Pharmacokinetics of Sodium Tungstate in Rat and Dog: A Population Approach

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ABSTRACT

Sodium tungstate has been found to correct hyperglycemia in insulin- and noninsulin-dependent models of diabetes when administered in drinking fluid with a low degree of toxicity; thus, it provides a potential treatment for diabetes. In the present report, pharmacokinetic studies with sodium tungstate were carried out in the Sprague-Dawley rat and beagle dog. This drug was administered either i.v. (8.97 mg/kg in rat; 25 and 50 mg/kg in dog) or orally in the form of solution (35.9 and 107.7 mg/kg in rat; 25 and 50 mg/kg in dog). Tungsten was quantified using an inductively coupled plasma method. Pharmacokinetic parameters were estimated using a population approach. Sodium tungstate followed first order kinetics, and plasma concentration-versus-time data were adequately described by a two-compartment model. In rat, bioavailability was high (92%), whereas it was lower in dog (approximately 65%). The total volume of distribution expressed by unit of body weight was much higher when the animal was smaller (0.46 l/kg in rat versus 0.23 l/kg in dog). The total body clearance normalized by weight, 0.19 l/h/kg in rat versus 0.043 l/h/kg in dog, changed as for the volume of distribution. The elimination half-life was two times higher in dog (approximately 4 h) than in rat (approximately 1.7 h). In the range of 35.9 to 107.7 mg/kg after oral administration in rat and 25 to 50 mg/kg after oral and i.v. administration in dog, tungsten plasma concentrations increased in proportion to dose.

Transition metal derivatives have recently been found to possess antidiabetic activity. Vanadate was first described as able to lower blood glucose in insulin-deficient rats (Heyliger et al., 1988) and in animal models of insulin resistance (Briard et al., 1989). However, vanadate treatment was associated with significant side effects, including digestive troubles, which might be explained by its low bioavailability (10–20%). The antidiabetic activities of other transition metal derivatives such as chromium, molybdate, or selenate (Fillat et al., 1992; Battell et al., 1998; Anderson, 2000) have also been demonstrated. However, their toxicity decreases their interest for clinical use. Recently, sodium tungstate was found to correct hyperglycemia in insulin- and noninsulin-dependent models of diabetes when administered at a dosage of 169 to 418 mg/kg/day in drinking fluid for 15 days with low degree of toxicity (Barbera et al., 1994, 1997) and should be tested clinically. A biokinetic model for systemic tungsten in humans was recently published by Leggett (1997). This model is based on experimental data on the biokinetics of radiotungsten in laboratory animals and information on the kinetics of molybdenum or other physiological analogs of tungsten in humans and laboratory animals. An elimination half-life ($t_{1/2}$) of 12 to 14 h was reported by Mason et al. (1989) in sheep. Experimental results concerning the distribution of tungsten between plasma and red blood cells (RBCs) have been published. In beagle dogs receiving $^{185}$W as sodium tungstate, the ratio of concentration plasma to RBCs was approximately 3 during the first 24 h (Aamodt, 1973). Higher RBC-to-plasma ratios for radiotungsten have been determined in rodents than in larger animals (Kaye, 1968). In rats and mice, RBC-to-plasma ratios of approximately 9 and 14 were found at 3 to 4 days after administration. In sheep, $^{185}$Wtungstate was not protein bound (Mason et al., 1989).

This study was conducted to determine the pharmacokinetic profile of sodium tungstate after i.v. and oral administration in two different species: rat and dog. Individual pharmacokinetic parameters were estimated using an empirical model based on experimental data on the biokinetics of radiotungsten in laboratory animals and information on the kinetics of molybdenum or other physiological analogs of tungsten in humans and laboratory animals. An elimination half-life ($t_{1/2}$) of 12 to 14 h was reported by Mason et al. (1989) in sheep. Experimental results concerning the distribution of tungsten between plasma and red blood cells (RBCs) have been published. In beagle dogs receiving $^{185}$W as sodium tungstate, the ratio of concentration plasma to RBCs was approximately 3 during the first 24 h (Aamodt, 1973). Higher RBC-to-plasma ratios for radiotungsten have been determined in rodents than in larger animals (Kaye, 1968). In rats and mice, RBC-to-plasma ratios of approximately 9 and 14 were found at 3 to 4 days after administration. In sheep, $^{185}$Wtungstate was not protein bound (Mason et al., 1989).

