Pharmacokinetics of Oral Acyclovir in Neonates and in Infants: a Population Analysis

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Received 18 November 1999/Returned for modification 4 July 2000/Accepted 26 September 2000

Acyclovir is approved for the treatment of herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections in children by the intravenous and oral routes. However, its use by the oral route in children younger than 2 years of age is limited due to a lack of pharmacokinetic data. The objectives of the present study were to determine the typical pharmacokinetics of an oral suspension of acyclovir given to children younger than 2 years of age and the interindividual variabilities in the values of the pharmacokinetic parameters in order to support the proposed dosing regimen (24 mg/kg of body weight three times a day for patients younger than 1 month of age or four times a day otherwise). Children younger than age 2 years with HSV or VZV infections were enrolled in a multicenter study. Children were treated for at least 5 days with an acyclovir oral suspension. Plasma samples were obtained at steady state, before acyclovir administration, and at 2, 3, 5, and 8 h after acyclovir administration. Acyclovir concentrations were measured by radioimmunoassay. The data were analyzed by a population approach. Data for 79 children were considered in the pharmacokinetic study (212 samples, 1 to 5 samples per patient). Acyclovir clearance was related to the estimated glomerular filtration rate, body surface area, and serum creatinine level. The volume of distribution was related to body weight. The elimination half-life decreased sharply during the first month after birth, from 10 to 15 h to 2.5 h. Bioavailability was 0.12. The interindividual variability was less pronounced when the parameters were normalized with respect to body weight. Hence, dosage adjustment by body weight is recommended for this population. Simulations showed that the length of time that acyclovir remains above the 50% inhibitory concentration during a 24-h period was more than 12 h for HSV but not for VZV. The proposed dosing regimen seems adequate for the treatment of HSV infections, while for the treatment of VZV infections, a twofold increase in the dose seems necessary for children older than age 3 months.

Acyclovir is currently used for the prevention and treatment of herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections in children by the intravenous and oral routes. However, its use by the oral route in children younger than 2 years of age is limited due to a lack of pharmacokinetic data. The objectives of the present study were to determine the typical pharmacokinetics of an oral suspension of acyclovir given to children younger than 2 years of age and the interindividual variabilities in the values of the pharmacokinetic parameters in order to support the proposed dosing regimen (24 mg/kg of body weight three times a day for patients younger than 1 month of age or four times a day otherwise). Children younger than age 2 years with HSV or VZV infections were enrolled in a multicenter study. Children were treated for at least 5 days with an acyclovir oral suspension. Plasma samples were obtained at steady state, before acyclovir administration, and at 2, 3, 5, and 8 h after acyclovir administration. Acyclovir concentrations were measured by radioimmunoassay. The data were analyzed by a population approach. Data for 79 children were considered in the pharmacokinetic study (212 samples, 1 to 5 samples per patient). Acyclovir clearance was related to the estimated glomerular filtration rate, body surface area, and serum creatinine level. The volume of distribution was related to body weight. The elimination half-life decreased sharply during the first month after birth, from 10 to 15 h to 2.5 h. Bioavailability was 0.12. The interindividual variability was less pronounced when the parameters were normalized with respect to body weight. Hence, dosage adjustment by body weight is recommended for this population. Simulations showed that the length of time that acyclovir remains above the 50% inhibitory concentration during a 24-h period was more than 12 h for HSV but not for VZV. The proposed dosing regimen seems adequate for the treatment of HSV infections, while for the treatment of VZV infections, a twofold increase in the dose seems necessary for children older than age 3 months.

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was less than 12% over the entire calibration range.

Less than 15% was 0.01 fication of the assay (determined as the lowest concentration with a variability of
Pharmacology, Rene´ Huguenin Center, St. Cloud, France. The limit of quanti-
were stored and kept frozen (.

ambulatory children, a sample was obtained 4 h after dosing. Dosing history and
sampling schedule depended on the status of the child. For hospitalized children,
was retained because it corresponded to three graduations of the dosing syringe.

21): about 25 mg/kg per dose was expected to be adequate. The value of 24 mg/kg
younger than 1 month of age received acyclovir at 24 mg/kg of body weight qh.

