PHARMACOKINETICS OF BENZNIDAZOLE IN CHAGAS DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Background

Chagas disease is a neglected parasitic illness affecting approximately 8 million people, predominantly in Latin America. Benznidazole is the drug of choice for treatment, although availability has been limited. A paucity of knowledge of the pharmacokinetic properties of this drug have contributed to limited availability in several jurisdictions.

Objective

To conduct systematic literature review and Bayesian meta-analysis of pharmacokinetic studies to improve estimates of basic pharmacokinetic properties of benznidazole.

Methods

A systematic search of Embase, Medline, LILACS and Scielo was conducted. Eligible studies reported patient-level data from single 100mg dose pharmacokinetic evaluations of benznidazole in adults, or otherwise provided data relevant to the estimation of pharmacokinetic parameters which could be derived from such studies. A Bayesian hierarchical model was used for analysis. The use of secondary data (i.e. studies that did not include patient level, single 100mg dose data) was used for the generation of empiric priors for the Bayesian analysis.

Results

The systematic search identified nine studies for inclusion. Nine pharmacokinetic parameters were estimated including AUC, Cmax, Tmax, elimination (Kelim) and absorption (Ka) rate constants, absorption and elimination half-life, apparent oral clearance and apparent oral volume of distribution. The results showed consistency across

studies. The AUC and Cmax were 51.31mg*h/L (95% CrI: 45.01, 60.28) and 2.19mg/L (95% CrI: 2.06, 2.33), respectively. The ka and Kelim were 1.16h^{-1} (95% CrI; 0.59, 1.76) and 0.052h^{-1} (95% CrI; 0.045, 0.059), respectively, with corresponding absorption and elimination half-lives of 0.60h (95% CrI; 0.38, 1.11) and 13.27h (95% CrI; 11.79, 15.42). The oral clearance and volume of distribution were 2.04L/h (95%CrI 1.77, 2.32) and 39.19L (95%CrI; 36.58, 42.17), respectively.

Conclusions

A Bayesian meta-analysis was used to improve estimates of the standard pharmacokinetic parameters of benznidazole. This data can inform clinicians and policymakers as access to this drug increases.

Background

Chagas disease, also known as American trypanosomomiasis, is a parasitic illness affecting approximately 8 million people worldwide, with most cases found in continental Latin America.(1); although increasingly recognized in developed countries outside the traditional endemic area for vectorial transmission, due to migration and vertical transmission in offspring of infected migrant mothers. Chagas disease is primarily transmitted by the exposure to feces of infected triatomine bugs, also known as 'kissing bugs'. Infection can also occur through means, such as mother-to-child transmission, transfusion from the blood of an infected individual, through organ transplantation from an infected donor or foodborne. During the acute phase of infection, patients tend to have a variety of symptoms ranging from skin lesions and a swelling eye lid, to flu-like symptoms including fever, headache, and muscle pain. Chronic infection with Chagas disease can lead to more critical injury, with up to 30% of patients suffering from cardiac disorders and up to 10% suffering from digestive or neurological symptoms. As injury to the cardiovascular system progresses, Chagas disease can lead to sudden death or heart failure caused by progressive destruction of the heart muscle and its nervous system.(2, 3)

Two drugs are currently used for the treatment of Chagas disease and have been shown to be very effective if used early in the disease process. Benznidazole, a nitroimidazole derivative and nifurtimox, a nitrofuran, both act on the parasite through the formation of free radicals and/or electrophilic metabolites. Of these two drugs, benznidazole is the preferred agent because of a lower incidence of side effects.(4-6) Recent evidence suggests that benznidazole is also effective in the chronic phase of Chagas infection, although in a

randomized clinical trial treatment significantly reduced the detection of circulating parasites but did not reduce cardiac clinical progression.(7, 8) Availability of both treatments has been limited however, and Doctors Without Borders/Médecins Sans Frontières reported major shortages of benznidazole in 2011 as the primary manufacturer, Roche suspended production and transferred technology and license to LAFEPE labs, Brazil in 2003.(9) Bayer has since renewed production of nifurtimox, while production of benznidazole has been taken since 2012 by ELEA Argentina labs. Since 2014 ELEA started a jointly project with Liconsa labs (Chemo group) in Spain which is currently under FDA revision process. Recently, LAFEPE labs in Brazil announced the approval to their benznidazol by the Brazilian regulatory agency. In 2011, a 12.5mg pediatric dosage form (manufactured by LAFEPE and DNDi) was registered by the Brazilian Health Surveillance Agency to further improve the treatment of pediatric Chagas disease.

