

Inadequacy of Plasma Acyclovir Levels at Delivery in Patients With Genital Herpes Receiving Oral Acyclovir Suppressive Therapy in Late Pregnancy

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Abstract

Objective: Acyclovir therapy in late pregnancy among women with recurrent genital herpes is effective in decreasing genital lesion frequency and subclinical viral shedding rates at delivery, thereby decreasing the need for Caesarean section. Despite good adherence and increased dosing schedules, breakthrough lesions and viral shedding are still observed in some women at or near delivery. Anecdotal evidence suggests that low levels of herpes simplex virus replication at delivery may result in transmission to the neonate. Therefore, defining optimal acyclovir dosing during labour and delivery is warranted. Our objectives were to determine actual maternal and fetal acyclovir levels at delivery, and explore associations between acyclovir levels, duration of labour, and time since last acyclovir dose.

Methods: Twenty-seven patients were prescribed oral acyclovir 400 mg three times daily from 36 weeks' gestation. Cord blood (venous and arterial) and maternal venous blood samples were collected at delivery, and acyclovir levels measured using capillary electrophoresis. Correlations between duration of labour, and time since last acyclovir dose with acyclovir blood levels were calculated.

Results: Acyclovir levels were below the published mean steady-state trough value (180 ng/mL) in 52% of venous cord samples, 55% of arterial cord samples, and 36% of maternal samples. There was a significant inverse correlation between the time since last dose and venous cord levels ($r_{s19} = -0.57$, $P < 0.015$), arterial cord levels ($r_{s16} = -0.63$, $P < 0.01$), and maternal acyclovir levels ($r_{10} = -0.69$, $P < 0.03$).

Conclusion: Oral dosing of acyclovir in women in late pregnancy may result in insufficient levels at delivery to prevent viral shedding. Alternative approaches that incorporate acyclovir dosing through labour, either through oral or intravenous administration, should be evaluated to assess effects on viral shedding.

Résumé

Objectif : Le traitement à l'acyclovir aux derniers moments de la grossesse chez les femmes présentant un herpès génital récurrent est efficace pour ce qui est d'atténuer la fréquence des lésions génitales et les taux d'élimination virale subclinique au moment de l'accouchement, ce qui atténue par le fait même la nécessité d'avoir recours à la césarienne. Malgré une bonne observance du traitement et des schémas posologiques intensifiés, des lésions et une élimination virale en viennent tout de même à se manifester chez certaines femmes au moment de l'accouchement ou peu de temps avant. Des données empiriques laissent entendre que de faibles taux de réplication du VHS au moment de l'accouchement peuvent donner lieu à sa transmission au nouveau-né. Ainsi, il s'avère justifié de chercher à définir la posologie optimale d'acyclovir à mettre en œuvre au cours du travail et de l'accouchement. Nos objectifs étaient de déterminer les taux réels d'acyclovir chez la mère et le fœtus au moment de l'accouchement, et d'explorer les associations entre les taux

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d'acyclovir, la durée du travail et le temps écoulé depuis la dernière dose d'acyclovir.

Méthodes : Nous avons prescrit de l'acyclovir, à raison de 400 mg trois fois par jour par voie orale, à 27 patientes à partir de la 36^e semaine de gestation. Le sang de cordon (veineux et artériel) et des échantillons de sang veineux maternel ont été prélevés au moment de l'accouchement, et les taux d'acyclovir ont été mesurés par électrophorèse capillaire. Les corrélations entre la durée du travail et le temps écoulé depuis la dernière dose d'acyclovir en fonction des taux sanguins d'acyclovir ont été calculées.

Résultats : Les taux d'acyclovir se situaient en deçà de la valeur minimale moyenne à l'état stationnaire publiée (180 ng/ml) dans 52 % des prélèvements de sang de cordon veineux, dans 55 % des prélèvements de sang de cordon artériel et dans 36 % des prélèvements maternels. Une corrélation inverse significative a été constatée entre le temps écoulé depuis la dernière dose d'acyclovir et les taux de ce dernier dans le sang de cordon veineux ($r_{s19} = -0,57$, $P < 0,015$), dans le sang de cordon artériel ($r_{s16} = -0,63$, $P < 0,01$) et dans le sang maternel ($r_{10} = -0,69$, $P < 0,03$).