PNA (mo) 15.45 (8.80–33.10) 6.90 (1.80–13.0) 65.0 (43.0–95.0) 39.6 (22.0–98.0)

0–2 yr, per os 79 5.45 (0.10–23.10) 15.45 (8.80–33.10) 6.90 (1.80–13.0) 65.0 (43.0–95.0) 39.6 (22.0–98.0)

H cm) 101.6 (84.0–103) 61.0 (29.0–91.0)

Pediatric, intravenous 18 72.0 (3.0–204) 81.0 (10.0–213) 17.8 (2.4–62.0) 113 (37.0–168) 44.7 (35.4–72.2)

* Values are medians (ranges).
RESULTS

Patients. A total of 90 patients was enrolled in the study. However, data for six patients were not included in the pharmacokinetic database because the dosing and/or sampling times had not been recorded and the data for five patients were discarded from the per-protocol analysis because they were older than 2 years of age. Therefore, data for 79 patients could be considered for the main analysis of the disposition of acyclovir in neonates and infants after oral administration. The data for these 79 patients were combined with those for the 18 pediatric patients treated intravenously for the global analysis (n = 102) of acyclovir disposition. The demographic data are summarized in Table 1.

Acyclovir doses and levels. In the oral formulation study (n = 79), the median (range) of the actual dose of acyclovir was 164 mg (43 to 292 mg), corresponding to 24.1 mg/kg (21.7 to 32.6 mg/kg) or 446 mg/m² (280 to 574 mg/m²). In the intravenous study (n = 18), the actual doses ranged from 83 to 500 mg/m². A total of 212 samples were analyzed in the main study (1 to 5 samples per subject), while 131 samples (7 or 8 samples per subject) were considered for the intravenous study. There were 351 samples in the global analysis (n = 102). Figures 1A and B show the data for the oral and intravenous studies, respectively.

Model building for oral disposition. The main models and hypotheses tested are described in Table 2. The two-compartment model was used to describe oral data. The typical value of the apparent clearance of acyclovir (CL/F) was found to be related to the estimated glomerular filtration rate (GFR), BSA, and SCr, \( CL/F = \theta_1 \cdot GFR \cdot BSA/(1.73) \cdot (40/SCR), \) where \( GFR = (7.2 \times PCA^a)/(\theta_{\alpha} + PCA^a) (\theta_1, \theta_2, and \theta_3 are defined below), \) while the interindividual variability of \( CL/F \) was expressed as \( CL/F = (CL/F) \cdot \exp(\eta_{CL/F}). \)

The GFR was estimated as a function of BSA. With this relationship, GFR tends to a maximal value in adults, in whom it reaches 7.2 liters/h/1.73 m², i.e., 120 ml/min/1.73 m². The parameter \( \theta_2 \) is the PCA at which GFR reaches half its max-

Table 2. Main steps in population model building for oral data

<table>
<thead>
<tr>
<th>Step</th>
<th>Model</th>
<th>Objective function</th>
<th>Commentary</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Monocompartmental CL, ( V, k_a )</td>
<td>( \sigma^2 = 7.61 )</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>( CL ) linearly related to PNA</td>
<td>( \sigma^2 = 0.470; ) PNA influences ( CL )</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>( CL ) linearly related to PNA, ( F ) linearly related to BW</td>
<td>( \sigma^2 = 0.291; ) BW influences ( F )</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>( CL = \theta_2 \cdot GFR \cdot BSA/(1.73) \cdot (40/SCR) )</td>
<td>( \sigma^2 = 0.288; ) ( F ) is proportional to BW</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>( CL = \theta_3 \cdot GFR \cdot BSA/(1.73) \cdot (40/SCR) )</td>
<td>( \sigma^2 = 0.219; ) this clearance model is better</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>( \theta_2 \cdot (40/SCR) )</td>
<td>( \sigma^2 = 0.202; ) scatterplots are better than those in step 8</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Similar to step 10, but with zero-order absorption rate</td>
<td>( \sigma^2 = 0.554; ) the fit is worse than that in step 10</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Bicompartmental model, ( CL = \theta_2 \cdot GFR \cdot BSA/(1.73) \cdot (40/SCR) )</td>
<td>( \sigma^2 = 0.183; ) not significantly better than the one-compartment model</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: \( \theta_1 \) to \( \theta_3 \), population parameters to be estimated; \( \sigma^2 \), common error variance. To simplify notations, the subscript \( j \) on typical parameter values and covariates, the normalization of the covariates with respect to their median, and the ratio with \( F \) have been omitted. After step 5, \( F \) has the same definition in all remaining steps. After step 8, \( F \) has the same definition in all remaining steps.