With inconsistent availability of benznidazole throughout several countries, it is of critical importance that basic pharmacokinetic data be available to both clinicians and policy-makers to ensure evidence-informed decision making with regard to the drug approval process. Thus, there is a requirement for a meta-analysis of studies of the pharmacokinetics of benznidazole with special interest in the type of population studied (age, ethnic background, dose and regimen).

The purpose of this this study is to conduct a meta-analysis of pharmacokinetic studies in an effort to improve the estimates of the basic pharmacokinetic properties of benznidazole.

Methods

Systematic literature search

A comprehensive search of the literature was conducted using Embase, Medline, and the Latin American databases SciELO and LILACS. The Embase and Medline literature search strategies were conducted using the OVID platform. The search was conducted on May 4, 2016 and the search strategy is provided in **Appendix A**. The scope of the systematic literature review can be broken down into four components: Population, Interventions, Outcomes, and Study design (**Table 1**).

Study selection and data extraction

A study investigator scanned all abstracts and proceedings identified by the literature search that were potentially relevant in full-text. All citations selected for full text review were then reviewed in detail to determine final eligibility status. For all eligible studies, data on study characteristics, patient characteristics, and outcomes was extracted in duplicate by two investigators. Discrepancies observed between the data extracted by the two data extractors were resolved through discussion and, when discrepancies could not be resolved, a third reviewer was consulted. Where measures were only available in graphical format, the software DigitizeIt (Braunschweig, Germany) was used, when possible, to extract the relevant data. When individual patient data (IPD) was available, this was extracted preferentially to summary data. The following study characteristics were extracted: author, year, journal/source, number of patients enrolled, study region, drug dose, drug manufacturer, analytical method, inclusion/exclusion criteria. The following patient characteristics were extracted: age, sex, weight, BMI, serum creatinine, and

creatinine clearance. The following outcomes were extracted: drug plamsa concentration according to time, summary parameters when no IPD was provided, including oral clearance, oral volume of distribution, half-life, Cmax, Tmax, absorption and elimination rate constant, AUC.

Meta-analysis

Traditional meta-analysis uses summary data of different studies, which are often obtained from publications, to estimate parameters of interest. In this meta-analysis, data from individual patients were synthesized, resulting in an IPD meta-analysis. The IPD approach improves the quality of the data, the analyses and subsequently the reliability of the results. In addition, the information from summary statistics was also integrated into an all-encompassing meta-analysis. Given the complexity of the analysis, a Bayesian approach was favored for its ability to deal with complex hierarchical models.

Analysis

Bayesian methods involve formal combination of a prior probability distribution (that reflects a prior belief of the possible values of the model parameters) with a (likelihood) distribution based on the observed data to obtain a posterior probability distribution of model parameters.(10) The likelihood informs us about the extent to which different values for the parameter of interest are supported by the data. A major advantage of the Bayesian approach is that the method naturally leads into a decision framework.(10-12) The posterior distribution can be interpreted in terms of probabilities (e.g. “There is an x% probability that treatment A results in a greater response than treatment B”); frequentist approaches do not allow such an interpretation.(13)

143 The averaged likelihood is necessary in order for the posterior to be a distribution. By
144 definition, the calculation of the averaged likelihood (and because of that the posterior
145 distribution) involves integration. This integration can become exorbitant, especially when
146 the parameter of interest is high dimensional. For years, the popularity of Bayesian
147 statistics suffered from the impracticable numerical integrations necessary to obtain the
148 posterior distribution. This changed after the introduction of Markov Chain Monte Carlo
149 (MCMC) techniques, which resulted in a rise in popularity of Bayesian statistics because it
150 provides a tool to get round the integration process. The most important and famous
151 MCMC methods include the Gibbs sampler(14) and the Metropolis-Hasting algorithm.(15)
152 The Gibbs sampler is based on the characteristic that the multivariate distribution is
153 uniquely determined by its conditional distributions and was used throughout these
154 analyses.

155 ***3.3.2*** *Pharmacokinetics*

156 PK is a well-established field with many different models used to explain the absorption,
157 distribution and elimination of a drug within the blood stream. For this study, a single
158 compartment model was used with the following core equation used:

$$Concentration = \frac{F \times dose \times ka}{V \times (ka - kel)}\left(e^{-kel \times time} - e^{-ka \times time}\right) \quad (1)$$