Conclusion : Chez les femmes qui en sont aux derniers moments de la grossesse, les posologies d'acyclovir par voie orale peuvent donner lieu, au moment de l'accouchement, à des taux qui s'avèrent insuffisants pour assurer la prévention de l'élimination virale. D'autres approches (incorporant une posologie d'acyclovir mise en œuvre pendant le travail, qu'il s'agisse d'une administration par voie orale ou intraveineuse) devraient être évaluées en vue d'en déterminer les effets sur l'élimination virale.

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INTRODUCTION

Neonatal herpes infection is one of the most serious consequences of maternal herpes simplex virus infection and is a significant public health concern in many developed countries. The estimated incidence of neonatal herpes infection varies by geographical region and study methodology, ranging from 1 case per 20 000 to 60 000 live births in European countries,^{1–3} 1 case per 17 000 live births in Canada,⁴ and 1 case per 11 000 live births in Australia⁵ to 1 case per 3200 live births in parts of the United States.⁶ In at least 85% of cases, HSV infection in the newborn is due to transmission during the time of vaginal delivery from the infected mother's genital tract.⁷

To reduce the risk of perinatal transmission of HSV, the American College of Obstetricians and Gynecologists and the Society of Obstetricians and Gynaecologists of Canada have recommended that Caesarean section be performed in women presenting with genital herpes lesions at the onset of labour.^{8,9} This management strategy relies on the clinical recognition of genital infection. The increased morbidity

and mortality associated with CS compared with vaginal delivery has prompted evaluation of alternate strategies, including antiviral suppressive therapy near term,^{10–16} a strategy now recommended by ACOG and SOGC.^{8,9}

The antiviral agents acyclovir, valacyclovir, and famciclovir are effective in the suppression of recurrent genital herpes in non-pregnant women.¹⁷ Several studies have also evaluated the safety and effectiveness of oral acyclovir suppressive therapy in late pregnancy^{10–13,15,18} and found a significant reduction in both symptomatic genital herpes recurrence and viral shedding at delivery, as well as a reduction in rates of CS.¹⁹ The current recommendations in women with known recurrent HSV infection are to start oral acyclovir or valacyclovir therapy at 36 weeks' gestation and to continue until delivery.^{9,20}

While the pharmacokinetics of acyclovir in late pregnancy have been assessed,²¹ maternal and fetal levels of acyclovir at the time of delivery have not been evaluated. This information would be of value because the circumstances of labour and impending delivery may interrupt the dosing schedule of antiviral medication and potentially interfere with drug adherence and absorption. In turn, this could contribute to escape viral replication around the time of delivery. Therefore, the objectives of this study were

1. to determine the level of maternal and umbilical cord acyclovir in women who were prescribed and self-administered suppressive acyclovir from 36 weeks' gestation until delivery, and
2. to explore the relationship between the level of acyclovir and the duration of labour and time since last acyclovir dose. We hypothesized that the cord blood acyclovir concentrations would be inversely correlated with the time from last acyclovir dose and the duration of labour.

MATERIALS AND METHODS

The participants in this cohort study were women with recurrent genital HSV infection enrolled in a randomized placebo-controlled trial of acyclovir 400 mg three times daily versus placebo, from 36 weeks to delivery.¹⁵ The pharmacokinetics substudy was conducted at the University of British Columbia. Subjects were recruited between January 2000 and April 2003. Inclusion criteria included a normal 18–20 week obstetrical ultrasound, known recurrent symptomatic genital HSV infection, no serious medical conditions, including infection with HIV, and no known sensitivity to acyclovir. All participants in this substudy were prescribed oral acyclovir 400 mg three times daily from 36 weeks' gestation until delivery and had consented to provide additional umbilical cord and maternal blood samples at the time of delivery.

ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
CS	Caesarean section
HSV	herpes simplex virus

Maternal and neonatal characteristics, duration of labour and time since last acyclovir dose, and plasma acyclovir concentrations

Maternal characteristics	n (%)		
Ethnicity			
White	23 (88.5)		
Black	1 (3.8)		
Hispanic	1 (3.8)		
South Asian	1 (3.8)		
	Sample size	Mean (SE) / *Mode	Range
Age, years	27	31.6 (1.0)	20–40
Gravida	27	2*	1–5
Parity	25	0*	0–2
Maternal weight at study enrolment (32–36 wks), pounds	27	160.2 (4.2)	123–221
Neonatal characteristics			
Gestational age at delivery, weeks	26	39.9 (0.17)	37–41
Birth weight, grams	27	3375.2	2660–4410
Apgar score at 1 min	27	7.9 (0.31)	2–9
Apgar score at 5 min	27	9.0 (0.08)	7–10
Duration of labour, hours	27	17.0 (1.87)	2.4–44.3
Time since last acyclovir dose, hours	19	13.0 (1.54)	1.9–24.5

Maternal and neonatal information collected included maternal age, maternal ethnicity, gravidity, maternal weight at study onset (32–36 weeks' gestational age), duration of labour, time of last acyclovir dose before delivery, length of gestation, infant's birth weight, and Apgar scores. If CS was performed, the duration of labour was recorded as the time from admission to hospital until delivery.

Arterial and venous cord blood samples were collected from the clamped umbilical cord, and maternal venous samples were taken immediately after delivery. Cord and maternal samples were stored at 4°C for a maximum of 72 hours prior to centrifugation at 1200 rpm at 4°C for 10 minutes. The plasma was then stored at –70°C until analysis. Validation studies were performed to confirm acyclovir stability in the above conditions.²²

The concentration of acyclovir in the plasma samples was determined using a validated capillary electrophoresis assay, developed in the Sacks laboratory, with a limit of quantification of 20 ng/mL.²³ Briefly, plasma samples were purified using solid phase extraction and column elution. Separation and analysis of acyclovir in plasma components was performed on a Beckman MDQ automated capillary electrophoresis system, coupled with an ultraviolet detector (Beckman Instruments Inc., Mississauga, ON). The internal standard was 5-(2-hydroxyethyl)-2'-deoxyuridine (HEdU). Detection of acyclovir was monitored at the wavelength of

254 nm. Corrected peak-area ratios (ACV/HEdU) were calculated, and the acyclovir concentrations were determined using a constructed calibration curve.²²

Maternal weight at study onset, duration of labour, time since last acyclovir dose, and maternal acyclovir level data were approximately normal in distribution. Venous cord and arterial cord acyclovir concentration were not normally distributed; therefore, non-parametric tests were used in analyses of these variables. To investigate if there was a statistically significant association between plasma acyclovir concentration and maternal weight, duration of labour, and time since last acyclovir dose, correlational analyses using Pearson correlation coefficient (parametric) or Spearman's rho statistic (non-parametric) were used. All statistical analyses were two-tailed tests. Statistical analyses were performed using SPSS release 16.0.1 for Windows (SPSS Inc., Chicago, IL).