Some steps have been omitted for brevity.

Function to be minimized. The critical change is 3.84 for 1 degree of freedom at the 0.05 level.
inal value. The parameter $\theta_i$ is a sigmoidic coefficient, which is proportional to the steepness of the sigmoid curve at PCA equal to $\theta_s$. The coefficient (BSA/1.73) transforms the estimated GFR into liters per hour. The last term $(40/\text{SCR})$ takes into account the deviation of a given individual from the median SCR for this population. Finally, $\theta_i$ is a scaling factor which accounts for the unknown $F$ and for the fact that acyclovir clearance is higher than GFR owing to the tubular secretion of acyclovir.

The typical value of the apparent volume of distribution ($V/F$), was related only to BW: $V/F = \theta_4(BW/6.9)$, where 6.9 is the typical value of BW for this population. None of the demographic or biological indices was found to be related to the typical value of $k_a$: $k_a = \theta_5 \exp(\eta_{k_a})$.

Allowing for covariance between the $\eta$ values did not improve the fit; therefore, covariances were fixed to zero. The values of the parameters of the final model, based on the data for 79 patients, are summarized in Table 3. The interindividual CVs of the CL and $V$ of acyclovir after having taken into account the covariates were 49 and 57%, respectively. The variability of $k_a$ was estimated to be near zero. This should not be interpreted as reflecting the absence of interindividual variability in $k_a$, but, rather, as the inability to estimate the variability owing to the small amount of information on the absorption phase because of the sparse amount of data as a result of the sampling schedule.

A graph of the predicted concentrations versus the observed concentrations is presented in Fig. 2. No systematic deviation from the line of $y$ equal to $x$ is observed. The plot of the weighted residuals of the concentrations versus time (data not shown) showed no systematic deviation from the line of $y$ equal to 0. Other validation scatterplots did not reveal any particular trend (data not shown), so that the population model fit the data reasonably well. Individual curves based on post hoc estimates were also adequate.

According to the definition of the residual error model, the residual variabilities of the acyclovir concentrations, expressed as a CV, were 61% at 0.3 $\mu$M, 35% at 3 $\mu$M, and 20% at 30 $\mu$M.

The distribution of individual pharmacokinetic parameters for acyclovir (more precisely, of the post hoc estimates) is summarized in Table 4. The dispersion of the individual values was very large, even after normalization with respect to BW or BSA.

Figure 3 illustrates the variation of typical values for pharmacokinetic parameters for acyclovir as a function of age; the steep variation in the elimination half-life ($t_{1/2}$) in the first month of life as well as the large value for premature infants is clearly visible. The concomitant variations of BSA and BW are also represented, after scaling for the sake of clarity.

Model building for intravenous disposition. The two-compartment model was found to be much more adequate than the one-compartment model for description of the acyclovir disposition after intravenous dosing (difference in objective function values [DOFVs], 125). Relating the typical value of CL to GFR, BSA, and SCR and that of $V_c$ to BW by relationships similar to those used in the oral disposition population model increased further the adequacy of the model (DOFV, 133). Finally, typical values of $CL_{vd}$ and $V_p$ were modeled as being proportional to BW, which yielded a DOFV of 20. With this final model, the adequacy of the fit to the data was very good. The various scatterplots revealed no systematic deviation (data not shown). The distribution of the individual pharmacokinetic parameters (post hoc estimates) for acyclovir is summarized in Table 3.
ters were related to the covariates in the same way that they were in the final oral and intravenous models, respectively. The two-compartment model was found to be more adequate than the one-compartment model (DOFV, 231). The point estimate and standard error of $F$ were 0.118 and 0.026, respectively, while the interindividual variability of $F$ was 16%. Individual estimates of $F$ were plotted against the dose and the covariates to examine possible relationships. Specific models relating $F$ to dose and age were then tested, but these relationships were not found to be significant.