159 Where ka is the absorption rate, kel is the elimination rate, F is the bio-availability and V is
160 the volume of distribution. It turns out that all of the parameters of interest can be
161 expressed as a function of the three parameters: ka, CL and V. The volume of distribution
162 (V) is the parameter that describes the tendency of a drug to distribute out of the blood into

the tissues. It represents the volume of plasma necessary to account for all the drug in the body. The elimination process is defined as the irreversible removal of drugs from the body. The elimination mechanism is best described by its parameter clearance (CL). Clearance is the theoretical volume of blood, which is effectively cleared of drug per unit of time. The formulas for the remaining parameters are as follows

$$kel = \frac{CL}{V} \tag{2}$$

$$AUC = \frac{F \times dose \times ka}{V \times (ka - kel) \times kel} \tag{3}$$

$$T_{max} = \frac{1}{(ka - kel)} ln\left(\frac{ka}{kel}\right) \tag{4}$$

$$C_{max} = \frac{F \times dose \times ka}{V \times (ka - kel)} (e^{-kel \times T_{max}} - e^{-ka \times T_{max}}) \tag{5}$$

$$T_{a,1/2} = \frac{\ln(2)}{ka} \tag{6}$$

$$T_{el,1/2} = \frac{\ln(2)}{kel} \tag{7}$$

Thus, we used the PK model described in Equation (1) as the basis for the hierarchical model and derived the parameters in Equations (2)-(7) from the model parameters.

3.3.3 Hierarchical modeling

To discuss the modeling, let y_{ijk} *be the* k^{th} observation from the i^{th} individual from the j^{th} study, with the corresponding time t_{ijk}. The 3x1 vector of pharmacokinetic parameters for individual i in the j^{th} study by λ_{ij}. The first stage of the model was specified as:

$$p(y_{ijk}|\lambda_{ij},\tau) = N(f_{ijk},\tau^{-1}v_{ijk}) \quad (8)$$

where f_{ijk} is the pharmacokinetic model evaluated at time t_{ijk} with the individual PK parameters equal to λ_{ij} and v_{ijk} is the residual error structure.

The second stage of the model was to model at the study level and was specified as:

$$p(\lambda_{ij}|\theta_i,\Phi) = MVN(\theta_i,\Phi) \quad (9)$$

Where MVN() represents a multi-variate Normal distribution, θ_i (3×1) represents the mean kinetic behavior of the i^{th} individual and Φ (3×3) is corresponding variance-covariance matrix representing the within study variance.

The third stage of the hierarchical model represents the population parameter estimation and was defined by making the following distributional assumptions:

$$p(\theta_i|\mu,\Omega) = MVN(\mu,\Omega) \quad (10)$$

where μ (3×1) is the mean value of the individual mean parameter vector θ_i and Ω (3×3) is the corresponding variance-covariance matrix representing the between study variance.

The definition of the hierarchical model is completed by the specification of the fourth stage, in which prior densities are assigned to the parameters. In particular, the variance-

covariance matrices are defined using a Wishart prior distribution, the population PK parameters are given a multivariate Normal prior distribution, the residual variance factor is defined using an inverse uniform distribution.

In addition to using a hierarchical model to account for the within individual and study correlation, the model also used an adjustment for whether patients had had food or were fasting. This was accomplished by having a regression adjustment on the absorption rate parameter, such that ka was replaced by $(ka - \beta x)$ throughout equation (1). It was judged that food would affect absorption, but not volume of distribution or clearance.

In order to integrate the summary statistics from four studies, the information was used to create empirical priors for the clearance and volume. In this way, the analysis included a 5th stage by which the information from summary statistics was first integrated and then updated using the four hierarchical stages described above.

Data was analyzed in R (version 3.2.1). The Bayesian analyses were performed using a Markov Chain Monte Carlo (MCMC) method as implemented in JAGS (version 3.4.0) software package.(16) A first series of 60,000 iterations from the JAGS sampler was discarded as 'burn-in' and the inference was based on an additional 100,000 iterations using two chains.

Results

Evidence base

A total of 462 citations were identified through the database search and through a hand-search of the literature (**Figure 1**). Of these, 441 were excluded at the abstract-screening

stage. This resulted in 21 studies included in full-text screening. Of these, 12 were excluded: one for an ineligible study design, seven for studying populations that could not inform the primary analysis of interest (i.e. single dose pharmacokinetic analysis), two for not including the intervention of interest, and two for not including the outcome of interest. This resulted in a total of 9 studies that were included in the analysis.(17-25) There were no single-dose PK studies of benznidazole in children. A table of the final list of included studies is presented in **Table 2**.

The nine included studies were published or released between 1979 and 2016. One of these studies was a secondary publication of data contained in a prior study, and was therefore not included separately in the final data extraction sheets.(23) Three studies contained individual patient level data from benznidazole 100mg single dose studies.(17, 20, 22) One was a published study(22), one was an unpublished trial report(17) and one a PhD thesis(20), that also remained un-published and was obtained from the corresponding University archives with authorization for the purpose of this analysis. Three studies contained limited individual patient level data from multi-dose studies.(18, 20, 21) Of these, only the study by Raaflaub(21) provided data pertinent to the primary analyses. One additional study contained some further single dose summary data. This was a single dose study of 25mg/kg in oncology patients.(24) A further two studies evaluated benznidazole, using typical therapeutic doses, in a sample of patients with Chagas disease. These studies provided some summary kinetic parameters that were available for incorporation as priors into the final PK model.(19, 25)

228 Pharmacokinetic parameters

229 Nine pharmacokinetic parameters were estimated at the individual level, study level as
230 well as an overall estimate that included the use of empiric priors, when available. The
231 study-level and overall adjusted data along with 95% credible intervals are presented in

232 **Table** 3. The study-level and overall adjusted data along with 90% credible intervals are
233 presented in **Appendix B**.

