Kinetic analysis and comparison of uptake, distribution, and excretion of $^{48}$V-labeled compounds in rats

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Setyawati, I. A., K. H. Thompson, V. G. Yuen, Y. Sun, M. Battell, D. M. Lyster, C. Vo, T. J. Ruth, S. Zeisler, J. H. McNeill, and C. Orvig. Kinetic analysis and comparison of uptake, distribution, and excretion of $^{48}$V-labeled compounds in rats. J. Appl. Physiol. 84(2): 569–575, 1998.—Vanadium has been found to be orally active in lowering plasma glucose levels; thus it provides a potential treatment for diabetes mellitus. Bis(maltolato)oxovanadium(IV) (BMOV) is a well-characterized organovanadium compound that has been shown in preliminary studies to have a potentially useful absorption profile. Tissue distributions of BMOV compared with those of vanadyl sulfate (VS) were studied in Wistar rats by using $^{48}$V as a tracer. In this study, the compounds were administered in carrier-added forms by either oral gavage or intraperitoneal injection. Data analyzed by a compartmental model, by using simulation, analysis, and modeling (i.e., SAAM II) software, showed a pattern of increased tissue uptake with use of $^{48}$V-BMOV compared with $^{48}$VS. The highest $^{48}$V concentrations at 24 h after gavage were in bone, followed by kidney and liver. Most ingested $^{48}$V was eliminated unabsorbed by fecal excretion. On average, $^{48}$V concentrations in bone, kidney, and liver 24 h after oral administration of $^{48}$V-BMOV were two to three times higher than those of $^{48}$VS, which is consistent with the increased glucose-lowering potency of BMOV in acute glucose lowering compared with VS.

vanadium; compartmental modeling; simulation, analysis, and modeling software; diabetes; insulin mimic

Despite its ubiquitous presence in mammalian tissues (26), vanadium is an ultratrace element, the essentiality of which has not yet been conclusively demonstrated. Homeostatic mechanisms ensure low levels of absorption of dietary vanadium (30) and rapid clearance of vanadium from the bloodstream (31). Numerous studies have demonstrated the insulin-mimetic actions of vanadium both in vitro and in vivo (for reviews, see Refs. 27, 29, and 35). The most common physiologically relevant ions of vanadium are vanadate [$\text{V}\text{O}_4^{3-}$; $\text{V}$($\text{IV}$)] and vanadyl [$\text{VO}^{2+}$; $\text{V}$($\text{V}$)] (8). In vitro, $\text{VO}_3^-$ and/or $\text{VO}^{2+}$ has been shown to increase glucose uptake and to stimulate glycogen synthesis in rat diaphragm, liver, and fat cells (39), to enhance glucose transport and oxidation in rat adipocytes and skeletal muscle (9, 15, 34), and to inhibit lipolysis (16) and activate lipogenesis (36) in rat adipocytes.

A key advantage of vanadium over insulin is its effectiveness when administered orally (20). Unfortunately, poor absorption from the gastrointestinal (GI) tract into the blood, coupled with doses close to toxic levels for glucose- and lipid-lowering effects, has hampered efforts to develop vanadium compounds as therapeutic adjuncts for treatment of diabetes mellitus (19, 29, 33). Although both $\text{VO}^{2+}$ (10) and $\text{VO}_3^-$ (17) have recently shown positive results in limited clinical trials in humans, the search is underway for better absorbed and less toxic vanadium compounds (27).

One such compound that has been synthesized in our laboratories and has undergone extensive testing over the last several years is bis(maltolato)oxovanadium(IV) (BMOV) (Fig. 1) (25). BMOV can be readily synthesized (7) by combining vanadyl sulfate (VS) and maltol (3-hydroxy-2-methyl-4-pyrole), an approved food additive in both Canada and the US. Potentially useful properties of BMOV include significant water solubility, neutral charge, and lipophilicity, a combination designed to enhance GI absorption, probably through a passive diffusion process. BMOV is effective in lowering blood glucose at a lower dose than VS and does not show evidence of toxicity over a 6-mo period of administration in streptozotocin-diabetic rats (13, 42). Both oral gavage and intraperitoneal (ip) administrations indicate that BMOV is two to three times more potent than its parent compound, VS, in bringing about acute glucose lowering in this experimental model of insulin-dependent diabetes (41).