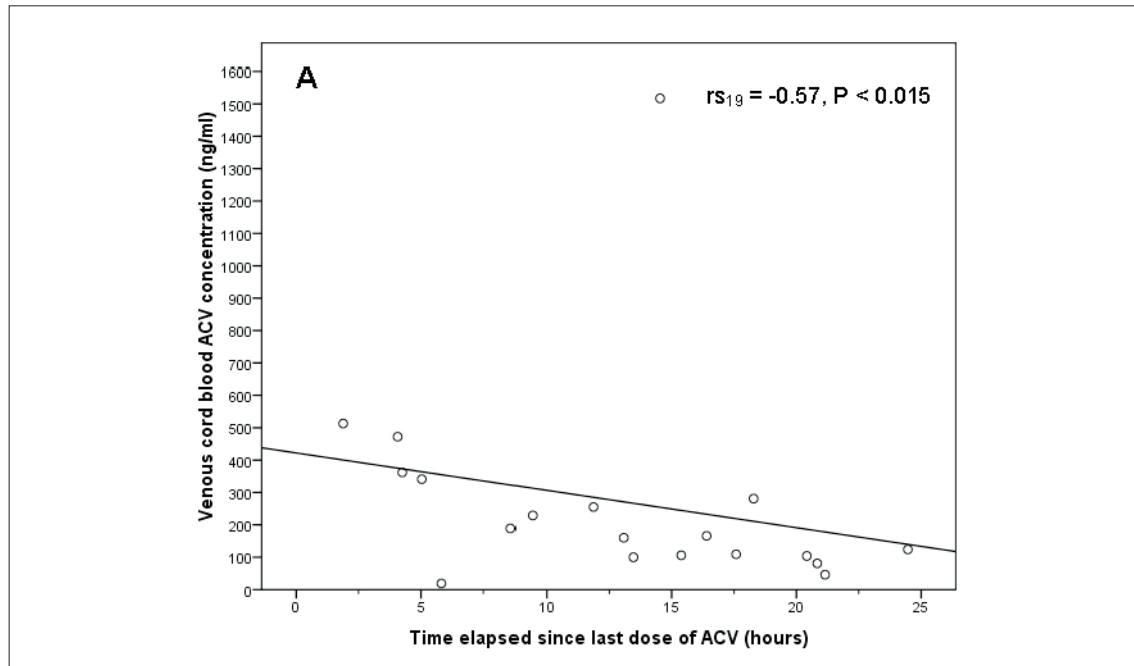
Approval for the study was provided by the UBC Clinical Research Ethics Board and the British Columbia's Children's and Women's Health Centre Research Review Committee.

RESULTS

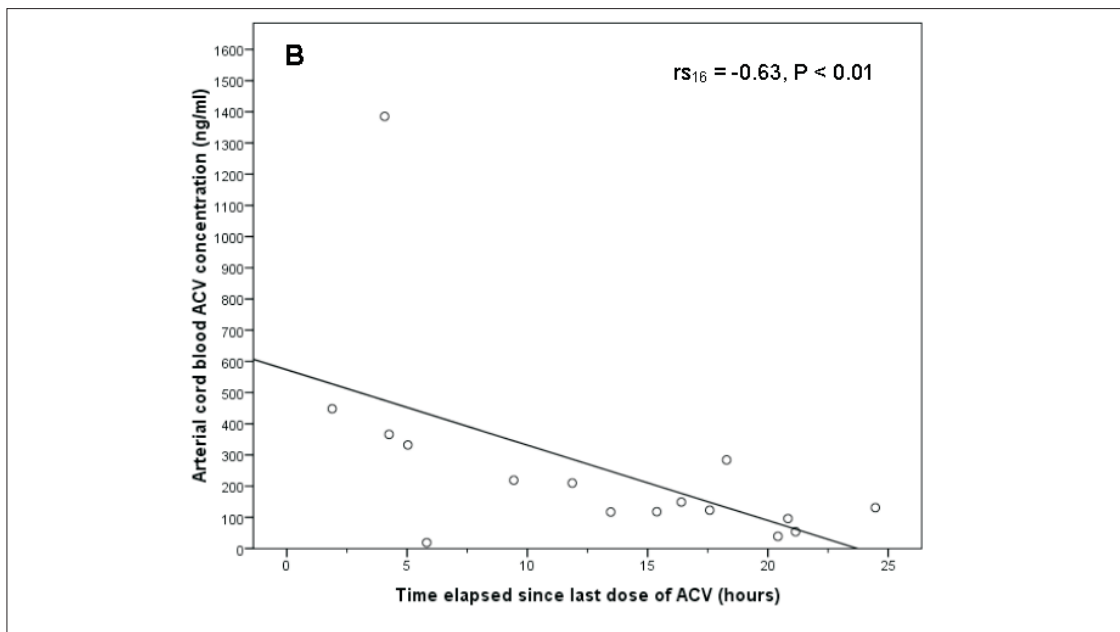
Twenty-seven women with a history of genital herpes infection who were taking suppressive acyclovir at term were included in the study (Table). All participating women were

Correlational analyses between time since last dose of acyclovir and (A) venous cord acyclovir levels, (B) arterial cord acyclovir levels, and (C) maternal acyclovir levels.