234 *Area under the curve*

235 The overall AUC for the final 100mg dose model, including all the available data, was 51.31
236 mg*h/L (95% CrI; 45.01, 60.28). Only three studies informed this parameter.(17, 20, 22)
237 The consistency between studies was excellent, with little heterogeneity from the visual
238 assessment of the Forest plot (**Figure 2**). The Forest plot with corresponding 90% credible
239 intervals is shown in **Appendix B**. The 90% credible intervals of the individual studies all
240 fell within 80% and 125% of the overall estimate, suggesting acceptable heterogeneity. The
241 study presented in the thesis by Peregrina Lucano deviated the most from the overall
242 parameter estimate, but only by approximately 6 percent.

243 *Maximum plasma concentration*

244 The overall Cmax for the final 100mg dose model, including all the available, data was
245 2.19mg/L (95% CrI; 2.06, 2.33). As with AUC, the same three studies informed this
246 parameter. Although the variability in Cmax between studies was higher than for AUC, the
247 90% and the 95% credible limits of each of the individual studies remained between 80%
248 and 125% of the overall estimate. **Figure 3** shows the Forest plot for Cmax, and it can be
249 observed that heterogeneity was minimal, with the point estimates being contained in all
250 the credible intervals.

251 *Time to maximum plasma concentration*

252 The overall calculated Tmax was 2.93h (95% CrI, 2.57, 3.48). As with AUC and Cmax, only
253 the three primary studies informed this analysis. The Tmax was more heterogeneous

between studies than either AUC or Cmax, but overall the variability is consistent with the degree of variability seen within studies (**Figure 4**). The variability in Tmax is primarily associated with the absorption rate constant (Ka), which in turn is affected by a variety of factors including the formulation administered and patient factors such as gastric emptying and potentially food effects. Given a constant elimination rate constant, as Ka decreases Tmax will increase. Since Ka is inherently more variable and difficult to measure, there is likely to be a higher degree of variability in parameters such as Tmax, than in Cmax or AUC.

Elimination rate constant

The elimination rate constant utilized the patient level data from the three primary studies, but was further informed by two additional studies that provided summary (study-level) data that could be incorporated as empirical priors into the Bayesian model.(21, 24) The overall elimination rate constant was $0.052h^{-1}$ (95% CrI; 0.045, 0.059). The study-level data of the three primary studies was very consistent with the overall estimates as visually depicted in **Figure 5**. The final estimate of the elimination half-life was 13.27h (95% CrI; 11.79, 15.42).

Absorption rate constant

The absorption rate constant was the parameter with a high degree of both within-study and between-study heterogeneity (**Figure 6, Appendix B**). This was reflected in the wide credible intervals at the study level and overall level estimates. The overall estimate was $1.16h^{-1}$ (95% CrI; 0.59, 1.76), with a resulting absorption half-life of 0.60h (95% CrI; 0.38, 1.11). The study presented in the thesis by Peregrina Lucano differed the most from the two other studies.

Apparent volume of distribution

The apparent volume of distribution was estimated and the overall results were remarkably consistent with the results (**Figure 7**). Although summary data from two additional studies(19, 25) was used to derive an empirical prior, the results remained consistent. The overall apparent volume (V/F) was 39.19L (95%CrI; 36.58, 42.17).

Apparent oral clearance

The apparent oral clearance was also estimated utilizing empirical priors for two studies. (19, 25) The overall clearance (Cl/F) was estimated to be 2.04L/h (95%CrI 1.77, 2.32), fitting in well with the results from the three primary studies in which the apparent oral clearance ranges from 1.95 to 2.10L/h. **Figure 8** shows the study-level Forest plot for Clearance, with results consistent with each other and the overall estimate.