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Bayes' methodology. The linearity of the kinetics was also investigated for different doses administered i.v. or orally. Our results indicate that after oral administration of 35.9 to 107.7 mg/kg sodium tungstate in rat and after oral and i.v. administration of 25 to 50 mg/kg sodium tungstate in dog, tungsten plasma concentrations increased in proportion to dose and that the bioavailability of sodium tungstate was relatively high (65% in dog and 92% in rat).

**Materials and Methods**

**Compound.** Sodium tungstate was obtained from Carlo Erba (Val de Reuil, France). Tungsten as the sodium salt was administered to animals in an aqueous solution containing 0.9% sodium chloride for the i.v. route and in distilled water for the oral route.

**Animals.** This study was conducted in male Sprague-Dawley rats and in male beagle dogs.

**Rats.** Two hundred sixteen Sprague-Dawley rats weighing 316 to 532 g (IFFA CREDO, L’Arbresle Cedex, France) at age 10 weeks were used (one animal per time point). Animals underwent an acclimatization of a minimum of 2 weeks before treatment. They were group housed in stainless steel cages with suspended wire-mesh floors (maximum of three rats per cage). The rats were fed a standard laboratory rodent diet (UAR sterile food, Usine d’Alimentation Rationnelle, Villemoisson, Epinay s/Orge, France) and allowed free access to drinking water. Rats were fasted overnight (12 h) before drug administration and then weighed.

**Dogs.** Six male beagle dogs (Harlan, Grannat, France) weighing 11.5 ± 0.24 kg were housed individually during the study in metabolism stainless steel cages with access to pelleted food (400 g/day/animal; Usine d’Alimentation Rationnelle). Tap water was distributed ad libitum. The animals underwent an acclimatization period of 10 days before the experiment.

The dogs were fasted for 24 h before each experiment and then weighted. The day of administration, food was distributed 12 h after drug intake. The same animals were dosed i.v. and orally; both administration routes were investigated after at least a 15-day wash-out period.

For all animals, the housing rooms had controlled environmental conditions with temperature and relative humidity of approximately 18–21°C and 40 to 70%, respectively, and artificial lighting, alternating on a 12-h light/dark cycle.

**Drug Administration.** Single i.v. (8.97 mg/kg) and oral (35.9 and 107.7 mg/kg) doses of sodium tungstate were administered to each rat. For which, three different solutions of sodium tungstate were prepared on the day of administration: one solution in 0.9% sterile isotonic saline (4.5 mg/ml) for i.v. administration and two solutions in distilled water (3.6 and 10.8 mg/ml) for oral administration. These solutions were used to treat animals, under the administered volume of 2 ml/kg (i.v.) and 10 ml/kg (oral).

Dogs received four different treatments: two i.v. doses (25 and 50 mg/kg) and two oral doses (25 and 50 mg/kg) of sodium tungstate. The vehicles used were 0.9% sterile isotonic saline (0.1 ml/kg b.wt.) for i.v. administration and double distilled water (1 ml/kg b.wt.) for oral administration.

For i.v. administration, the dose was administered over 1 min into the tail vein in the rat and the cephalic vein in the dog. For oral administrations, the drug was given by gavage through stomach tubing using a polypropylene catheter.

**Blood Sampling.** In rat, blood samples were collected (one sample per rat) at the following time points (six animals per time point): 5, 10, 15, and 30 min and 1, 2, 4, 8, 12, 16, and 24 h after drug administration. Untreated animals were used for basal tungsten level determination. Two minutes before sampling, rats were anesthetized with diethylether and then sacrificed by section of the carotid artery. Total blood was collected in heparinized polypropylene tubes (0.1 ml sodium heparinate per tube).

