range)	13.0 (4-20)

*Mean ± SEM.

All patients had been treated with sulfonylurea drugs, and six received, in addition, small doses of intermediate-acting NPH insulin (5 to 15 U) at bedtime. All medications were withheld on the morning of the clamps, but were otherwise continued throughout the study. The patients' body weight was stable for at least 2 months, and their diets contained a minimum of 250 g/d CHO for at least 2 days before the studies. Informed written consent was obtained from all subjects after explanation of the nature, purpose, and potential risks of the studies. The study protocol was approved by the Institutional Review Board of Temple University Hospital.

Experimental Design

All patients were admitted to the General Clinical Research Center at Temple University Hospital the night before the study and underwent a 4-hour euglycemic-hyperinsulinemic clamp the following morning. Thereafter, they received VS (50-mg capsules) and were discharged from hospital. The patients were instructed to take 1 capsule (50 mg) twice each day (with breakfast and dinner) and to continue their usual diet, exercise, and medication regimens and monitor fingerstick glucose concentrations with a glucometer. They returned to the hospital once per week for inspection of the home glucose record and had blood drawn for determination of a complete blood cell count and blood chemistry analysis including liver and kidney function tests and urinalysis. After 4 weeks, the patients were readmitted, the 4-hour clamp was repeated, and VS treatment was discontinued. Six of eight patients agreed to continue with the study. They had a third euglycemic-hyperinsulinemic clamp 2 to 4 weeks after the second clamp, followed by 4 weeks of treatment with placebo capsules (50 mg lactose), followed by a final (fourth) clamp study.

Euglycemic-Hyperinsulinemic Clamps

The studies began at about 8 AM after an overnight fast with the subjects reclining in bed. A short polyethylene catheter was inserted into an antecubital vein for infusion of insulin and glucose. Another catheter was placed into a contralateral forearm vein for blood sampling. This arm was wrapped with a heating blanket (70°C) to arterialize venous blood. Regular human insulin (HumulinR; Eli Lilly & Co, Indianapolis, IN) was infused intravenously at a rate of 6 pmol/kg · min for 4 hours starting at 0 minutes. Glucose concentration was allowed to decrease to approximately 5 mmol/L and was then clamped at that concentration for 2 hours by a feedback-controlled infusion of 20% glucose.

Measurements

Glucose turnover was determined with 3-^{3}H-glucose. The tracer infusion (40 μCi over 1 minute followed by 0.4 μCi/min) was started 90 minutes before initiation of the clamp to ensure isotope equilibration. Glucose was isolated from blood for determination of 3-^{3}H-glucose specific activity as previously described.[19] Changes in specific activity during hyperinsulinemia were avoided by adding 3-^{3}H-glucose to the unlabeled glucose that was infused at variable rates to maintain euglycemia.[20] Rates of total-body glucose appearance (G_{Ra}) and disappearance (G_{Rd}) were calculated using Steele's equation for steady-state conditions.[21]

Glycolytic flux was determined according to the method reported by Rossetti and Giaccari[22] with minor modifications. Tritium in the 3-carbon position of glucose is lost into water during glycolysis. We have recently validated the assumption that the rate of tritiated water formation in plasma reflects the intracellular detritiation of 3-^{3}H-glucose.[23] The rate of glycolysis was obtained by dividing the whole-body ^3H_2O production rate by the specific activity of its precursor, ie, plasma 3-^{3}H-glucose.

Whole-body glycogen synthesis rates were obtained by subtracting rates of glycolysis from rates of glucose uptake (G_{Rd}). We have documented the validity of this noninvasive approach.[23,24]

CHO oxidation was determined by indirect calorimetry[25] with a metabolic measurement cart (Beckman, Palo Alto, CA). Rates of protein oxidation were estimated from urinary N excretion after correction for changes in urea N pool size.[26] Rates of protein oxidation were used to determine the nonprotein respiratory quotient.