Discussion

This is the first meta-analysis of pharmacokinetic studies of benznidazole. Using a Bayesian meta-analytic framework, all pharmacokinetic data relevant to the parameters of interest for a single dose 100mg PK studies in adults were utilized, thereby producing better estimates than could otherwise be derived using a typical frequentist framework. The primary oral PK parameters of interest, including AUC, Cmax, Tmax, Kelim, Vd/F and Cl/F showed remarkable consistency between the three primary studies providing patient level data. Although at the individual level there was significant heterogeneity (i.e. within study heterogeneity), the between study heterogeneity was modest, suggesting that each study was estimating the population parameter reasonably well and further suggesting that the use of meta-analytic technique to combine data is well justified. When available, additional

298 data from multi-dose studies and other single dose studies were used to provide empiric
299 priors to further strengthen the final parameter estimates. These data did not substantially
300 change any parameter estimates, further strengthening the reliability of these results.

301 An important consideration in meta-analysis is between study heterogeneity. The degree to
302 which heterogeneity influences the interpretation of results is often subjective and has
303 been widely debated.(26) With few meta-analyses of PK studies, the interpretation of
304 between study heterogeneity is even less well established. As the primary objective of this
305 meta-analysis was to improve the estimates of the oral PK parameters derived from a
306 single-dose studies, it must be the cases that the included studies actually be sufficiently
307 similar to be combinable. The acceptance criteria for bioequivalence by the Food and Drug
308 Administration is that the 90% confidence intervals of the mean AUC and Cmax for the test
309 formulation are within 80% and 125% of the reference formulation.(27) Taking the
310 reference formulation as the combined estimate and the test formulations as the individual
311 studies, the bioavailability criteria would be met with both AUC and Cmax. Furthermore,
312 heterogeneity, as visually assessed with the Forest plots, shows consistency between the
313 three primary studies for these outcomes, as well as the other pharmacokinetic
314 parameters.

315 This study is subject to several limitations. First, this study began with the assumptions of a
316 one-compartment model with first order elimination. While not a limitation *per-se*, it
317 assumed that prior studies done on the pharmacokinetics of benznidazole to determine its
318 basic kinetic properties were correct. A careful examination of the individual level data
319 presented in **Appendix C**, however, does confirm that the model reflects the data well.

Second, although a major advantage of this meta-analysis is the use of patient level data, this data was collected over a period of more than 30 years, utilizing various populations, a variety of formulations, and different analytic techniques for drug quantification in plasma. However, given the consistency of our results despite these factors further strengthens that subsequent studies on the pharmacokinetic characteristics of benznidazole would produce similar parameter estimates.

The treatment of Chagas disease, a paradigmatic case of a Neglected Tropical Disease, suffers the lack of resources both at the research and implementation aspects; therefore, new developments are scarce and there are plenty of unsolved aspects of the currently available treatments. In view of these limitations, efforts in solving pieces of these uncertainties through innovative validated analytic methods like this meta-analysis, helps in the process of knowledge acquisition regarding drugs like benznidazol around which clear clinical benefits have been observed in certain situations like acute infections and vertical transmission, but not in others.(28)

While this meta-analysis addresses the single-dose pharmacokinetic parameters of benznidazole in adults, these methods could also be applied to both existing pediatric data and multi-dose data. The advantage of our Bayesian approach was its incorporation of empiric priors into the final analysis. Using this approach, IPD multi-dose data, such as that presented by Raaflaub (21), could be analyzed along with other population based PK studies. Furthermore, utilizing the single-dose data derived in this meta-analysis, models could be further improved by the incorporation of relevant PK parameters, not derived from multi-dose studies.

342 In conclusion, this meta-analysis of pharmacokinetic studies has provided improved
343 estimates of the pharmacokinetic parameters under fasting conditions, of a single 100mg
344 dose of benznidazole in adults. The overall results reflect the individual studies from which
345 it was derived. These summary parameters can be used by clinicians and policymakers as
346 treatment of Chagas disease is scaled throughout Latin America.