Because BMOV displays favorable chemical and physiological properties, we were interested in its biodistribution after oral or ip administration. To this end, we prepared BMOV and VS, each containing $^{48}$V as a tracer. $^{48}$V has a half-life of 16 days and decays to nonradioactive $^{48}$Ti by means of positron and gamma emission ($\gamma = 511, 983, 1,312$ KeV). $^{48}$V was isolated as non-carrier-added $^{48}$VS (43); the compounds used in these biodistribution studies were carrier-added $^{48}$VS and $^{48}$V-BMOV. Incorporation of $^{48}$V into both BMOV and VS permitted direct comparison of the uptake and tissue distribution characteristics of these two compounds. Previous studies have looked at biodistributions after intratracheal, intragastric, or intravenous (iv) administration of $^{48}$V-radiolabeled tracers over periods of several days to several weeks (21, 31, 40). In our study, early time points were emphasized to elucidate the curve of uptake, and comparison of the two compounds over a period of 24 h permitted prediction of kinetic parameters in a variety of tissues.

To gain an integrated picture of whole body vanadium biolocalization, compartmental analysis of the tracer data was undertaken (5). An existing compartmental model of vanadium metabolism (28) was used as a starting point for model construction by using
simulation, analysis, and modeling (SAAM II) software (SAAM Institute, Seattle, WA) (4).

MATERIALS AND METHODS

Three sets of experiments were run: an initial oral gavage (experiment A), a second oral gavage experiment in which excreta were collected (experiment B), and an ip set (experiment C).

Animals and diets. Male Wistar rats (University of British Columbia Animal Care Unit, Vancouver, BC), weighing between 190 and 220 g, were housed in polycarbonate cages. During experiments A and C, rats were housed three per cage. For experiment B, animals were transferred to individual metabolic cages immediately after administration of the compound. These cages were equipped with fecal and urinary collection containers. The animals were kept in a room maintained at 22–25°C in a 12:12-h light-dark cycle and were cared for in accordance with the principles and guidelines of the Canadian Council on Animal Care. A commercial diet (Purina rat chow, Ralston Purina, St. Louis, MO) and tap water were offered ad libitum for several days before and throughout the experimental period.

Materials. Maltol was purchased from Sigma Chemical (St. Louis, MO) or Pfizer (Veltol, New York, NY), and VOSO$_4$·3H$_2$O was from Aldrich Chemical (Milwaukee, WI). With the exception of drinking water, all water was deionized (Barnstead D8902 and D8904 cartridges) and distilled (Corning MP-1 Megapure Still). $^{48}$V, in the form of non-carrier-added $^{48}$VS, was prepared as described in Zeisler and Ruth (43).

Preparation of carrier-added $^{48}$V-labeled complexes. In the initial oral and ip experiments (experiments A and C, respectively), carrier-added $^{48}$VS was prepared by mixing an appropriate volume of $^{48}$VS (in 0.01 M H$_2$SO$_4$) with 0.2 mmol (50 mg) of VOSO$_4$·3H$_2$O. Immediately before administration of the solution, the pH was adjusted to between 3.5 and 4 by dropwise addition of 1 M NaOH. The total volume was then increased to 12 ml with the addition of water.

In the preparation of $^{48}$V-BMOV in the subsequent oral gavage administration (experiment B), 0.08 mmol (18 mg) of VOSO$_4$·3H$_2$O and 4 eq of maltol were mixed in water. After dissolution of the solid, 0.8 ml of 0.2 M NaOH was added dropwise over a 10-min period. To this mixture was added an appropriate amount of ($^{48}$VS (0.005 M H$_2$SO$_4$). The pH of the solution was finally adjusted to between 3.5 and 4 with 0.2 M NaOH before gavage. $^{48}$VS in experiment B was prepared by dissolving 0.07 mmol (15 mg) of VOSO$_4$·3H$_2$O and $^{48}$VS (0.005 M H$_2$SO$_4$) in water. The pH of this solution was adjusted to 4 by adding 0.2 M NaOH.