Hepatic glucose output (HGO) was calculated as the difference between G_{Ra} and the rate of glucose infused to maintain euglycemia during the clamps.

Glycerol turnover was determined with $^2H_5$-glycerol by gas chromatography—mass spectrometry as described previously.[27] Enrichment of $^2H_5$-glycerol was at steady state during the last 2 hours of the clamps. Turnover rates were therefore calculated using steady-state equations corrected for the amount of infused isotope.[28] Rates of lipolysis were calculated as $\text{glycerol}_{Ra} \times 3$.[27]

Plasma glucose level was measured with a glucose analyzer (Beckman Instruments, Palo Alto, CA). Serum insulin was determined by radioimmunoassay (RIA)[29] after deproteinization with polyethylene glycol,[30] using a RIA with minimal cross-reactivity with proinsulin (<0.2%; Linco, St. Charles, MO). Blood urea nitrogen[31] was determined colorimetrically. Urinary nitrogen level was measured by the method of Kjeldahl.[32] Fatty acids were determined according to the method used by Lorch and Gey,[33] after extraction as described by Dole and Meinertz.[34]

Serum vanadium levels were measured according to the method of Mongold et al.[35] Briefly, samples of test serum were dried at 105°F. Vanadium was then extracted from the dried samples with 0.1N HNO_3 overnight at room temperature; this extraction procedure produced results not significantly different from those obtained by hot-ashing with concentrated HNO_3-H_2SO_4. Ten-microliter aliquots of extracts from test serum and standards (vanadium pentoxide) were assayed for vanadium with a Perkin-Elmer atomic absorption spectrophotometer (model 3030, Norwalk, CT) equipped with a graphite furnace.

Statistical Analysis

Statistical significance was assessed by ANOVA with repeated measures and a paired *t* test, where applicable.

RESULTS

Adverse Effects of VS

To determine how well the drug was tolerated, patients were questioned about adverse effects during their weekly visits to the hospital. Two of eight patients experienced no side effects. Four complained of diarrhea (three to six loose bowel movements per day), which was associated with abdominal cramps in three and flatulence in one. One patient complained only of flatulence and another of slight nausea. In one patient, diarrhea and abdominal cramps

lasted for 11 days; in the others, all symptoms disappeared during the first week of drug use.

Vanadium Absorption and Blood Levels

Approximately 2 months before the VS treatment, serum vanadium levels were measured in the morning after an overnight fast in three of the study subjects before and then for 24 hours after oral administration of 100 mg VS. Before administration of VS, serum vanadium concentrations were barely detectable (0.2 to 0.4 μmol/L, or 10 to 20 ng/mL). After VS administration, vanadium levels increased starting at about 2 hours, reaching a peak of 3.3 ± 0.6 μmol/L (167 ± 32 ng/mL) at approximately 8 hours. After that, levels declined with a calculated $t_{1/2}$ of approximately 18 hours and remained elevated (1.7 ± 0.7 μmol/L, or 83 ± 35 ng/mL) after 24 hours (Fig 1).

Effect of VS on Fasting Plasma Glucose

The higher pre-VS versus preplacebo glucose levels (9.3 ± 1.8 *v* 6.7 ± 1.4 mmol/L) were caused by the two patients who did not continue in the placebo trial and who had very high plasma glucose levels. Treatment with VS for 4 weeks was associated with a decrease in fasting plasma glucose in six of eight subjects (mean plasma glucose decreased from 9.3 ± 1.8 to 7.4 ± 1.4 mmol/L, −20%, $P < .05$). During placebo treatment, fasting plasma glucose remained essentially unchanged (6.7 ± 1.4 *v* 7.1 ± 1.6 mmol/L, NS) (Fig 2).