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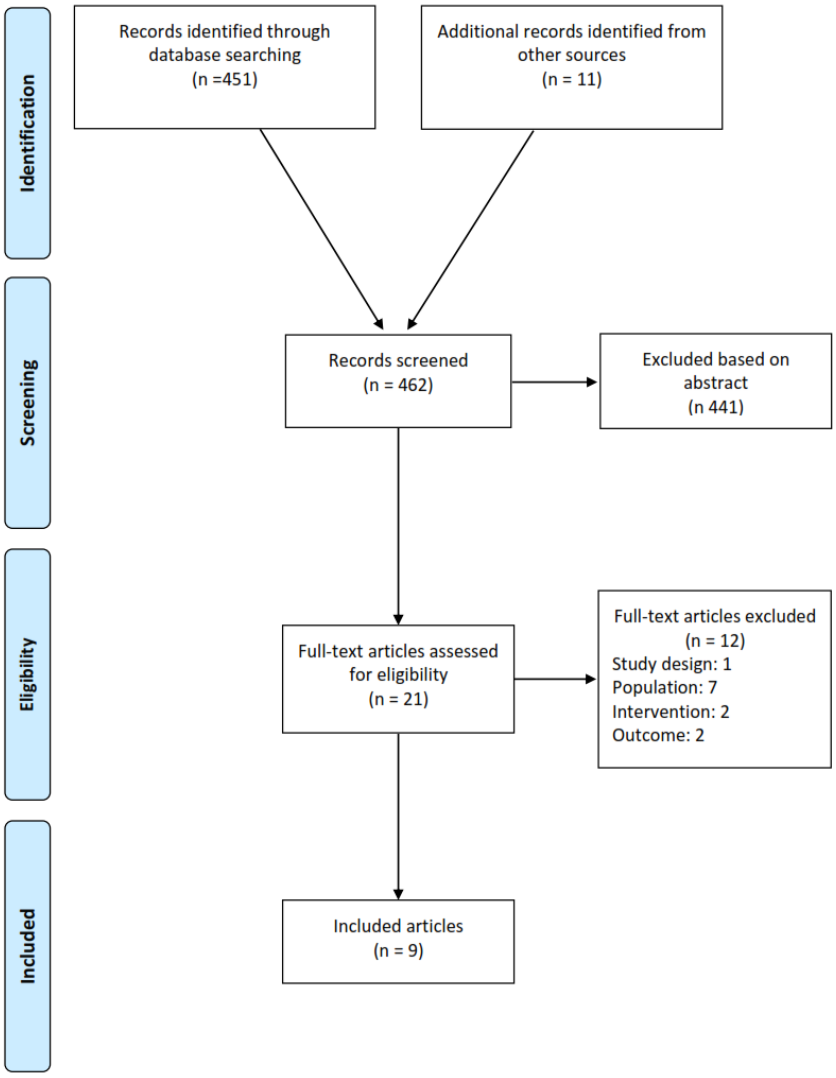
348 **Figure 1. PRISMA flow diagram of systematic literature search**



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351 **Table 1. Scope of review in terms of PIOS criteria**

Population	Healthy population and patients with Chagas disease
Interventions	Benznidazole
Outcomes	In adults receiving a single 100mg dose of Benznidazole, the following outcomes will be evaluated: 1. Peak plasma concentration (Cmax) 2. Time to reach Cmax (Tmax) 3. Area under the concentration-time curve (AUC_{0-t} and $AUC_{0-\infty}$) 4. Apparent oral clearance (CL/F) 5. Apparent oral volume of distribution (V/F) 6. Elimination rate constant and half life 7. Absorption rate constant and absorption half life
Study design	All trial types with PK evidence able to inform any of the above outcomes

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354 **Table 2. Study characteristics of included studies**

Study ID	Title	Treatment duration (days)	N	Treatment	Analytical method	Drug manufacturer
Raaflaub et al, 1979(22)	Single Dose Pharmacokinetics of the Trypanosomicide Benznidazole in Man	1	6	Benznidazole 100mg (single dose)	Differential pulse polarography	Hoffman-La Roche & Co
Bronn et al, 2015(17)	A study to evaluate the food effect of a new formulation containing 100mg benznidazole. A monocentric, open, randomized, single dose, two-period crossover trial in healthy volunteers	1	18	Benznidazole 100mg (single dose)	LC/MS-MS	Laboratorios Liconsa S.A., Spain
Soy et al, 2015(25)	Population pharmacokinetics of benznidazole in adult patients with Chagas disease	56	49	Benznidazole 2.5mg/kg BID	HPLC	Elea Laboratory, Argentina
Raaflaub, 1980(21)*	Multiple-dose kinetics of the trypanosomocide Benznidazole in Man	25	8	Benznidazole 3.5mg/kg BID	Differential pulse polarography	Hoffman-La Roche & Co
Fernandez et al, 2016(18)	Pharmacokinetic and pharmacodynamic responses in adult patients with Chagas disease treated with a new formulation of benznidazole	60	6	Benznidazole (various doses)	HPLC	Elea Laboratory, Argentina
Peregrina Lucano, 2004(20)	Population Pharmacokinetics of benznidazole in Mexican patients with Chagas disease	1	11	Benznidazole 100mg (single dose) + 2.5mg/kg BID	HPLC	Roche
Bournissen, 2013(19)	E1224 pharmacokinetics report	60	45	Benznidazole 2.5mg/kg BID	NR	NR
Roberts et al, 1984	A Phase I study of the combination of benznidazole and CCNU in Man	various	11	Benznidazole 25mg/kg	HPLC	Hoffman-La Roche

355 * The study by Richle and Raaflaub(23) is not reported in this table since the relevant data
356 is already included with Raaflaub, 1980(21)

