Abstract

Background: Evaluation of the effects of ganciclovir (GCV) therapy in symptomatic congenital cytomegalovirus (CMV) infection on hematological parameters in newborns. Methods: Neonates with symptomatic congenital CMV infection assigned to receive treatment with intravenous GCV. During and after GCV treatment complete blood count was performed. The individual doses of GCV were used and its blood levels were analyzed with HPLC method. A total of 40 newborns with a history of congenital CMV infection, hospitalized at Neonatology Department & NICU between January 2002 and December 2004, treated with GCV were included in the study. Results: The mean duration of therapy was 20 days. The mean daily dose of GCV was 11.1 ± 5.1 mg/kg/day. The following side effects were noted: neutropenia in 11 (27.5%) cases, anemia in 13 (32.5%) newborns. No thrombocytopenia was observed as the effect of GCV treatment. Treatment with GCV decreased neutrophils count in all patients, but it was statistically significant (p < 0.001) only in the group with initially normal neutrophils count. Treatment with GCV increased platelets count (p < 0.001) in all patients and decreased hemoglobin concentration also in all patients (p < 0.001). Conclusions: GCV was well tolerated in newborns if serum concentration monitoring and the individual doses were used. The most frequent side effects were neutropenia and anemia. Treatment with GCV increased platelet count.

Key words: ganciclovir, cytomegalovirus, newborn

Abbreviations: CMV – cytomegalovirus, GCV – ganciclovir, CNS – central nervous system, CID – cytomegalic inclusion disease, HPLC – high performance liquid chromatography

Congenital cytomegalovirus infection is the most common viral infection transmitted via placenta, with rates ranging from 0.4% to 2.3% in the general population [1, 2]. Congenital CMV is associated with symptomatic disease at birth in only 10% of infants, who subsequently may develop serious sequelae later in life including mental retardation, chorioretinitis, hearing loss, seizures, optic atrophy and learning disabilities.

At the present time, there is no highly effective treatment of congenital CMV infection. Ganciclovir (GCV) is the drug administered to treat symptomatic congenital CMV infection in newborns [1-4]. GCV is the synthetic analog of guanosine, which blocks replication of virus both in vitro and in vivo. There is large interpatient variability in pharmacokinetic parameters. Mean half-life in infants less than 49 days postnatal age is 2.4 hours. Metabolism is minimal. Almost all drug is excreted unchanged in the urine via glomerular filtration and active tubular secretion. Because of adverse reactions, the serum levels of GCV must be monitored and safety biochemical analyses performed. Doses of GCV are individually determined and the duration of treatment depends on severity of the illness. The Neonatal Intensive Care Unit at the Children’s Memorial Health Institute in Warsaw is experienced with using GCV as a treatment of symptomatic congenital CMV infections. We tried to determine whether GCV has any effects on selected hematological parameters in newborns.

Methods

A total of 40 newborns with a history of symptomatic congenital CMV infection hospitalized at Neonatology Department & NICU between January 2002 and December 2004, treated with GCV were included in the study. 31 (77.5%) neonates were term babies and 9 (22.5%) preterm (< 37 wks) respectively. Intrauterine growth retardation (IUGR) was observed in 4 (10%) newborns. There were 2 (5%) small for gestational age premature newborns. There were 21 (52.5%) males and 19 (47.5%) females in the study group.

All seropositive, symptomatic neonates had diagnosis established or confirmed by urine polymerase chain reaction (PCR) within the first 3 weeks of life. Newborns with evidence of symptoms of congenital CMV such as:
cytomegalic inclusion disease (CID) (petechiae, hepatosplenomegaly, thrombocytopenia, anemia, jaundice) or central nervous system (CNS) disease (intracranial calcifications, ventriculomegaly, seizures, sensorineural hearing loss, chorioretinitis) were included in the study. Treatment with GCV was started within first 4 weeks of life. The duration of treatment was determined by severity of illness (usually 2-4 weeks). The individual doses of GCV were used and its blood levels in newborns were analyzed with (HPLC – high performance liquid chromatography) at 2 different time points (0 h and 4.5 h after the end of GCV infusion). The initial dose of GCV was 5 mg/kg twice a day. In case of adverse reactions, the dose of medication was either reduced or treatment was stopped. Complete blood count (neutrophils count, platelet count, hemoglobin concentration, reticulocyte count) was performed at baseline, during treatment (at the 7th, 14th and 21st day) and post treatment. Differences between selected groups were tested with Wilcoxon matched pairs test. P value less than 0.05 was considered statistically significant. Kolmogorov-Smirnov & Lilliefors tests were used to determine normality of distribution of selected variables. Statistica for Windows 6.0 was used for all statistical analysis.