In dog, blood samples (8 ml) were collected from a superficial vein of the forelimbs into polypropylene tubes coated with sodium heparinate before the oral and i.v. doses; after 5, 10, 15, 30, 45, and 60 min and 2, 4, 8, 12, 16, 24, and 36 h for the i.v. route; and after 10, 20, 40, and 60 min and 2, 4, 8, 12, 16, 24, and 36 h for the oral route.

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**TABLE 1**

Population pharmacokinetic parameters of sodium tungstate in rat

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Distribution</th>
<th>Mean (nM)</th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (l/h/kg)</td>
<td>Normal</td>
<td>0.186</td>
<td>27.4</td>
</tr>
<tr>
<td>V (l/kg)</td>
<td>Normal</td>
<td>0.210</td>
<td>30.0</td>
</tr>
<tr>
<td>k_{12} (h(^{-1}))</td>
<td>Normal</td>
<td>1.30</td>
<td>41.9</td>
</tr>
<tr>
<td>k_{21} (h(^{-1}))</td>
<td>Normal</td>
<td>1.51</td>
<td>41.5</td>
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<tr>
<td>k_a (h(^{-1}))</td>
<td>Normal</td>
<td>0.36</td>
<td>33.5</td>
</tr>
<tr>
<td>F</td>
<td>Normal</td>
<td>0.92</td>
<td>28.7</td>
</tr>
<tr>
<td>Sigma(^{a})</td>
<td>Normal</td>
<td>0.235</td>
<td>17.7</td>
</tr>
</tbody>
</table>

ML, maximum likelihood.  
\(^{a}\) The sigma value (random effect) is for all parameters.
Tubes containing blood samples were immediately and gently agitated to prevent coagulation and then centrifuged at 2000 g for 20 min. Plasma was removed, transferred into two polypropylene tubes, and then stored at −20°C until assay.

**Assay Method.** Concentrations were expressed in tungsten metal. Tungsten plasma concentrations were determined using an inductively coupled plasma emission spectrometric method at a wavelength of 207.91 nm (Poucheret et al., 2000). Samples (500 μl) were directly nebulized; each determination was performed in replicate (n = 5). Calibration curves were obtained in the range 134 to 1300 ng/ml. Precision ranged from 0.4 to 17%, and accuracy was between 89 and 105%. Dilution has no influence on the performance of the method, which could then be used to quantify plasma samples containing up to 90 μg/ml. The limit of quantification was 100 ng/ml, it was defined as the lowest drug concentration that can be determined with an accuracy of 100 ± 20% and a relative standard deviation of ±20% on a day-to-day basis. Using quality control samples at this level, the precision averaged 17%.

**Population Pharmacokinetic Analysis.** Individual pharmacokinetic parameters were estimated using an empirical Bayes’ methodology (Sheiner et al., 1972). In this analysis, population characteristics of the parameters to be estimated were used as prior information to estimate each individual pharmacokinetic parameter.

In rat, a preliminary analysis was carried out using the Pk-fit software (version 1.1.4, 1999; RDPP, Montpellier, France), to compute pharmacokinetic parameters from the average concentration values at each time points. Such an analysis allowed us to estimate the initial pharmacokinetic parameters that will be used in the population analysis and to choose the pharmacokinetic model. Individual pharmacokinetic parameters were then determined using a population approach and the baseline-corrected plasma concentrations.

In dog, plasma concentration-versus-time data were first analyzed using a noncompartmental approach (Pk-fit software). Such an analysis allowed us to verify that drug concentration increased in proportion to dose. Then, despite the few number of dogs, the data obtained in each dog from the whole treatment (i.v. plus oral administration) were analyzed using a population approach. Such an analysis 1) avoided a possible bias in the estimation of the t_{1/2 elim}. Indeed, at low doses, 36 h after administration, tungsten concentrations were below the limit of quantification of the analytical method in the majority of animals, so the t_{1/2 elim} could not be estimated with the same accuracy at low and high doses. 2) It allowed us to use the same model after i.v. and oral routes (the distributive phase being poorly detectable after oral administration, so using a classic approach, this phase cannot be accurately fitted). 3) It allowed a better estimation of individual pharmacokinetic parameters, including bioavailability. Moreover, this ap-