357 NR: not reported; LC-MS: liquid chromatography-Mass spectrometry; HPLC: high
358 performance liquid chromatography

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362 **Table 3. Final overall model pharmacokinetic parameters, reporting 95% credible**
363 **intervals**

	Overall Mean (95% CrI)	Bronn, 2015 Mean (95% CrI)	Peregrina Lucano, 2004 Mean (95% CrI)	Raaflaub, 1979 Mean (95% CrI)
AUC (mg*h/L)	51.31 (45.01, 60.28)	50.05 (45.91, 54.34)	54.82 (48.20, 64.40)	49.76 (44.66, 55.38)
Cmax (mg/L)	2.19 (2.06, 2.33)	2.20 (2.06, 2.34)	2.11 (1.92, 2.29)	2.26 (2.09, 2.44)
Kel (h^{-1})	0.05 (0.04, 0.06)	0.05 (0.05, 0.06)	0.05 (0.04, 0.06)	0.05 (0.05, 0.06)
T½ (h)	13.27 (11.79, 15.42)	12.95 (12.03, 13.95)	14.02 (12.26, 16.66)	12.94 (11.84, 14.28)
Tmax (h)	2.93 (2.57, 3.48)	2.75 (2.41, 3.17)	3.65 (2.77, 5.27)	2.35 (1.92, 2.93)
T½abs (h)	0.60 (0.38, 1.11)	0.59 (0.49, 0.72)	0.85 (0.58, 1.44)	0.47 (0.36, 0.64)
Ka (h^{-1})	1.16 (0.59, 1.76)	1.18 (0.96, 1.41)	0.82 (0.48, 1.20)	1.46 (1.08, 1.92)
V/F (L)	39.19 (36.58, 42.17)	39.16 (36.69, 42.04)	39.38 (36.79, 42.55)	39.04 (36.27, 42.01)
Cl/F (L/h)	2.04 (1.77, 2.32)	2.09 (1.93, 2.29)	1.95 (1.65, 2.23)	2.09 (1.87, 2.33)

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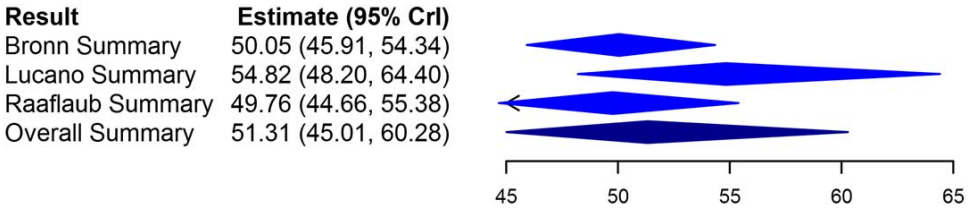
366 **Figure 2. Study-level Forest plot for AUC (mg*h/L)**

367 The mid-line of each estimate (row) represents the point estimate for the individual study (light blue) and the pooled
368 estimate (dark blue). Each estimate extends to include the lower (left) and upper (right) bounds of the 95% credible
369 interval. The small arrow at the ends of some of the estimates indicate that the credible interval extends slightly
370 beyond the scale of the x-axis.



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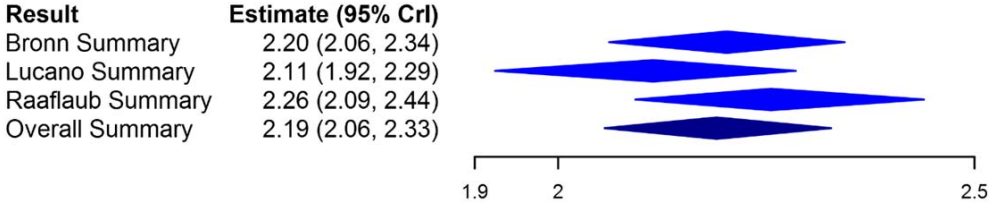
373 **Figure 3. Study-level Forest plot for Cmax (mg/L)**

374 The mid-line of each estimate (row) represents the point estimate for the individual study (light blue) and the pooled
375 estimate (dark blue). Each estimate extends to include the lower (left) and upper (right) bounds of the 95% credible
376 interval.



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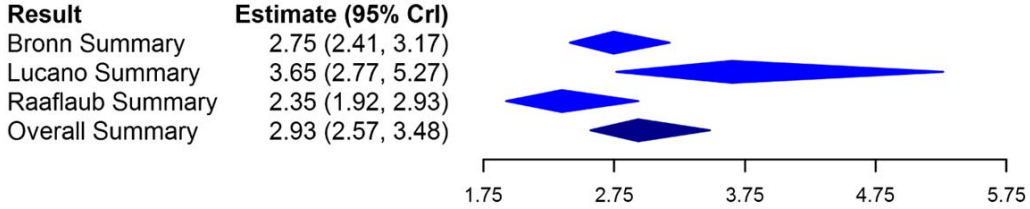
380 **Figure 4. Study-level Forest plot for Tmax (h)**

381 The mid-line of each estimate (row) represents the point estimate for the individual study (light blue) and the pooled
382 estimate (dark blue). Each estimate extends to include the lower (left) and upper (right) bounds of the 95% credible
383 interval.