Biodistribution studies. In experiment A, $^{48}$V-BMOV (3.8 mg V) or $^{48}$VS (2.6 mg V), 0.012 mmol/animal and containing 200 µCi/animal of each compound, was administered by oral gavage. In experiment C, $^{48}$V-BMOV (1.9 mg V) or $^{48}$VS (2.2 mg V), 0.006 and 0.010 mmol/animal, respectively, and containing 100 µCi $^{48}$V for BMOV/rat or 150 µCi $^{48}$VS for VS/rat, was administered by ip injection. In these two experiments (A and C), rats (n = 3/time point) were euthanized, and tissue and blood samples were collected at time points of 15 and 30 min and 1, 4, and 24 h after administration. In experiment B, $^{48}$V-BMOV (3.2 mg V, 0.010 mmol) or $^{48}$VS (2.0 mg V, 0.009 mmol), containing 170 or 50 µCi of $^{48}$V/rat, respectively, was administered, also by oral gavage. Collection times in experiment B were 2, 6, 10, 14, 19, and 24 h after administration.

At each time point in all studies, three rats were anesthetized with halothane, blood was obtained from the carotid artery, and the anesthetized animals were then killed by cervical dislocation. Tissues were collected and placed in preweighed receptacles. Liver, kidney, muscle, spleen, lung, testicle, bone, heart, and brain samples were rinsed in normal saline, weighed, and blotted dry before freezing. In the second oral gavage study (experiment B), urine, fecal, stomach, and GI tissue samples were also collected. All tissue samples were stored frozen at –20°C until counted for $^{48}$V activity. The activity was recorded in a well gamma counter (Canberra Packard, Cobra II, Auto-gamma/3-in. crystal). The percentage of administered dose (%AD) was calculated as a fraction of the “standard counts” for that time period, determined by counting the equivalent volume of radiolabeled solution with the same set of samples (Fig. 2, as %AD/organ). In this carrier-added study, calculating %AD corrects for variation of two to three times in the amount of $^{48}$V and even a small variation in the dose of cold vanadium. The total blood (7.8% of body wt), bone (12% of body wt), and muscle (45% of body wt) masses were calculated according to reported methods (24).

Kinetic modeling. Simulation of $^{48}$V uptake, distribution, and excretion was carried out by using SAAM II software (version 1.0.2) (4, 5). Data, in %AD/g tissue, from the initial oral gavage study (experiment A) were used to modify a model of vanadium metabolism published previously (28). The fractional transfer coefficients ($k_{ij}$), where $i$ and $j$ are compartments, derived from experiment A were then used as a starting point for modeling the data from the second oral gavage study (experiment B). Initial values were varied by iteration until a consistent set of parameters was obtained for each compound, with the greater variability of the second data set for each compound tested having been accounted for. Experiment C, with the highest overall coefficient of variation (CV; 0.9), was modeled last as an extension of the combined oral gavage studies, according to a previously established paradigm (37). In accordance with standard modeling nomenclature (14), $k_{ij}$ represents the fraction of material moving from compartment $j$ to compartment $i$ per unit time (h). Residence time is equivalent to the inverse of $k_{ij}$ for those compartments having only one egress; for blood, residence time is defined as 1/$k_{ij}$, where compartment 1 represents blood (Fig. 3) (22). Absorption of vanadium 24 h postadministration was calculated as (intake − fecal excretion) as a percentage of administered oral dose (22).

