The effects of induced diabetes and cutaneous Leishmania infection on the pharmacokinetics of antimony in hamsters

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Patients with certain diseases appear to be at greater risk of developing adverse drug interactions, either because of the disease state itself or the drugs used to treat it. The effects of streptozotocin-induced diabetes and/or cutaneous Leishmania major infection on the pharmacokinetics of antimony (SbV) have now been investigated, in hamsters treated with sodium stibogluconate (Pentostam). The animals were randomly divided into five groups, each of 20 hamsters, known as D (for diabetes without leishmaniasis), DL (diabetes induced prior to the leishmaniasis), L (leishmaniasis without diabetes), LD (diabetes induced after leishmanial infection) and C (the control group, of animals with neither diabetes nor leishmaniasis). After its diabetes and/or leishmaniasis (if any) was established, each animal was given an intramuscular dose of sodium stibogluconate (80 mg/kg) each day for 3 weeks. Blood samples were collected after the first or last doses, to allow the pharmacokinetic parameters of SbV after single and multiple dosing to be compared.

Although the between-dose interval (24 h) was more than 10 times longer than the terminal elimination rate constant (tK) at steady state, there was a significant increase in the mean peak SbV concentration (Cmax), as the result of multiple dosing, in all five groups (P<0.001 for each). The hamsters with diabetes showed the least accumulation of SbV in their blood, whether or not they were infected with L. major. In the non-diabetic animals of groups L and C, the apparent total clearance of SbV (CL/F) was decreased by multiple dosing, being, respectively, 34.5% and 23.0% lower after the 21st dose than after the first. An increase in urine volume was the reason for the significant increase in CL/F in group D (P<0.001), and this offset the decrease in CL/F seen in the L group, resulting in no change in CL/F in the animals of the DL group.

Three weeks of antileishmanial treatment produced no significant reductions in the leishmanial lesions on the parasite-inoculated foot-pads of the hamsters in the L or DL groups but such reductions were detected in the animals of the LD group (P<0.001).

In conclusion, it appears that the administration of SbV over a few weeks may cause renal toxicity and, in clinical use, should therefore be accompanied by the regular monitoring of renal function. A cautious increase in SbV dosing may be necessary for the effective treatment of L. major (and perhaps other species of Leishmania) in diabetic patients.

Patients with certain diseases appear to be at greater risk of developing adverse drug interactions, either because of the disease state itself or the drugs used to treat it. Diabetes mellitus is a common, serious disease characterised by hyperglycaemia. The disease can be divided into two major subclasses: insulin-dependent diabetes mellitus (type-I diabetes) and non-insulin-dependent diabetes mellitus (type-II diabetes; WHO, 1985). Hyperglycaemia-induced disorders are thought to initiate a sequence of events leading to the development of nephropathy in some diabetic subjects. Although it remains unclear which abnormalities are critical in the aetiology of this morbidity, several mechanisms have been postulated to be involved, including increased polyol-pathway activity,
activation of protein kinase C, accumulation of advanced-glycation end products, and increased oxidative stress (Bach, 1995; Kikkawa et al., 2003). Many patients with diabetes have renal dysfunction that can cause difficulties with both drug excretion and glucose monitoring. Compared with individuals with normal glucose metabolism, patients with diabetes also show higher incidences of severe, life-threatening infections and venous thrombo-embolism (Langdon and Shriver, 2004).

Research on diabetes was facilitated when it was found that an injection of streptozotocin (STZ), at 24–100 mg/kg, produced a dose-dependent hyperglycaemia in laboratory animals that could be used as a model of human diabetes (Junod et al., 1969; Ito et al., 2001). In rats, for example, morbidity that resembled type-I or type-II diabetes could be induced using STZ at doses of >50 and <50 mg/kg, respectively (Junod et al., 1969; Tsuji et al., 1988; Ar’rajab and Ahren, 1993; Striffler and Nadler, 2004). Thus, injection of rats with 35 mg STZ/kg gave a model of type-II diabetes whereas a markedly higher dose (65 mg STZ/kg) gave rise to type-I diabetes (Mihm et al., 2001; Striffler and Nadler, 2004).