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385
386
387 **Figure 5. Study-level Forest plot for Kelim (h^{-1})**

388 The mid-line of each estimate (row) represents the point estimate for the individual study (light blue) and the pooled
389 estimate (dark blue). Each estimate extends to include the lower (left) and upper (right) bounds of the 95% credible

interval. The small arrow at the ends of some of the estimates indicate that the credible interval extends slightly beyond the scale of the x-axis.

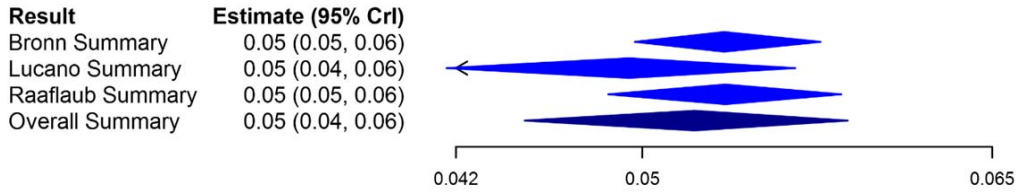


Figure 6. Study-level Forest plot for Ka (h^{-1})

The mid-line of each estimate (row) represents the point estimate for the individual study (light blue) and the pooled estimate (dark blue). Each estimate extends to include the lower (left) and upper (right) bounds of the 95% credible interval.

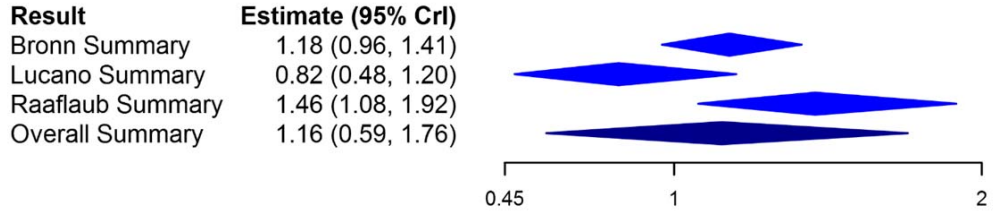


Figure 7. Study-level Forest plot for Vd/F (L)

The mid-line of each estimate (row) represents the point estimate for the individual study (light blue) and the pooled estimate (dark blue). Each estimate extends to include the lower (left) and upper (right) bounds of the 95% credible interval. The small arrow at the ends of some of the estimates indicate that the credible interval extends slightly beyond the scale of the x-axis.

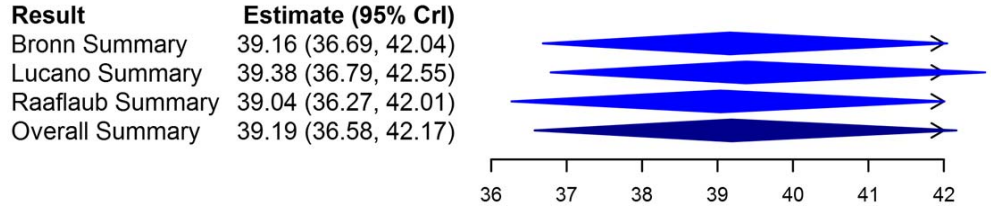
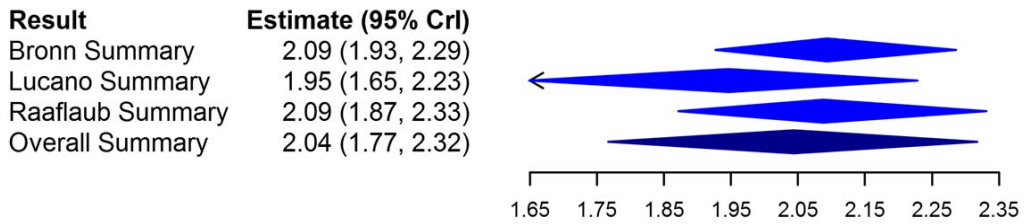


Figure 8. Study-level Forest plot for Cl/F (L/h)

The mid-line of each estimate (row) represents the point estimate for the individual study (light blue) and the pooled estimate (dark blue). Each estimate extends to include the lower (left) and upper (right) bounds of the 95% credible

interval. The small arrow at the ends of some of the estimates indicate that the credible interval extends slightly beyond the scale of the x-axis.



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