RESULTS

Overall, for oral administration the highest concentrations of $^{48}$V (expressed as %AD/g wet wt of tissue) were seen in kidney, followed by bone, blood, liver,
The concentrations in the above tissues did not exceed 0.6 %AD/g at any one time point. In most other tissues, 48V concentration did not exceed 0.1 %AD/g of oral dose. The concentration of 48V in bone exceeded that of kidney at 24 h after oral gavage. CVs for experiment B were considerably higher than those for experiment A (average CVs of 0.3 and 0.5 for experiments A and B, respectively). Ip injection of 48V-labeled compounds (experiment C) resulted in a higher apparent uptake in kidney and bone (not exceeding 1.6 %AD/g tissue), with little change in uptake for most other tissues between 4 and 24 h after injection, compared with either of the oral gavage experiments. The relative concentrations of 48V in bone and kidney exceeded that of kidney at 24 h after oral gavage. CVs for experiment B were considerably higher than those for experiment A (average CVs of 0.3 and 0.5 for experiments A and B, respectively). Ip injection of 48V-labeled compounds (experiment C) resulted in a higher apparent uptake in kidney and bone (not exceeding 1.6 %AD/g tissue), with little change in uptake for most other tissues between 4 and 24 h after injection, compared with either of the oral gavage experiments.

Fig. 2. Average tissue distribution of 48V in rats (n = 3 for each time point) after administration of 48V-BMOV (A and C) or vanadyl sulfate-48 (48VS; B and D) by oral gavage, in %administered dose/organ or tissue (on the assumption that bone mass is 12% of body wt, muscle mass is 45% of body wt, and that these values, together with individual organ weights, were used to calculate total 48V content from radioactivity (counts·min⁻¹·g tissue⁻¹) in representative samples from each tissue).

Fig. 3. Compartmental model of vanadium metabolism. Ovals are kinetically homogeneous and distinct compartments; nos., compartment nos. in mathematical model; arrows, transfer pathways; tissues, combination of soft organ tissues (heart, lung, brain, pancreas, and muscle). Sampling sites included in construction of model were liver, kidney, bone, and testes. Blood, urine, and fecal data were used to verify model. GIₐ and GIₐb, equivalent gastrointestinal compartments.

1 For tables of overall data from experiments A–C, order NAPS Document 05438 from NAPS, c/o Microfiche Publications, PO Box 3513, Grand Central Station, New York, NY 10017.
after ip administration were also considerably higher than those after an oral dose (see below).

Soft tissue uptake from oral gavage of $^{48}$VS and $^{48}$V-BMOV, as %AD/organ (Fig. 2), on the basis of average total tissue or organ weights, was greatest overall in liver > kidney > spleen > heart > testes > lung. The highest $^{48}$V content at 24 h after oral gavage was seen in bone, liver, and kidney (Fig. 2); however, muscle also took up appreciable amounts of $^{48}$V (Fig. 2) because of the high percentage of body weight (45%) represented by muscle.

A 13-compartment model (including urinary and fecal "sinks") adequately described the data for both $^{48}$V-BMOV and $^{48}$VS carrier-added doses by oral gavage (Fig. 3). High variation in the data, both within data sets and between experiments A and B, precluded a more complex model (14). Hence, the tissues represented (see Fig. 3) were chosen on the basis of previous studies showing uptake into these tissues (12). Remaining tissues sampled (heart, brain, spleen, lung, pancreas, and muscle) were included in a "lumped" compartment, labeled as compartment 7. A kinetic heterogeneity in kidney was apparent, with the data fitting best to a two-compartment kidney. The three-compartment GI represents a delay between oral input and fecal output and does not signify physiological differences between these compartments (38).

Compartmental analysis revealed a pattern of increased uptake from an oral dose of $^{48}$V-BMOV compared with that of $^{48}$VS. The greatest difference in uptake was seen in liver, which had a four times greater uptake of $^{48}$V-BMOV relative to $^{48}$VS. The schematic of the model (Fig. 3) shows oral input proceeding through a three-compartment GI, with absorbed $^{48}$V taken up into the blood and from there being distributed to short- and long-stay tissues. Unabsorbed $^{48}$V was excreted via the feces, whereas excretion of absorbed $^{48}$V was via the urine through the second kidney compartment. Recirculation of $^{48}$V is possible through both biliary secretion from the liver and resecretion back to blood from the second kidney compartment. Simulations of tracer disappearance by using the combined data sets, in %AD/g tissue, are presented in Fig. 4 ($^{48}$VS and $^{48}$V-BMOV). Most tissues showed a gradual uptake, peaking at 2–6 h after gavage, with a decline thereafter; however, bone, liver, and kidney uptakes remained high at 24 h, indicating continued accumulation or slow clearance.