Euglycemic-Hyperinsulinemic Clamps

Plasma glucose was clamped for 2 hours at 4.8 ± 0.2 mmol/L before and 4.7 ± 0.1 mmol/L after VS. Respective values preplacebo and postplacebo were 4.8 ± 0.2 and 5.0 ± 0.2 mmol/L. Postabsorptive serum insulin concentrations were 232 ± 50 and 209 ± 39 pmol/L (NS) pre- and post-VS, respectively, and 145 ± 15 and 138 ± 27 pmol/L (NS) preplacebo and postplacebo, respectively. Serum insulin was clamped at 767 ± 49 pmol/L before and a 758 ± 72 pmol/L after VS. Respective values preplacebo and postplacebo were 795 ± 123 and 733 ± 117 pmol/L.

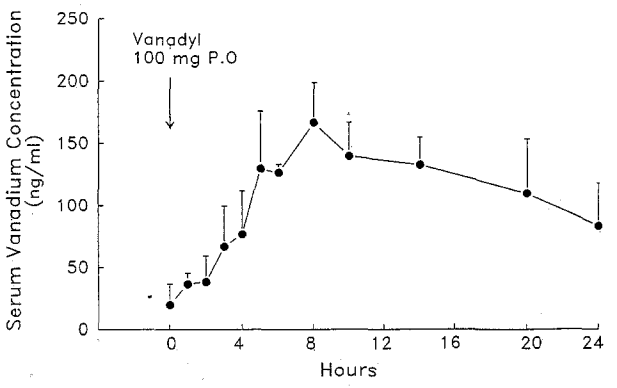

Fig 1. Serum vanadate concentration before (0 minutes) and after oral intake of 100 mg VS in 3 patients with NIDDM. Results are the mean ± SE.

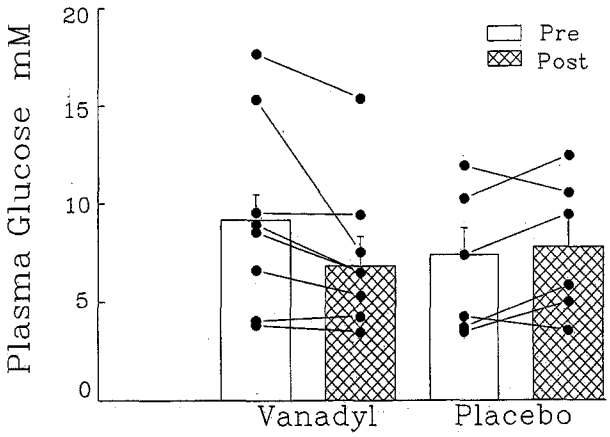

Fig 2. Plasma glucose concentration pretreatment and posttreatment with VS (100 mg/d) or placebo for 4 weeks. $P < .05$, pre- *v* post-VS.

Effect of VS on HGO

During hyperinsulinemia, HGO was slightly but significantly less suppressed before VS treatment (from 13.9 ± 1.9 to 5.0 ± 1.0 μmol/kg min, −64%) than after (from 12.6 ± 2.2 to 3.1 ± 0.9 μmol/kg min, −75%). Greater insulin-induced suppression of HGO after VS was seen in seven of eight patients and was statistically significant ($P < .02$). In contrast, insulin-induced suppression of HGO was the same before and after placebo treatment (Fig 3).

Effect of VS on Glucose Uptake and Intracellular Glucose Utilization

Basal rates of glucose uptake (G_{Rd}), glycolysis, and CHO oxidation and rates of G_{Rd}, glycolysis, glycogen synthesis, and CHO oxidation during euglycemic-hyperinsulinemic clamping were virtually identical before and after VS treatment, and were not different from the respective rates determined before and after placebo treatment. Basal rates of glycogen synthesis were higher before VS than after (6.0 ± 2.1 *v* 0.9 ± 2.4 μmol/kg min, $P < .05$), presumably