The leishmaniases are diseases produced by invasion of the reticulo-endothelial system of a vertebrate host by parasites of the genus *Leishmania*. The clinical manifestations of such infection are dependent both on the infecting species of *Leishmania* and on the immune response of the host. Although the parasites are found as motile promastigotes in the sandflies that transmit them between vertebrate hosts, they transform into amastigotes when engulfed by the vertebrate hosts’ macrophages and develop in the acidic environment of these cells’ secondary lysosomes (Alexander and Russell, 1992). The human leishmaniases are major health problems in many tropical and subtropical areas and in some temperate settings. In the Mediterranean region, for example, leishmaniases caused by *L. infantum* has emerged as an important opportunistic infection in individuals left immunocompromised by HIV infection (Montalban et al., 1990; Dedet et al., 1993). Pentavalent antimonial agents (SbV), in the form of sodium stibogluconate (Pentostam®; GlaxoSmithKline, Brentford, U.K.) or N-methyl-D-glucamine antimoniate (Glucantime™; Aventis, Paris), are the first-line drugs for the treatment of cutaneous leishmaniasis (CL) in the New World and visceral leishmaniasis (VL; Marsden, 1985; Berman et al., 1988). Despite their clinical use for over half a century, the mode of action of these compounds remains poorly understood. They may be rapidly excreted. Valladares et al. (1996) found, for example, that 80% of the SbV in an intravenous dose of N-methyl-D-glucamine antimoniate was excreted in the urine within 9 h of the injection.

In Saudi Arabia, both VL and CL are endemic but CL is the more prevalent and wide-spread form of the disease, with >25,000 cases reported annually (unpubl. obs.). Many cases of leishmaniases in the country must also be diabetic, since 4004 (23.7%) of the 16,917 adults investigated by Al-Nozha et al. (2004), in a household survey that ran between 1995 and 2000, were found to have diabetes mellitus. In this survey, the prevalence of diabetes in the male subjects was significantly higher than that in the females (26.2% vs. 21.5%; P<0.00001), and many (27.9%) of the diabetics detected were unaware of their diabetes.

There appears to have been no published research on the ways in which diabetes might influence the pharmacokinetics of SbV in human cases of CL or rodent models of CL. The aim of the present study was to explore the effects of STZ-induced diabetes and experimental cutaneous *Leishmania* infection in hamsters on the pharmacokinetics of SbV given once or daily for 3 weeks.
ANIMALS AND METHODS

Hamsters
Overall 100 Syrian hamsters of both sexes, each weighing 100–140 g, were used in the experiments. These were obtained from the animal facility at the King Faisal Specialist Hospital and Research Centre in Riyadh. The sexes were separated, to prevent any breeding. The hamsters were offered water ad libitum but were fasted for about 12 h prior to each measurement of blood glucose. They were kept on a 12-h-light/12-h-dark photoperiod.

Parasites
Leishmania parasites were isolated, by culture, from a case of CL who had presented at the dermatology clinic at Al-Kharj, which lies 105 km to the south–east of Riyadh, the capital of Saudi Arabia. The parasites have been identified as zymodeme LON4 of L. major by iso-enzyme analysis (data not shown). The primary culture was cryopreserved in liquid nitrogen and only thawed for one subculture, on NNN medium (Evans et al., 1989), to give the promastigotes used as an inoculum in the experiments described here. The subculture was incubated for 4–5 days, until the parasites reached a stationary phase of growth, and then the liquid overlay was diluted with phosphate-buffered saline (pH 7.2) to give an inoculum containing $10^8$ parasites/ml.