**Simulation of acyclovir kinetics.** The final population model describing the kinetics of acyclovir after oral administration (Table 4 was used to generate the acyclovir concentration profile for 500 fictitious individuals by simulation in order to visualize the evolution of the typical acyclovir concentration profile as a function of age. Figure 4A shows the median concentration-versus-time curves at steady state after the administration of 24 mg/kg q8h to neonates (PNA, 0 to 1 months) of various gestational ages (7, 8, or 9 months). Figure 4B shows the corresponding curves after administration of 24 mg/kg according to a schedule of 0, 4, 8, 12, and 24 h to children with various PNA ranges: 1 to 3, 3 to 12, and 12 to 24 months. The lengths of time that the acyclovir concentrations remain above 2.5 and 5 $\mu$M at steady state, according to several dosing schedules, are reported in Table 6.

**DISCUSSION**

The pharmacokinetics of acyclovir administered by the oral route were well described, as in earlier studies with adults, by a one-compartment model with first-order absorption and elimination. Therefore, only four parameters were needed to characterize the disposition of acyclovir, namely CL, $V$, $k_a$, and $F$. The population approach based on a mixed-effects modeling approach enabled the estimation of the typical values of these parameters and their interindividual variabilities; it also enabled correlation of some of the demographic and biological indices to variations in these parameters. A possible limitation of our approach is that data for the intravenous route were mainly from older children, whereas data for the oral route were mainly from younger children. Hence, the estimation of $F$ is reliable only if the variation of CL with age is appropriately described by the covariate model. In this respect, the absence of any trend in the scatterplot of CL (actually $n_{CL}$) versus age is reassuring.

The $F$ of acyclovir administered as an oral suspension was about 12%. This value is in the range of $F$ values estimated for adults (20% for the 200-mg dose, 12% for the 800-mg dose) for various pharmaceutical forms (tablets, solution, etc.) (11, 24). From a practical point of view, it implies that for a given dosing regimen, mean acyclovir concentrations are about eight times...
lower after oral administration than after intravenous administration to the same patients, so that doses administered by the oral route must be about eight times higher than those administered by the intravenous route to ensure the same exposure. This relationship may not hold for higher dosages, since the F of acyclovir decreases as the dose increases owing to saturation of the absorption.

The interindividual variability in the pharmacokinetic parameters for acyclovir in the pediatric population studied in the present investigation was found to be very large, but it depends on the way in which the variability is expressed. The “crude” variability is reflected by the dispersion of the individual values for the parameters when they are expressed in their “natural” units, i.e., liters per hour for CL and liters for $V$: the ratios between the 95th and the 5th percentiles are about 55 and 6.7 for CL and $V$, respectively (Table 4). If the individual parameters are normalized to BW or BSA, the same ratio is reduced to 16 for CL in liters per hour per kilogram and 2.3 for $V$ in liters per kilogram but only to 27 for CL in liters per hour per square meter and 3.1 for $V$ in liters per square meter. Hence, the values of the parameters normalized with respect to BW are less variable than those normalized with respect to BSA. Comparison of these ratios for CL and $V$ also shows that the interindividual variability of CL is much larger than that of $V$, probably because $V$ is mainly related to body size, while CL is related to body size as well as to maturity and to all the factors that influence the renal handling of acyclovir. The population model shows how several covariates are quantitatively related to CL and $V$: CL was found to be related to PCA, BSA, and $S_{CR}$, while $V$ was related to BW. The deviation of the values of the individual parameters from the typical value (calculated according to the covariate model and the values from the covariate model for that individual) represents the residual (unexplained) variability of the parameters once the contribution of the covariates (PCA, BSA, $S_{CR}$, BW) has been taken into account. As described in the Results section, these residual variabilities correspond to CVs of 49 and 57% for CL and $V$, respectively. Hence, about half of the interindividual variability in CL and $V$ remains unexplained, so that the uncertainty about predicted acyclovir concentrations in a given individual for a given dosing schedule remains large. However, it is possible to obtain a confidence interval of the acyclovir concentration profile by several techniques, e.g., by Monte-Carlo simulation.