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Route</th>
<th>Dose (mg/kg)</th>
<th>Mean</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>t_{1/2 elim} (h)</td>
<td>i.v.</td>
<td>8.97</td>
<td>1.72</td>
<td>0.36</td>
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<tr>
<td></td>
<td>Oral</td>
<td>35.9</td>
<td>1.68</td>
<td>0.24</td>
</tr>
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<td></td>
<td>Oral</td>
<td>107.7</td>
<td>1.79</td>
<td>0.32</td>
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<tr>
<td>CL (l/h/kg)</td>
<td>i.v.</td>
<td>8.97</td>
<td>0.19</td>
<td>0.016</td>
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<td></td>
<td>Oral</td>
<td>35.9</td>
<td>0.18</td>
<td>0.014</td>
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<tr>
<td>V (l/kg)</td>
<td>i.v.</td>
<td>8.97</td>
<td>0.21</td>
<td>0.0028</td>
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<tr>
<td></td>
<td>Oral</td>
<td>35.9</td>
<td>0.20</td>
<td>0.0022</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>107.7</td>
<td>0.21</td>
<td>0.016</td>
</tr>
<tr>
<td>V_s (l/kg)</td>
<td>i.v.</td>
<td>8.97</td>
<td>0.47</td>
<td>0.114</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>35.9</td>
<td>0.44</td>
<td>0.0555</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>107.7</td>
<td>0.47</td>
<td>0.0555</td>
</tr>
<tr>
<td>t_{1/2 k_a} (h)</td>
<td>Oral</td>
<td>35.9</td>
<td>1.89</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>107.7</td>
<td>2.05</td>
<td>0.37</td>
</tr>
<tr>
<td>F</td>
<td>Oral</td>
<td>35.9</td>
<td>0.95</td>
<td>0.0933</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>107.7</td>
<td>0.88</td>
<td>0.132</td>
</tr>
</tbody>
</table>

*Expressed in sodium tungstate.

*After oral dosing, CL, V, and V_s were corrected from bioavailability.

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**Fig. 2.** Mean tungsten plasma concentration-versus-time curve after i.v. (25 and 50 mg/kg) and oral (25 and 50 mg/kg) administrations of sodium tungstate in dog.
On the basis of the examination of the objective function and of the characterized by a population mean and an interindividual variance. The residual distribution showed that the error variance was better described by normal distribution. In dog, for CL and V, the probability distribution of the random effect parameters was better described by log-normal rather than normal distribution; for the other parameters (k_{12}, k_{21}, k_a, t_{lag}, and F), a normal distribution was used.

The t_{1/2\,elim} area under the plasma concentration-time curve (AUC) and the steady-state volume of distribution (V_d) were calculated as follows:

\[ t_{1/2\,elim} = \frac{0.693 \times 2}{(k_{12} + k_{21} + k_a) - \sqrt{(k_{12} + k_{21} + k_a)^2 - 4 \times k_{21} \times k_a}} \]

From this model, the plasma concentration of tungsten at any time can be easily computed using the empirical Bayes' estimate of the pharmacokinetic parameters.

**Consistency Check of Pharmacokinetic Parameter Estimates.** To check the error model assumptions and the distribution of the estimated population pharmacokinetic parameters, P-PHARM estimates the expected concentrations (C_{exp}) for each individual in the population and computes appropriate statistical tests to evaluate the distribution properties of the differences between the expected and the observed data. For each concentration, a standardized concentration prediction error (SCPE) is calculated as follows: SCPE = [C_\text{obs} - C_{\text{exp}}]/S.D.(C_{\text{exp}}), where C_\text{obs} represents the observed concentrations, and S.D.(C_{\text{exp}}) represents the estimated standard deviation for the expected values computed using all sources of random variability, including the residual error.

To assess the posterior distribution properties of the residuals and the individual parameters, the t test was used to compare the mean of SCPE with zero; the Kolmogorov-Smirnov test was used to compare the sampled distribution to the expected one [N(0,1)].