Induction of Leishmanial Infection and/or Diabetes
The hamsters were randomly divided into five groups (20 hamsters/each), known as D (for diabetes without leishmaniasis), DL (diabetes induced prior to the leishmaniasis), L (leishmaniasis without diabetes), LD (diabetes induced after leishmanial infection) and C (the control group, of animals with neither diabetes nor leishmaniasis).

Each hamster to be infected with the parasites was injected in one hind foot-pad with a 0.1-ml subsample of diluted overlay; the thickness of the inoculated foot-pad and that of the uninoculated hind foot-pad were measured and compared daily. The infection was considered to be established 2–3 weeks post-inoculation, when a cutaneous lesion appeared at the inoculation site and the inoculated foot-pad was found to be markedly thicker than the uninoculated. Response to antileishmanial treatment was measured as the difference in thickness between the inoculated and corresponding uninoculated footpads.

Following the results of pilot trials with various doses of STZ (Sigma), diabetes was induced using three intraperitoneal injections of STZ, of 50 mg/kg on day 1, 40 mg/kg on day 2, and 40 mg/kg on day 3. Diabetes was considered established when the fasting blood glucose reached at least 300 mg/dl. The STZ was freshly dissolved in 0.1 M citrate buffer (pH 4.5) and kept on ice prior to use. The hamsters in the L and C groups received similar injections of STZ-free citrate buffer. The hamsters in the DL group were inoculated with L. major as soon as their diabetes was confirmed whereas the hamsters in the LD group had their diabetes induced once their leishmanial infection was established. To follow blood glucose concentrations, small (20-μl) blood samples were collected, from a random selection of six hamsters each from the D, DL or LD groups, at the start of the experiment and then every 3 days. The glucose concentrations were measured using Haemo-Glukotest® strips (Boehringer Mannheim, Mannheim Germany) and a Reflolux® S blood-glucose monitor (Boehringer Mannheim). The precision of the glucose assay was found to be within ±5% and the measurable glucose levels ranged between 10 and 500 mg/dl.

Antileishmanial Treatment
All the hamsters were treated daily with intramuscular Pentostam, at 80 mg/kg.day, for 3 weeks. Antileishmanial treatment was initiated as soon as the diabetes had been
confirmed (groups D and LD), as soon as the leishmanial infection had established (groups L and DL) or about 2 weeks after the start of the experiments (group C).

**Antimonial Pharmacokinetics**

The pharmacokinetics of SbV were followed in the hamsters of the D, DL, L and C groups (the hamsters in the LD group were only used for the measurement of their foot-pad lesions). For this, 0.5-ml blood samples were collected (from each of 10 mice in each group) 15 min, 45 min, 1 h, 3 h and 8 h after the first dose of Pentostam, and another four 0.5-ml samples were collected (from each of the other 10 mice in each group) 30 min, 2 h, 4 h and 6 h after the last dose of Pentostam. Each sample was collected, from the orbital venous plexus of a hamster, into an EDTA K₃ Vacuette® tube (Greiner Bio-One, Kremsmünster, Austria) and immediately diluted, 1:19 (for samples collected within the 2 h of a dose) or 1:4 (otherwise), with 2% (v/v) Triton X-100 in de-ionized water, before storage at 4°C until its SbV content could be assayed.

**Measuring SbV Concentrations in Whole Blood**

Antimony was measured in the diluted samples of whole blood by flameless atomic absorption spectrophotometry (Al Jaser et al., 1995). Each diluted sample was vortex-mixed for 30 s and then centrifuged at 1000 × g for 5 min. A 0.5-ml sample of the resultant, clear, supernatant solution was transferred into an atomic-absorption plastic sample cup and then investigated in a fully automated spectrophotometer, using the parameters recommended by the manufacturer (Varian, Mulgrave, Australia) and an autosampler programmed to inject 20 µl of the test sample.