A. Venous cord acyclovir levels



B. Arterial cord acyclovir levels

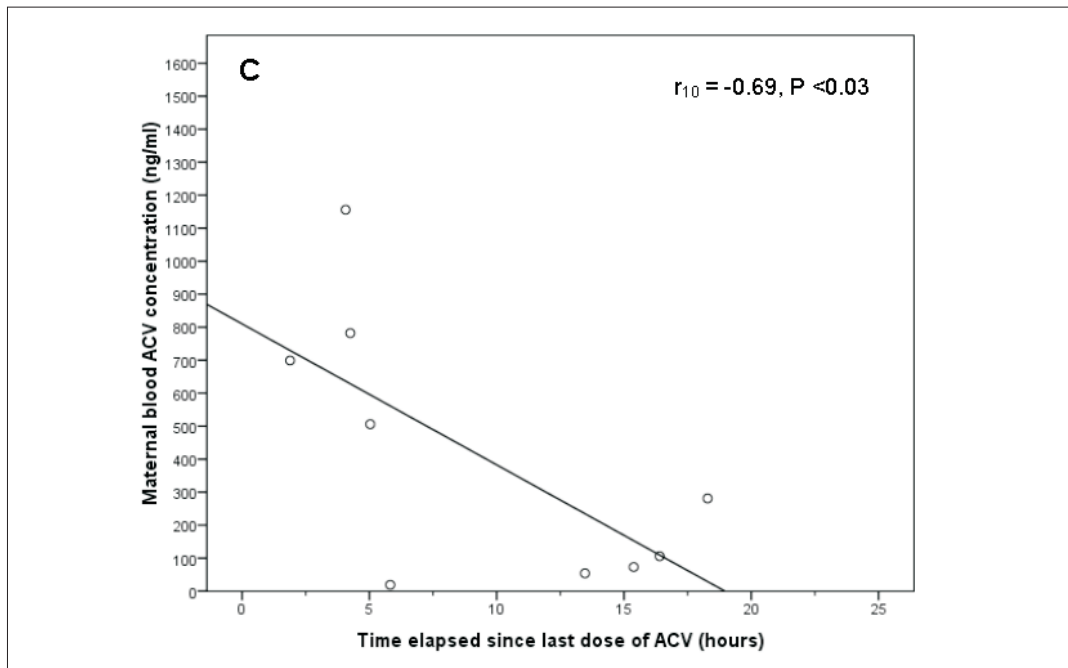


given a medication dosing schedule (400 mg three times daily) and reported > 95% acyclovir adherence rates in the week preceding delivery, but were not instructed regarding any specific management after labour began. All of the women were anticipating a vaginal delivery, although seven women underwent CS for failure to progress in labour ($n = 3$), breech presentation ($n = 2$), fetal distress ($n = 1$), or genital

herpes prodrome ($n = 1$). None of the women had clinically evident genital herpes lesions at delivery, and none of the infants developed neonatal herpes infection. Additional neonatal outcome data are presented in the Table.

In the labour and delivery wards where study participants delivered, priority was always given to patient care and collection of samples for routine clinical diagnostics, which

C. Maternal acyclovir levels.



occasionally resulted in missed study sample collections, or collection of an insufficient volume of blood for analysis. Because of these logistical issues, it was not always possible to obtain paired cord and maternal blood samples for all of the study participants; final sample sizes are reported in the Table. The mean concentration of acyclovir was 244.5 ng/mL in venous cord plasma, 236.0 ng/mL in arterial cord plasma, and 421.7 ng/mL in maternal plasma (Table). Fourteen of 27 venous cord acyclovir levels (52.0%), 12 of 22 arterial cord acyclovir levels (54.5%), and 4 of 11 maternal acyclovir levels (36.4%) were below the published mean steady-state trough concentration of 0.8 μ M (\sim 180 ng/mL).^{21,23}