Apparent absorption of $^{48}$V-BMOV was greater than that of $^{48}$VS. The primary route of elimination was via the feces. On the basis of compartmental analysis of combined data sets (experiments A and B), 75% of $^{48}$VS and 62% of $^{48}$V-BMOV were excreted unabsorbed in the feces within 24 h after oral gavage. Although the time frame of this experiment was too short to accurately determine absorption, the model-predicted apparent vanadium absorption was 25% for $^{48}$VS and 38% for $^{48}$V-BMOV. These values are most likely a considerable overestimate of vanadium absorption because they are based on estimates from 24-h data sets only. The model-predicted absorption values were adequate to indicate a trend toward greater absorption of $^{48}$V-BMOV compared with $^{48}$VS, ~1.5 times greater.

The bone-to-kidney-to-liver ratios of $^{48}$V concentrations (in %AD/g) 24 h after oral gavage predicted by the model were 0.326:0.116:0.082 for $^{48}$V-BMOV and
Residence times of $^{48}\text{V}$ (and the fractional transfer coefficients on which they were based) for the tissues modeled are given in Table 2. The shortest residence times were in blood; the longest in bone. Residence times in blood were calculated to be 7 min for $^{48}\text{V}$-BMOV and 5 min for $^{48}\text{V}$S; in bone, residence times of 31 days for $^{48}\text{V}$-BMOV and 11 days for $^{48}\text{V}$S were calculated.

**DISCUSSION**

These results clearly demonstrate the increased tissue uptake from an oral dose of $^{48}\text{V}$-BMOV compared with that of $^{48}\text{V}$S. This is in accordance with comparisons in tissue uptake between iron sulfate and the iron maltol complex, tris(maltolato)iron(III) (2, 3, 23). These studies have shown that, by forming a stable, neutral complex with Fe$^{3+}$, maltol enhanced Fe$^{3+}$ absorption across the rat small intestine in vivo and that not only was the Fe$^{3+}$ held in soluble form but it was also efficiently carried into the mucosa. At the same time, regulatory processes to prevent Fe$^{3+}$ overload were not bypassed. In our study, complexation of labeled vanadium(IV) with maltol resulted in enhanced uptake and slower excretion of $^{48}\text{V}$-BMOV compared with $^{48}\text{V}$S (Fig. 4, Tables 1 and 2). Absorption was also greater with $^{48}\text{V}$-BMOV than with $^{48}\text{V}$S. This greater absorption and tissue uptake are also consistent with the increased pharmacological potency in lowering in vivo blood glucose levels seen previously (41).

The long residence time of $^{48}\text{V}$ in bone (11.1 days with use of $^{48}\text{V}$S and 31.3 days with use of $^{48}\text{V}$-BMOV) predicted by our model is in agreement with earlier studies (1, 28). Subcutaneous injection of rats with $^{48}\text{V}$-VO$_3^-$ (1.8 mg V/kg) analyzed with a two-compartment model for each tissue (1) predicted a half-life for bone of 376 h (15.6 days), which would be equivalent to a residence time of 22.6 days ($t_{1/2} = \ln 2/RT$, where RT is residence time). Prediction of a previous vanadium model (28) (assuming that the unspecified long-stay tissue in the model of Patterson et al. (28) represents bone) was $> 10^4$ h, or ~42 days, also reasonably close to the residence times predicted by our model. Variability within data sets, and between the first and second oral gavage studies (experiments A and B), resulted in high error terms for the fractional transfer coefficients representing movement of vanadium between compartments and, as a consequence, also for calculated residence times.