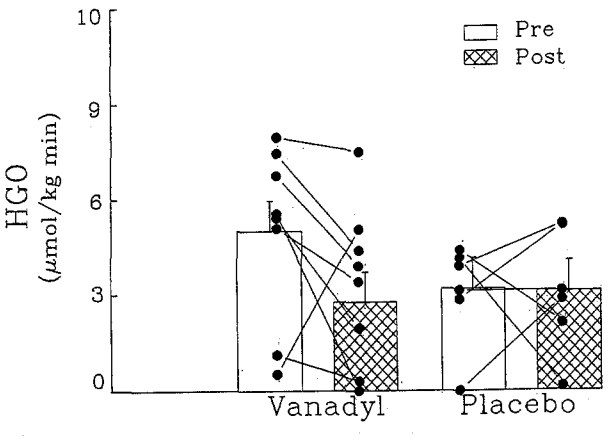

Fig 3. Rates of HGO pre- and post-VS (n = 8) or placebo (n = 6) in patients with NIDDM. Results are the mean ± SE and individual values obtained after 2 hours of euglycemic hyperinsulinemia. Pre- and post-VS, $P < .02$.

due to higher fasting glucose concentrations pre-VS (Table 2).

Effects of VS on Lipolysis and Plasma FFA

Basal rates of lipolysis and plasma FFA concentrations before and after VS or placebo treatment were not significantly different from each other. During euglycemic-hyperinsulinemic clamping, lipolysis and plasma FFA both decreased, but there were no significant differences in lipolysis rates and plasma FFA concentrations when comparing pre- and post-VS or preplacebo and postplacebo groups (Table 3).

DISCUSSION

One objective of the study was to assess the safety of oral administration of 100 mg VS for 1 month in patients with NIDDM. We found that six of eight patients experienced adverse effects, all gastrointestinal (diarrhea, abdominal cramps, flatulence, and nausea). These side effects were transient and disappeared by the end of the first week in all except one patient, in whom they lasted for 11 days. No abnormalities were detected during weekly blood tests (including liver function tests, complete blood cell counts, electrolytes, and urinalysis). Hence, VS at the dose given appeared to be fairly well tolerated, confirming the experience of others who have given this drug to human subjects.[16,17,36] However, there is much less information relative to the long-term effects of vanadium salts in humans. Somerville and Davies[37] treated 10 patients with coronary artery disease with 125 mg/d diammonium oxy-tartrato vanadate for about 5 months. Five patients experienced persistent abdominal pain, anorexia, and weight loss. These symptoms improved in three patients when the dose was reduced. In the other two patients, the drug had to be discontinued after 4 months. An additional concern with long-term vanadium use is its known accumulation in many organs, including the kidneys, liver, lungs, and bone.[2]

The main study objective was to determine whether VS could decrease insulin resistance and glucose levels in patients with NIDDM. We found that mean fasting plasma glucose concentrations decreased by 20% (from 9.3 to 7.4 mmol/L, $P < .05$; Fig 2) during VS therapy, but remained unchanged during placebo treatment (from 6.7 to 7.1 mmol/L, NS). Similar results have recently been reported by Cohen et al,[17] who found a 15% decrease in fasting plasma glucose concentrations (from 11.7 to 10.0 mmol/L) in six patients with NIDDM after 3 weeks of therapy with 100 mg VS.

To determine whether VS could improve the insulin resistance in these patients, we measured HGO, peripheral glucose uptake, and intracellular utilization (glycogen synthesis, glycolysis, and CHO oxidation), as well as lipolysis and plasma FFA levels during euglycemic-hyperinsulinemic clamping. In these studies, plasma glucose and insulin levels were clamped, FFA levels were suppressed, and VS treatment was the only known variable.

Before VS, rates of HGO were abnormally high (compared with rates in normal subjects[24]) after 4 hours of insulin infusion (the last 2 hours at euglycemia) in six of eight patients (Fig 3). After 4 weeks of VS, insulin-suppressed HGO had declined in seven of eight patients.