**Data Analysis**

The Excel 2003 software package (Microsoft) was used to store and analyse all the data. Pharmacokinetic parameters were estimated using model-independent methods (Gibaldi and Perrier, 1982). The terminal elimination rate constant (λn) was estimated by linear-regression analysis of the terminal portion of the log-linear plot of blood concentration vs. time. The mean peak drug concentration (Cₘₐₓ) and the time to reach Cₘₐₓ (Tₘₐₓ) were derived directly from blood concentrations observed in each subject. The area under each curve of drug concentration vs. time (AUC), up to the last data-point, was calculated by the linear trapezoidal rule and extrapolated, to time infinity, by the addition of Cₙₐₛₜ/λn, where Cₙₐₛₜ is the drug concentration in the last blood sample investigated. The area under the first moment (AUMC) was determined using the rules for AUC calculation. The mean residence time (MRT) was estimated as AUMC/AUC, whereas the terminal elimination half-life (t½) was calculated as 0.693/λn. The apparent total clearance (CL/F) at steady state was calculated, using non-compartmental methods, as dose/AUC. The accumulation index (Rₐₐₜ) was calculated as Cₘₐₓ₁/Cₘₐₓ₁, where Cₘₐₓ₁ is the mean peak drug concentration at steady state and Cₘₐₓ₁ is the mean peak drug concentration after a single dose.

All data were compared using Student’s t-tests, analysis of variance (ANOVA), and Tukey’s tests, as appropriate. A P-value of <0.05 was considered indicative of a statistically significant difference.

**RESULTS**

In the present study, the effects of induced diabetes and/or experimental cutaneous *Leishmania* infection on the pharmacokinetics of SbV were investigated in hamsters, both after a single dose of an antimonial drug and after 21 daily doses.

**Single Dose**

Figure 1 shows the mean blood concentrations of SbV recorded at various times after a
single intramuscular dose, of 80 mg Pentostam/kg, in the non-diabetic, uninfected controls (C), the non-diabetic hamsters with cutaneous *Leishmania* infection (L), the uninfected diabetic animals (D), and the hamsters that had both diabetes and cutaneous *Leishmania* infection (DL). The corresponding non-compartmental pharmacokinetic parameters of SbV are shown in Table 1. In the control hamsters the SbV in the single dose was rapidly absorbed from the intramuscular tissue, giving a mean maximum blood concentration ($C_{\text{max}}$), of 11.6 μg/ml, just 0.25 h after the Pentostam injection. It was also rapidly distributed in, and eliminated from, the bloodstreams of the control hamsters, with a mean $t_{\text{K}}$ of just 1.7 h. Although generally similar trends were seen in the hamsters of the L, D and DL groups, the mean $C_{\text{max}}$ observed in each of these groups was significantly higher than the control value ($P<0.001$ for each; Table 1). The diabetic but uninfected animals of group D took three times as long to reach $C_{\text{max}}$ (0.75 h) than the animals of groups C, L and DL. No SbV could be detected in any blood sample collected 8 h after dosing.

The DL animals showed the highest $C_{\text{max}}$ (mean=23.2 μg/ml) but the C, L, D and DL animals gave similar values of $t_{\text{K}}$ after a single SbV administration (Table 1). There were several between-group differences in AUC, MRT and CL/F (see Table 1), group D having an AUC that was significantly higher than the control value and a CL/F that was significantly lower than the control value. The AUC and CL/F values of the animals in groups L and DL were similar to those seen in the control animals.