In another study, at 24 h postinjection, %AD (of $^{48}$V-vanadyl chloride added to ammonium metavanadate) was 1.25% in blood, 17.9% in bone, and 2.65% in muscle (1) compared with 3.55% in blood, 8.62% in bone, and 1.14% in muscle with use of $^{48}\text{V}$-BMOV in our study. In Conklin et al. (11), oral gavage of $^{48}\text{V}$-V$_2$O$_5$ (40 µg/rat, ~0.3 mg/kg) resulted in 0.65 %AD in bone 3 days after dosing. The low solubility of V$_2$O$_5$ compared with VO$_3^-$, VO$^{2+}$, or BMOV is probably the cause of this low localization; however, the longer time frame is also a factor. Hamel and Duckworth (18) predicted longer residence times than we calculated for a variety of soft tissues (bone vanadium was not measured) in rats on the basis of patterns of uptake and redistribution of low levels of dietary vanadium, as detected by neutron-activation analysis over a longer time period. The significant difference in dose and the chronic, rather than acute, nature of the study may explain this discrepancy. The researchers (18) also observed that 2.7% of a gavage dose was in the blood (total) at 24 h, which is in good agreement with our calculations.

The kinetic heterogeneity in kidney predicted by our model suggests that the longer-stay kidney compartment may represent stored vanadium, whereas the short-stay kidney compartment may represent a vana-

| Table 1. Relative concentrations of $^{48}\text{V}$ 24 h after oral gavage |
|-----------------|-----------------|-----------------|
| Liver           | Kidney          | Bone            |
| $^{48}\text{V}$ | 0.0212          | 0.0856          | 0.1131          |
| $^{48}\text{V}$-BMOV | 0.082           | 0.1163          | 0.3265          |
| $^{48}\text{V}$-BMOV/$^{48}\text{V}$ | 3.9             | 1.4             | 2.9             |

Percent administered dose (%AD; as %AD/g tissue) predicted by model (Fig. 3) at 24-h time point. Average %AD of $^{48}$V-bis (maltolato)oxovanadium(IV) (BMOV)/vanadyl sulfate-48 ($^{48}$VS) for liver, kidney, and bone was 2.7.

| Table 2. Fractional transfer coefficients and residence times for $^{48}\text{V}$ in compartmental model |
|-----------------|-----------------|-----------------|
| Transfer Coefficients | $^{48}\text{VS}$ | $^{48}\text{V}$-BMOV |
| $k_{12}$ (kidney1→kidney2) | 0.75 ± 0.28 | 0.26 ± 0.05 |
| $k_{14}$ (liver→plasma) | 0.26 ± 0.09 | 0.15 ± 0.04 |
| $k_{15}$ (tests→plasma) | 0.63 ± 0.13 | 0.29 ± 0.10 |
| $k_{16}$ (bone→plasma) | 0.0038 ± 0.0022 | 0.0028 ± 0.0011 |
| $k_{13}$ (kidney2→plasma) | 4.9 ± 2.3 | 0.63 ± 0.50 |
| $k_{33}$ (kidney2→urine) | 7.4 ± 0.7 | 5.5 ± 0.5 |

Residence Times

<table>
<thead>
<tr>
<th>Component</th>
<th>$^{48}\text{VS}$</th>
<th>$^{48}\text{V}$-BMOV</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT$_1$ (blood)</td>
<td>5.0 min</td>
<td>7.0 min</td>
</tr>
<tr>
<td>RT$_2$ (kidney1)</td>
<td>4.9 min</td>
<td>9.7 min</td>
</tr>
<tr>
<td>RT$_4$ (liver)</td>
<td>3.8 h</td>
<td>6.8 h</td>
</tr>
<tr>
<td>RT$_5$ (tests)</td>
<td>1.7 h</td>
<td>3.4 h</td>
</tr>
<tr>
<td>RT$_6$ (bone)</td>
<td>11 days</td>
<td>31 days</td>
</tr>
<tr>
<td>RT$_{13}$ (kidney2)</td>
<td>1.3 h</td>
<td>3.8 h</td>
</tr>
</tbody>
</table>

Fraction of vanadium pool moving from compartment $i$ to compartment $j$ per unit time (h) = $k_{ij}$. Note that compartment $k_{ij}$ is the same as that compartment. Kidney1 and kidney2, kinetically distinct compartments that could be either physiologically or biochemically distinguishable, with no anatomic separation implied; numbers, compartment numbers in model (Fig. 3). *$RT_1 = 1/2k_{11}$. **$RT_2 = 1/2k_{13}$.
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