The improvement in suppression of HGO during VS treatment was maintained during the placebo phase. Similar prolonged effects after discontinuation of vanadium treatment have been observed in rats[11] and humans.[17] This phenomenon should be explored further, since it may permit long-term treatment with intermittent administration of vanadium salts without loss of efficacy.

It has been suggested that the glucose-lowering effect of vanadium in STZ-diabetic rats could be explained by its hypophagic effect.[38] However, loss of appetite did not seem to be a problem in our patients, who were specifically questioned about anorexia and who gained weight, if anything (88.8 *v* 89.9 kg pre- *v* post-VS, respectively, NS).

In contrast to its effect on HGO, VS had no significant effects on insulin stimulation of glucose uptake (26.7 ± 4.8 *v* 28.0 ± 5.3 μmol/kg min, NS) or on intracellular glucose utilization (Table 2). Pre- and post-VS rates of glycogen synthesis (14.0 ± 2.6 *v* 14.9 ± 3.5 μmol/kg min, NS), glycolysis (12.7 ± 2.6 *v* 13.9 ± 2.0 μmol/kg min, NS), and CHO oxidation (5.0 ± 0.9 *v* 9.2 ± 1.5 μmol/kg min, NS) were not different. Cohen et al[17] have reported small but significant increases in insulin-stimulated glucose uptake and glycogen synthesis after VS. The reason for the difference between

Table 2. CHO Metabolism (μmol/kg · min)

	Pre-VS	Post-VS	Preplacebo	Postplacebo
Glucose uptake (G_{Rd})				
Basal	15.9 ± 2.0	12.9 ± 1.9	10.5 ± 1.0	9.3 ± 1.2
Clamp	26.7 ± 4.8	28.0 ± 5.3	22.7 ± 5.7	23.2 ± 8.4
Glycogen synthesis				
Basal	6.0 ± 2.1 $P < .05$	0.9 ± 2.4	0.8 ± 2.0	0.0 ± 1.8
Clamp	14.0 ± 2.6	14.9 ± 3.5	10.1 ± 3.2	10.7 ± 2.7
Glycolysis				
Basal	10.0 ± 1.0	11.9 ± 1.5	9.8 ± 1.4	10.3 ± 1.5
Clamp	12.7 ± 2.6	13.9 ± 2.0	12.6 ± 2.6	12.5 ± 2.9
CHO oxidation				
Basal	1.8 ± 0.9	2.9 ± 0.9	4.9 ± 2.6	3.9 ± 1.3
Clamp	5.0 ± 0.9	9.2 ± 1.5	11.1 ± 2.7	9.7 ± 3.3

NOTE. Results are the mean ± SEM.

Table 3. Lipid Metabolism

	Pre-VS	Post-VS	Preplacebo	Postplacebo
Lipolysis (μmol/kg · min)				
Basal	4.74 ± 0.75	5.07 ± 1.35	4.91 ± 0.81	5.11 ± 0.88
Clamp	3.17 ± 0.59*	2.93 ± 0.58*	3.17 ± 0.89‡	3.22 ± 0.62*
FFA (μmol/L)				
Basal	672 ± 102	562 ± 53	667 ± 95	643 ± 98
Clamp	179 ± 37†	104 ± 26†	135 ± 36†	90 ± 28†

NOTE. Results are the mean ± SE.
*$P < .05$.
†$P < .01$: basal *v* clamp.
‡Not significant.