### Multiple Doses

The concentration–time profiles observed after 3 weeks of daily administrations of Pentostam (see Figures 2 and 3) were generally similar to those seen after the single doses. The pharmacokinetic parameters of SbV after multiple dosing, at

![Antimony Pharmacokinetics](image-url)

**FIG. 1.** Mean blood concentrations of antimony recorded, at various times after a single intramuscular injection of 80 mg Pentostam/kg, in the control hamsters (●), non-diabetic hamsters with leishmanial infection (○), diabetic hamsters without leishmanial infection (■), and diabetic hamsters with leishmanial infection (□). The vertical lines indicate S.E.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>C</th>
<th>L</th>
<th>D</th>
<th>DL</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (μg/ml)</td>
<td>11.6 (1.4)</td>
<td>17.3 (0.3)</td>
<td>17.2 (0.7)</td>
<td>23.2 (0.9)</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>0.25</td>
<td>0.25</td>
<td>0.75</td>
<td>0.25</td>
</tr>
<tr>
<td>$t_{\text{K}}$ (h)</td>
<td>1.7 (0.3)</td>
<td>1.5 (0.2)</td>
<td>1.7 (0.2)</td>
<td>1.7 (0.5)</td>
</tr>
<tr>
<td>AUC (μg/h.ml)</td>
<td>26.8 (2.9)</td>
<td>28.0 (1.2)</td>
<td>48.1 (1.8)</td>
<td>30.1 (3.0)</td>
</tr>
<tr>
<td>CL/F (litre/h.kg)</td>
<td>3.0 (0.4)</td>
<td>2.9 (0.2)</td>
<td>1.7 (0.1)</td>
<td>2.7 (0.3)</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>2.6 (0.3)</td>
<td>2.1 (0.3)</td>
<td>2.7 (0.2)</td>
<td>1.6 (0.2)</td>
</tr>
</tbody>
</table>

**TABLE 1.** The pharmacokinetics of antimony after a single intramuscular dose of Pentostam, in control hamsters (C), non-diabetic hamsters with leishmanial infection (L), diabetic hamsters without leishmanial infection (D), and diabetic hamsters with leishmanial infection (DL).
steady state (Table 2), did, however, show some differences with those seen after a single dose (Table 1). At steady state, for example, $C_{\text{max}}$ was higher than the corresponding value recorded after a single dose, irrespective of the group of animals being considered ($P<0.001$ for each). The highest increase in $C_{\text{max}}$ was seen in group L (49%) while the lowest increase was observed in group DL (13.2%). Surprisingly, AUC was significantly decreased in group D (22% decrease; $P<0.001$), virtually unchanged in group DL (6% increase; $P>0.05$), and significantly increased in groups C (32% increase; $P<0.001$) and L (51% increase; $P<0.001$). In contrast, multiple dosing led to significant increases in CL/F for group D ($P<0.001$), no significant changes in this parameter for group DL ($P>0.05$) and significantly lower CL/F values in groups C and L ($P<0.001$ for each). Therefore, in the non-diabetic hamsters, CL/F was decreased after multiple dosing whether

FIG. 3. Mean blood concentrations of antimony recorded, at various times after a single intramuscular injection ($\bullet$) or 21 intramuscular injections ($\bigcirc$) of Pentostam, in the control hamsters (a), diabetic hamsters without leishmanial infection (b), non-diabetic hamsters with leishmanial infection (c), and diabetic hamsters with leishmanial infection (d). The vertical lines indicate S.E.
the animals were infected with *Leishmania* (34.5% decrease) or not (23% decrease).

The pharmacokinetic parameters of SbV at steady state in the control hamsters were compared with the corresponding values for the animals in groups L, D and DL (Table 2). This revealed that the diabetic animals had minimal SbV accumulation ($R_{ac}$) in their blood and that *Leishmania* infection did not affect this accumulation. After multiple doses of Pentostam, the $t_{\frac{1}{2}}$ of group DL was significantly higher than that of the control group ($P<0.05$) whereas the MRT of group D was significantly lower than that of the control group ($P<0.001$).