Maternal weight was not correlated with venous cord levels ($r_{s27} = -0.183$, $P = 0.4$), arterial cord levels ($r_{s22} = -0.013$, $P > 0.5$), or maternal cord acyclovir levels ($r_{11} = -0.153$, $P = 0.7$). There was no significant correlation between duration of labour and venous cord levels ($r_{s27} = 0.097$, $P = 0.6$), arterial cord levels ($r_{s22} = 0.003$, $P > 0.5$), or maternal cord acyclovir levels ($r_{11} = 0.0334$, $P = 0.3$). However, in a subset of 19 women for whom time since last dose of acyclovir before delivery was known, there was a significant inverse correlation between time since last dose and venous cord levels ($r_{s19} = -0.57$, $P < 0.015$), arterial cord levels ($r_{s16} = -0.63$, $P < 0.01$), and maternal acyclovir levels ($r_{10} = -0.69$, $P < 0.03$) (Figure).

DISCUSSION

Our results suggest that plasma acyclovir levels at the time of delivery are often suboptimal in women receiving oral acyclovir during late pregnancy. Previous studies have reported that the mean steady state trough level is 180 ng/mL for oral acyclovir 400 mg given three times daily. Over 50% of the cord blood samples and 35% of maternal blood samples collected in the study had levels below this value. As expected, maternal and cord blood acyclovir concentrations were inversely correlated with time since last dose of acyclovir. Although we did not detect any significant correlation between duration of labour and acyclovir levels as hypothesized, this may be due to the higher degree of variability between individuals in the duration of labour, or to the fact that several women (9/19) took their last dose of acyclovir during the first phase of labour. Therefore, time since last dose was a more accurate baseline from which to explore temporal changes in acyclovir levels.

The primary concern with the utilization of acyclovir suppression in any clinical setting is clinical breakthrough and subclinical viral shedding. In the context of pregnancy, the goal has been both clinical and virologic suppression in order to obviate the need for Caesarean section, but also to minimize the risk of exposure of the infant to the virus. However, these approaches may not specifically incorporate maintenance of the acyclovir dosing schedule throughout labour, or recommend alternate modes of delivery of

acyclovir for labouring women who are unable to take oral medications.

This study has demonstrated that if the administration of acyclovir in labour is not specifically addressed, an increased proportion of women and their infants may be exposed to subtherapeutic acyclovir levels. This could potentially result in reactivation of genital herpes during labour at a time when virologic suppression is most critical. While the minimum infectious titre of HSV required for transmission is unknown, case reports indicate that even low levels of virus in maternal secretions can result in transmission to the infant.²⁴ Our data indicate that further studies are needed to evaluate acyclovir dosing during labour, through either oral or intravenous delivery.

Although it is difficult to determine whether the suboptimal concentrations are due to non-compliance or to the physiological circumstances of labour, the inverse relationship with last dose and level suggests pharmacokinetics in response to doses taken during labour are typical. Physiological changes during pregnancy can cause alterations in pharmacokinetics, such as the increase in renal clearance.²⁵ However, previous studies have found no notable differences in plasma levels and drug clearance rates among pregnant versus non-pregnant adults if pregnant women are given an increased dose and frequency of acyclovir.^{21,23,26} Nevertheless, the controlled environment of a pharmacokinetic study may not accurately depict real-life conditions during labour and delivery, when events such as vomiting and decreased gastric emptying may present as significant barriers to optimal drug bioavailability.²⁸ Because of the short elimination half-life of acyclovir (2–3 hours),²⁸ frequent dosing is required when oral therapy is used.

This study provides an important exploration of the levels of acyclovir at delivery and issues related to acyclovir administration around labour of varying duration. External generalizability would be strengthened by a larger sample; nevertheless, this study suggests the currently recommended antiviral regimen may result in subtherapeutic levels at the time of delivery. This highlights the need for further research to examine the clinical significance of neonatal exposure to sub-therapeutic acyclovir levels, and to explore alternative dosing regimens that will ensure optimal acyclovir levels throughout labour.

CONCLUSION

Women with genital herpes who choose to take acyclovir to reduce the risk of Caesarean section should continue to take oral acyclovir throughout labour until delivery to minimize the risk of genital tract viral replication at the time of delivery.

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