We examined the acyclovir concentration profile by simulation for different age ranges. It was found that prematurity had a profound influence on the kinetics of acyclovir since within the first three PCA ranges (7 to 8, 8 to 9, and 9 to 10 months), an increase of one age range led to a twofold decrease in the acyclovir concentration. The question arises whether the dosing regimen used in the study is adequate or whether a new dosing regimen must be proposed. The efficacy of acyclovir is dependent on the daily dose, the number of doses per day, and the 50% inhibitory concentration (IC$_{50}$) for the viral strain. For example, the proportions of 1,050 patients free of genital HSV recurrence after 1 year of treatment with valaciclovir at 250, 500, or 1,000 mg once daily were 22, 40, and 48%, respectively, while the mean daily areas under the concentration-time curve (AUCs) for acyclovir were 22.0, 45.8, and 80.4 $\mu$M·h, respectively (15). In the same study, 50% of the patients treated with valaciclovir at 250 mg twice daily (mean daily AUC for acyclovir, 55.1 $\mu$M·h) were free of recurrence after 1 year of treatment; i.e., 250 mg twice daily had the same efficacy as 1,000 mg once daily, despite a lower daily AUC. This finding and other results (4) support the assumption that the length of time that the acyclovir concentration remains above a given threshold (the IC$_{50}$) is also an important criterion for efficacy. It has been suggested that maximal efficacy is reached when the length of time that the acyclovir concentration remains above the IC$_{50}$ is greater than 12 h in each 24-h period of treatment (17, 20). For VZV infections, a higher acyclovir AUC is required because the IC$_{50}$ for VZV isolates is higher. It has been shown that the time to healing in 994 adult patients is related to the daily AUC for acyclovir after oral administration of acyclovir or valaciclovir (S. Weller and M. R. Blum, Population pharmacokinetics of acyclovir after administration of valaciclovir or oral acyclovir to patients for the treatment of herpes zoster, internal document, Glaxo Wellcome Co.). The mean daily AUCs for acyclovir at the doses approved for the treatment of herpes zoster in adults are 107 $\mu$M·h (acyclovir at 800 mg five times per day) and 253 $\mu$M·h (valaciclovir at 1,000 mg q8h), respectively, with the latter treatment having a greater efficacy. On the basis of these

Table 5. Median and range of individual pharmacokinetic parameters (post hoc estimates) for acyclovir after intravenous administration

| Value       | CL (liters/h) | CL (liters/h/kg) | $V_{c}$ (liters) | $V_{c}$ (liters/kg) | CL$_{CR}$ (liters/h) | CL$_{CR}$ (liters/h/kg) | $V_{c}$ (liters) | $V_{c}$ (liters/kg) |
|-------------|---------------|-----------------|-----------------|---------------------|----------------------|------------------------|-----------------|----------------|----------------|
| Median      | 9.7           | 0.44            | 10.0            | 0.57                | 4.79                 | 0.21                   | 13.7            | 0.62            |
| Minimum-maximum | 0.76–22.5  | 0.24–0.79       | 1.7–27.1        | 0.28–0.71           | 0.12–18.2            | 0.02–0.45              | 1.4–25.6        | 0.40–1.24       |
| CV (%)      | 59            | 32              | 67              | 20                  | 100                  | 62                     | 62              | 27              |

Table 6. Daily AUC and length of time that acyclovir concentration remains above 2.5 and 5 $\mu$M at steady state in a 24-h interval, calculated by simulation with data for 500 fictitious individuals