### Antileishmanial Activity

The foot-pad measurements of the hamsters infected with *Leishmania* (i.e. groups L, DL and LD) are summarized in Figure 4. All of these hamsters had ‘control’ footpads (i.e. uninoculated hind foot-pads) that were of similar and unchanging thickness. The induction of diabetes, prior to Pentostam treatment, had no significant effect on the thicknesses of the *Leishmania*-inoculated or -uninoculated foot-pads. Three weeks of Pentostam treatment failed to reduce the size of the foot-pad lesions, which gradually and significantly increased in size in all three groups of infected hamsters. After the 3 weeks of treatment, the animals that had their diabetes induced after their *Leishmania* infection had established (i.e. the animals in the LD group) had significantly smaller lesions ($P<0.001$) than the hamsters in the L and DL groups.

### DISCUSSION

Bell and Hye (1983) described the use of STZ-treated Syrian hamsters as a useful model of human type-I diabetes, which is characterised by the destruction or dysfunction of pancreatic beta cells. The STZ

**TABLE 2.** The pharmacokinetics of antimony after 21 intramuscular doses of Pentostam, in control hamsters (C), non-diabetic hamsters with leishmanial infection (L), diabetic hamsters without leishmanial infection (D), and diabetic hamsters with leishmanial infection (DL)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>C</th>
<th>L</th>
<th>D</th>
<th>DL</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{max}$ (µg/ml)</td>
<td>16.7 (2.8)</td>
<td>25.8 (0.3)*</td>
<td>23.7 (1.2)*</td>
<td>26.2 (0.4)*</td>
</tr>
<tr>
<td>$T_{max}$ (h)</td>
<td>1.00</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>$R_{ac}$ (h)</td>
<td>1.5 (0.2)</td>
<td>1.5 (0.0)</td>
<td>1.2 (0.1)*</td>
<td>1.1 (0.1)*</td>
</tr>
<tr>
<td>$t_{\frac{1}{2}}$ (h)</td>
<td>1.3 (0.2)</td>
<td>1.5 (0.1)</td>
<td>1.1 (0.1)</td>
<td>1.6 (0.4)†</td>
</tr>
<tr>
<td>AUC (µg/h.ml)</td>
<td>35.2 (1.8)</td>
<td>42.2 (1.0)*</td>
<td>37.7 (0.9)</td>
<td>31.7 (4.0)*</td>
</tr>
<tr>
<td>$CL/F$ (litre/h.kg)</td>
<td>2.3 (0.1)</td>
<td>1.9 (0.0)*</td>
<td>2.1 (0.1)</td>
<td>2.6 (0.3)*</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>1.9 (0.1)</td>
<td>1.9 (0.1)</td>
<td>1.5 (0.1)*</td>
<td>1.7 (0.2)</td>
</tr>
</tbody>
</table>

*Significantly different from control value ($P<0.001$).
†Significantly different from control value ($P<0.05$).

**FIG. 4.** Mean thicknesses of the uninoculated ‘control’ footpads (Control) and the inoculated footpads before any Pentostam treatment and after 21 doses of Pentostam, in the hamsters given diabetes before (■) and after (□) leishmanial infection and in the non-diabetic hamsters with leishmanial infection (■). The vertical lines indicate s.e.
regimen used in the present study, of a total dose of 130 mg/kg divided into three daily doses, induced diabetes which, given the results of earlier studies (Junod et al., 1969; Tsuji et al., 1988; Ar’rajab and Ahren, 1993; Mihm et al., 2001; Striffler and Nadler, 2004), is assumed to have been of type I. The human leishmaniases are a group of diseases with a spectrum of clinical manifestations ranging from self-healing cutaneous ulcers to severe visceral disease and even death (Handman and Bullen, 2002). With notable exceptions, the form (visceral, cutaneous, diffuse cutaneous or mucocutaneous) and severity of disease are a function of the infecting *Leishmania* species and the host’s genes that affect the host’s inflammatory and immune responses to the parasites (Colmenares et al., 2002). In the present study, hamsters were used as models both of human diabetes and human cutaneous leishmaniasis.