**Statistical Evaluation.** Results in the text are presented as mean ± S.D.

In rat, differences in pharmacokinetic parameters (CL, V_d, t_{1/2\,elim}) were compared among the three treatment groups by using the Kruskal-Wallis test (Siegel and Castellan, 1988). The effect of the administered dose (35.9 versus 107.7 mg/kg sodium tungstate) was also assessed by comparing AUC.

In dog, a two-way ANOVA was performed to assess the effect of the administered dose on parameters determined by noncompartmental approach (i.e., AUC after i.v. administration of 25 and 50 mg/kg sodium tungstate, and C_{max} and AUC after oral administration of 25 and 50 mg/kg sodium tungstate). Before the statistical analyses, CL, V_d, C_{max} and AUC were log-transformed; C_{max} and AUC were normalized to the same administered dose. A 5% level of statistical significance was used.

**Results**

**Pharmacokinetics in Rat.** The mean endogenous tungsten concentration was 137 ng/ml. Semilogarithmic plots of the mean plasma concentration-time curve after i.v. bolus injection of 8.97 mg/kg and oral administrations of 35.9 and 107.7 mg/kg sodium tungstate are shown in Fig. 1. Data were

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**TABLE 3**

Population pharmacokinetic parameters of sodium tungstate in dog

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Distribution</th>
<th>Mean value</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (l/h/kg)</td>
<td>Log-normal</td>
<td>0.0422</td>
<td>27.7</td>
</tr>
<tr>
<td>V (l/kg)</td>
<td>Log-normal</td>
<td>0.171</td>
<td>38.3</td>
</tr>
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<td>k_{12} (h^{-1})</td>
<td>Normal</td>
<td>0.407</td>
<td>42.2</td>
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<td>k_{21} (h^{-1})</td>
<td>Normal</td>
<td>1.44</td>
<td>19.1</td>
</tr>
<tr>
<td>k_a (h^{-1})</td>
<td>Normal</td>
<td>0.901</td>
<td>30.1</td>
</tr>
<tr>
<td>t_{lag} (h)</td>
<td>Normal</td>
<td>0.053</td>
<td>73.0</td>
</tr>
<tr>
<td>F</td>
<td>Normal</td>
<td>0.86</td>
<td>12.1</td>
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<tr>
<td>Sigma</td>
<td></td>
<td>1.39</td>
<td></td>
</tr>
<tr>
<td>ML</td>
<td></td>
<td>-841.7</td>
<td></td>
</tr>
</tbody>
</table>

ML: maximum likelihood.

* The sigma value (random effect) is for all parameters.

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The posterior individual pharmacokinetic parameter estimates were then assumed to arise from a normal or log-normal distribution characterized by a population mean and an interindividual variance. On the basis of the examination of the objective function and of the inspection of weighted residuals and individual predicted-versus-observed concentration plots, results indicate that in rat, for all parameters, the probability distribution of the random effect parameters [sigma(CL), sigma(V), sigma(k_{12}), sigma(k_{21}), sigma(k_a), sigma(F)] was better described by normal distribution. In dog, for CL and V, the probability distribution of the random effect parameters was better described by log-normal rather than normal distribution; for the other parameters (k_{12}, k_{21}, k_a, t_{lag}, and F), a normal distribution was used.

The t_{1/2\,elim} area under the plasma concentration-time curve (AUC) and the steady-state volume of distribution (V_d) were calculated as follows:

\[ t_{1/2\,elim} = \frac{0.693 \times 2}{(k_{12} + k_{21} + k_a) - \sqrt{(k_{12} + k_{21} + k_a)^2 - 4 \times k_{21} \times k_a}} \]

with

\[ k_{\text{al}} = \frac{[CL/F]/[V/F]}{2} \]

\[ \text{AUC} = \frac{[\text{dose} \times F]}{CL} \]

\[ V_d = (CL \times t_{1/2\,elim})/0.693 \]

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From this model, the plasma concentration of tungsten at any time can be easily computed using the empirical Bayes' estimate of the pharmacokinetic parameters.
The aim of this study was to determine the pharmacokinetic profile of sodium tungstate after single i.v. or oral (gavage) administration in two different species: rat and dog. In these two species, doses have been chosen according to the maximum tolerated dose for each route of administration. In dog, side effects occurred at doses higher than 50 mg/kg for both oral or i.v. routes. In rat, the highest oral dose of 107.7 mg/kg did not produce any apparent side effects and was close to the doses used in efficacy studies performed by Barbera et al. (1994, 1997). In these two published studies, sodium tungstate (154–205 mg/kg/day in healthy rats and 169–418 mg/kg/day in diabetic rats) was administered in drinking water. However, the maximum i.v. tolerated dose was lower in rat than in dog (8.97 mg/kg).