<table>
<thead>
<tr>
<th>PNA (mo)</th>
<th>Dose (mg/kg), times daily$^a$</th>
<th>Median AUC$^b$ ((\mu)M·h)</th>
<th>Time &gt; 2.5 (\mu)M (h)</th>
<th>Time &gt; 5 (\mu)M (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>24.3</td>
<td>441 (283–690)</td>
<td>24.0 (24.0–24.0)</td>
<td>24.0 (24.0–24.0)</td>
</tr>
<tr>
<td>1–3</td>
<td>24.4</td>
<td>269 (185–448)</td>
<td>24.0 (21.1–24.0)</td>
<td>22.3 (17.3–24.0)</td>
</tr>
<tr>
<td>3–12</td>
<td>24.4</td>
<td>93 (63–157)</td>
<td>17.8 (13.4–22.6)</td>
<td>8.4 (0.0–18.5)</td>
</tr>
<tr>
<td></td>
<td>48.4</td>
<td>166 (126–314)</td>
<td>17.8 (13.4–22.6)</td>
<td>–</td>
</tr>
<tr>
<td>12–24</td>
<td>24.4</td>
<td>76 (52–102)</td>
<td>16.3 (10.1–18.7)</td>
<td>2.6 (0.0–10.8)</td>
</tr>
<tr>
<td></td>
<td>48.4</td>
<td>152 (104–204)</td>
<td>16.3 (10.1–18.7)</td>
<td>–</td>
</tr>
</tbody>
</table>

$^a$ Dosing schedule is q8h if three times daily or at 0, 4, 8, 12, and 24 h if four times daily.

$^b$ –, not done because the lower dose is adequate.
considerations and the results of our simulations for thresholds of 2.5 and 5 μM, which correspond to a worst-case IC₅₀ for HSV strains and a bad-case IC₅₀ for VZV strains (Table 6), respectively, the proposed dosing regimen (24 mg/kg q8h for patients younger than 1 month of age or q.i.d. otherwise) seems to be appropriate for the treatment of HSV-1 and HSV-2 infections in children up to age 2 years. For VZV infections, a twofold increase in the dose (i.e., 48 mg/kg according to a schedule of treatment at 0, 4, 8, 12, and 24 h) seems to be necessary in order to ensure maximal efficacy in children older than age 3 months. These suggestions should serve as starting point for the design of clinical efficacy studies.

APPENDIX

The population pharmacokinetic method based on a nonlinear mixed-effects modeling approach is as follows. Two levels of variability were considered. The first level of variability, i.e., residual (intraindividual) variability, accounted for the deviation of the observed acyclovir concentration at time i in individual j (Cᵢⱼ) from the predicted concentration (Ĉᵢⱼ) according to the equations Cᵢⱼ = Ĉᵢⱼ + εᵢⱼ · Ĉᵢⱼ and Ĉᵢⱼ = f(Pⱼ, tᵢⱼ), where εᵢⱼ is a random variable with a normal distribution with zero mean and variance σ², and b is a parameter of the residual error model. σ² and b are parameters to be estimated. The predicted concentration is given by the pharmacokinetic model f(·) for a given set (vector) of individual pharmacokinetic parameters Pⱼ. This error model assumes that residual errors are uncorrelated and that the residual error variance increases as a function of concentration, a pattern which is very common in pharmacokinetics.

The second level of variability accounted for interindividual variability. Individual pharmacokinetic parameters Pⱼ were assumed to arise from a multivariate lognormal distribution whose typical value, P(j) (i.e., the median), depends on the set (vector) of covariate values of individual j (Xⱼ) according to a covariate model h(·): Pⱼ = h(P, Xⱼ) and Pⱼ = P(j) exp(ηⱼ), where P is a set (vector) of population parameters called fixed effects (P = θ₁, θ₂, . . .) and ηⱼ is a set (vector) of random effects with normal distribution, zero mean, and Ω variance-covariance matrix. With this model, the distribution of the individual parameters

FIG. 4. Simulation of the median acyclovir concentration-versus-time curve at steady state from 500 fictitious individuals after oral administration of 24 mg/kg q8h to children ages 0 to 1 month (A) or after administration q.i.d. at 0, 4, 8, 12, and 24 h to children ages 1 to 24 months (B).
in all subjects having the same covariates \(X_i\) is skewed to the right and negative values are avoided. The goal of the population analysis was to determine the most adequate models for \(f(\cdot)\) and \(h(\cdot)\) and to estimate the parameters \(P\), \(\Omega\), \(\sigma^2\), and \(b\).

ACKNOWLEDGMENT

This work was supported in part by a grant from Glaxo-Wellcome.

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