In the present study, curiously, the mean $C_{\text{max}}$ recorded, after a single dose of Pentostam, in the non-diabetic animals with *Leishmania* infection (17.2 µg/ml) was much lower than observed, in similar animals given the same dose of Pentostam, by Radwan et al. (2002). The difference may reflect differences in the experimental setting or, more likely, in the methods used to measure SbV concentrations.

Although pharmacokinetic parameters measured after a single dose of a drug may be indicative of drug behaviour after multiple doses, it is clear, from the present results, that those recorded after single and multiple doses may differ markedly. Despite the inter-dose period in the present study (24 h) being more than 10-fold longer than the $t_{1/2}$ at steady state, multiple dosing led to very significant increases in the SbV $C_{\text{max}}$, compared with that recorded after one dose, in all the groups investigated. Multiple dosing also led to significant decreases in CL/F in the non-diabetic animals, whether they had leishmanial infections or not. In other hamsters infected with *L. major*, Radwan et al. (2002) also found that multiple dosing with Sb^V led to a significant (20%) decrease in mean CL/F. Sb^V is mainly eliminated by renal excretion (Valladares et al., 1996). In the present study, with only once-daily administration, accumulation would not be expected. The observed decreases in CL/F are therefore probably indicative of renal toxicity, which has already been associated with Sb^V. When, for example, Sampaio et al. (1997) increased the Sb^V dose they were using to treat Brazilian cases of mucocutaneous leishmaniasis, from 20 to 40 mg/kg.day, this resulted in a severe nephrotoxic effect and an increase in the number of leucocytes in the urine.

The hyperglycaemia of diabetes causes thirst, hunger and increased urine volume (Marks and Raskin, 2000; Torffvit and Agardh, 2001). To minimize any pharmacokinetic interactions with the antimony, the diabetic hamsters investigated in the present study were not given any glucose-control treatment and they therefore probably excreted more urine than their non-diabetic counterparts. This higher urine volume may be responsible for the significant increase in CL/F in the hamsters of group D, an increase which, in group DL at steady state, may have offset the decrease observed in group L.

In humans, type-I diabetes accounts for approximately 10%–15% of the diabetic population world-wide (WHO, 1985). Type-II, which results from a variable combination of insulin resistance and insulin deficiency, generally develops in adults (DeFronzo, 1988; Yki-Jarvinen, 1994) but can also develop at a younger age, as in the maturity-onset diabetes of the young (Pirart, 1978). Type I and II can both cause microvascular and macrovascular complications, resulting in increased morbidity and mortality (Fajans and Conn, 1965). At the start of the present study it was assumed that diabetes-attributable vascular pathology and/or hyperglycaemia would affect the development of the foot-pad lesions in *Leishmania*-infected diabetic hamsters (groups DL and LD). Diabetes appeared
to have no effect on the leishmaniasis, however, and, very surprisingly, 21 days of daily treatment with Pentostam also had no or little effect on the disease. As the Pentostam showed little antileishmanial activity in any of the hamster groups, it seems unlikely that its lack of effect can be attributed to any immunosuppression caused by the diabetes and/or the L. major.

In conclusion, the present results confirm that multiple doses of SbV may be toxic to the kidney. The increased urine excretion associated with diabetes may make SbV treatment of leishmaniasis less effective in diabetic patients than in the non-diabetic. To keep blood concentrations of SbV at effective concentrations, it may therefore be necessary to give diabetic patients relatively high doses. Kidney function should always be monitored in patients given multiple doses of SbV. Hamsters treated with streptozotocin can be used to create a useful animal model of type-I diabetes. The present results indicate, however, that hamsters are poor models for research on the treatment of human cutaneous leishmaniasis, as foot-pad lesions caused in hamsters by inoculations with L. major appear relatively insensitive to Pentostam. The efficacy and pharmacokinetics of SbV, in various doses, need investigating in other animal models. The effects of the multiple administration of SbV on the kidneys of treated animals also need further investigation, in a better animal model of cutaneous leishmaniasis.

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