The results found in this study indicated that absorption of sodium tungstate when administered in solution form was rapid ($t_{max} = 1–2 \, h$). In rat, bioavailability was high (approximately 92%). However, lower results of 40 to 70% were found after the administration of radiotungsten as tungstate (Ballou, 1960; Fleschman et al., 1966; Kaye, 1968), whereas uptake of radiotungsten administered as tungstic acid was only 1% (Ballou, 1960). Cardin and Mason (1976) found that the maximum rate of transport of tungstate through the small intestine of the rat, as studied in vitro using the everted sac technique, occurs in the lower ileum.
in the rat by a common transport system subject to competitive inhibition. In dog, the bioavailability averaged 65%. These results are higher than that of 25% reported by Aamodt (1975) after the intragastric administration of a weakly acidic aqueous suspension of tungstic oxide in beagle dog.

In both species, over the sampling times monitored, plasma concentration profiles versus time were compatible with a two-compartment model and first-order kinetics. These results were in accordance with those found by Leggett (1997). In rat, after oral administration of 107.7 mg/kg sodium tungstate, mean concentration-versus-time curve showed a double-peak phenomenon during the input process. However, further investigations carried out on rat after re-

![Figure 4](imageurl)
peated administrations (data not shown) did not confirm such a result. The total volume of distribution ($V_d = 0.46 \text{ l/kg}$ in rat versus 0.23 l/kg in dog) and the total body clearance (0.19 l/h/kg in rat versus 0.043 l/h/kg in dog) normalized by body weight were both much higher when the animal was smaller. No relationship occurred between weight and CL or $V_d$. The $t_{1/2 \text{ elim}}$ was twice higher in dog (approximately 4 h) than in rat (approximately 1.7 h). These results confirmed the findings of Leggett (1997) that rats appear to excrete tungsten at a much higher rate than do larger animals. This relatively high excretion rate could be related to the unusually low requirements of the rat for the chemically similar element molybdenum (Higgins et al., 1956). After oral administration of 35.9 to 107.7 mg/kg sodium tungstate in rat and after oral and i.v. administration of 25 to 50 mg/kg sodium tungstate in dog, tungsten plasma concentrations increased in proportion to dose.

These pharmacokinetic properties indicate that tungsten is relatively unique among pharmacologically active metals. Indeed, although tissue storage was not specifically studied in the present work, the short $t_{1/2 \text{ elim}}$ of sodium tungstate suggests a rather limited tissue accumulation. Moreover, a major difference between tungstate and vanadate is the bioavailability. Vanadate bioavailability is still a matter of debate; it was reported in rat to vary from 5% (Conklin et al., 1982; French and Jones, 1993; Nielsen, 1988) to a maximum of 30% (Bodgen et al., 1982; Setyawati et al., 1998; Wiegmann et al., 1982). This low bioavailability was associated with digestive side effects (e.g., cramps and diarrhea) in correlation with the pharmacological activity of the metal on the digestive tract (Goldfine et al., 1995; Soulié et al., 1996) and led to the development of organomineral compounds (Yuen et al., 1997). In this perspective, the high bioavailability of sodium tungstate will certainly constitute a major advantage.

In conclusion, this report represents valuable information about the pharmacokinetics of sodium tungstate in rat and dog. Because this study was conducted in healthy animals, it was not possible to correlate tungsten plasma levels to a pharmacological response. Future studies will explore pharmacodynamic/pharmacokinetic relationships in diabetic animals.

Acknowledgment

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References