their findings and our findings is not entirely clear, but may be related to the fact that their patients were more insulin-resistant than ours (glucose uptake after 3 hours of hyperinsulinemia was ~21 in their patients *v* ~27 μmol/kg · min in our patients after only 2 hours). In addition, Goldfine et al[16] have reported that 125 mg/d sodium metavanadate given orally for 2 weeks to five patients with NIDDM improved glucose metabolism (M) during euglycemic-hyperinsulinemic clamping. Glucose disposal increased by 29% with the 0.5-mU/kg · min insulin dose (from 9.4 ± 2.2 to 12.2 ± 1.7 μmol/kg · min, $P = .05$) and nonsignificantly with the 1.0-mU/kg · min insulin dose (from 22.8 ± 5.6 to 31.7 ± 7.2 μmol/kg · min, $P < .08$) and did not change significantly in five patients with IDDM.[16] Since this study was not placebo-controlled, it is difficult to be certain that the observed modest improvement in M (glucose uptake − HGO) was due to an increase in glucose uptake caused by vanadate. Nevertheless, our data, together with the two other published studies,[16,17] suggest that vanadium salts exert some insulin-like activity in humans while having only modest side effects.

However, it is obvious that the magnitude of the reported in vivo effects of vanadium in humans are modest compared with the striking effects reported in diabetic animals.[9-12] There are several possible explanations for these differences, including differences in vanadium blood levels and species-specificity of the insulin-like activity of vanadium. In three of our patients in whom blood levels were tested, peak serum vanadium concentration increased to 110 to 220 ng/mL (2.2 to 4.4 μmol/L) after oral intake of 100 mg VS (Fig 1). Cohen et al[17] reported serum vanadium levels of 73.3 ± 22.4 ng/mL (1.5 ± 0.4 μmol/L) after administration of the same amount of VS for 3 weeks, whereas Goldfine et al[16] reported a mean serum vanadium level of 142 ± 40.6 ng/mL (2.8 μmol/L) in five patients with NIDDM who received 125 mg sodium metavanadate for 2 weeks. By comparison, blood levels of vanadium that improved glucose tolerance in obese Zucker fa/fa rats were approximately 1,000 ng/mL,[39] and whole-blood vanadium levels that decreased blood glucose in STZ-diabetic rats were between 700 and 800 ng/mL,[10] ie, several times higher than the reported effective concentration in human patients.[16,17]

The relatively low vanadium blood levels (Fig 1) can also explain why patients tolerated this compound reasonably well without signs of systemic toxicity. (The observed gastrointestinal discomfort, increased flatulence, or mild diarrhea may have been caused by local irritation of the gastrointestinal mucosa.) In contrast, serious toxicity problems with vanadium have been recognized in rats.[4,9,10,18] For instance, sodium vanadate given to rats in doses of 0.6 to 0.8 mg/mL (12 to 16 mmol/L) in the drinking water, producing blood levels of about 1.2 μg/mL (~24 μmol/L), "was ultimately fatal".[10] Moreover, small amounts of vanadium given intravenously or intraperitoneally have been shown to be extremely toxic.[40,41]

Another reason for the differences in the human and animal experience with vanadium salts may be species-specificity of the insulin-like activities of vanadium. As shown by Lonnroth et al[42] and our laboratory,[43] 1 mmol/L sodium vanadate produced maximal glucose uptake in isolated rat adipocytes, whereas concentrations up to 10 mmol/L were ineffective in human adipocytes. It is presently not known whether similar species-specificity is present in muscle. Nevertheless, the unresponsiveness of human fat cells to vanadate raises the possibility that vanadium salts may be less effective in human subjects than in rats, even at higher and presumably more toxic blood levels.

In summary, VS (100 mg/d) given orally for 4 weeks to eight patients with NIDDM was associated with transient gastrointestinal side effects but otherwise well tolerated. It decreased fasting plasma glucose concentrations by 20% and decreased hepatic insulin resistance (presumably by improving insulin-mediated suppression of HGO), but had no significant effects on peripheral (muscle) insulin resistance, neither with respect to glucose uptake and intracellular glucose utilization nor with respect to lipolysis.

The effects of long-term (>1 month) administration of VS, relative both to decreasing blood glucose and to adverse effects, need to be explored very carefully before this compound can be considered for use in diabetic patients.

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