Results

The mean gestational age of patients was 38.68 ± 2.07 weeks. The mean birth weight was 3135.95 g ± 734.64, the mean Apgar score was 9.13 ± 1.15 points. In the study group cytomegalic inclusion disease (CID) was diagnosed in 35 (87.5%) newborns and central nervous system (CNS) disease in 5 (12.5%).

Table 1. Characteristics of examined group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight</td>
<td>3135 ± 734 (1200-4450)</td>
</tr>
<tr>
<td>1 min Apgar score (pts.)</td>
<td>9.13 ± 1.15</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>38.68 ± 2.07 (33-41)</td>
</tr>
</tbody>
</table>

The mean duration of therapy was 20 days in the analyzed group.

The mean GCV dose was 4.42 mg/kg/dose (0.7 mg/kg/dose to 7 mg/kg/dose). The mean daily GCV dose was 11.1 ± 5.1 mg/kg/day.

The mean serum concentration was 6.62 ± 1.49 mcg/ml and 1.91 ± 0.81 mcg/ml at 0 h and 4.5 h after the end of GCV infusion respectively. The drug was administered every 12 hours in 15 (37.5%) and every 8 hours in 25 (62.5%) newborns.

The effects of GCV treatment on selected hematological parameters were analyzed. The following side effects were noted: neutropenia (neutrophils < 1500/ mm^3) in 11 (27.5%), anemia (Hb < 13.5 mg/dl within the first week of life and/or < 12.0 mg/dl after the first week
of life) in 13 (32.5%) newborns. No thrombocytopenia (platelets count < 150,000/mm³) was observed. Because of the side effects the therapy was terminated in 9 (22.5%) newborns.

The influence of GCV treatment on several hematological parameters such as neutrophil count, hemoglobin concentration, reticulocyte count and platelets count were analyzed. Correlation of these parameters with duration of treatment and with GCV dose was evaluated.

GCV in dose normally used for the treatment influenced neutrophil count. GCV decreased neutrophil count in all groups, but the difference was statistically significant (p < 0.001) only in the group, which initially had normal neutrophil count.

There was no statistically significant correlation between daily dose GCV and neutrophil count. There was no correlation between duration of therapy and post-treatment neutrophil count.

Treatment with GCV increased (p < 0.001) platelets count in all patients. There was no statistically significant correlation between daily GCV dose or duration of therapy and final platelets count.

In all patient groups decreased hemoglobin concentration was observed after treatment with GCV (p < 0.001).

There was no correlation between daily GCV dose or duration of therapy and hemoglobin concentration.

Treatment with GCV affected not only hemoglobin concentration but also resulted in increased reticulocyte count in the whole study group, but the difference was not statistically significant.

**Discussion**

Neonates with symptoms of HCMV infection at birth have higher rates of hearing impairment and neurodevelopmental sequelae [5-7]. They need to be treated after birth, but there is no highly effective and safe antiviral therapy currently available for the treatment of congenital CMV infection. Clinical trials are in progress [8-12]. Ganciclovir is the most promising antiviral drug, which blocks replication of the cytomegalovirus. Till now GCV is administered only in newborns with evidence of CMV disease at birth, when benefits predominate possible side effects. Previous uncontrolled studies with GCV treatment of symptomatic CMV infection do not provide convincing evidence of efficacy, however recent clinical outcomes are more promising. Clinical trial of Collaborative Antiviral Study Group (CASG) – involving randomized newborns with symptomatic congenital CMV infection and evidence of CNS disease shows inhibiting effect of GCV therapy on hearing loss progression [9]. Unfortunately, in spite of its beneficial properties, GCV also causes serious side effects (neutropenia, thrombocytopenia, anemia) and it also might be teratogenic and carcinogenic. Currently, there is no recommendation for GCV use in the treatment of asymptomatic congenital CMV infection to prevent hearing loss.

In our study, similarly as in Prober’s and Kimberlin’s trials, the side effects of GCV treatment, such as neutropenia and decreased hemoglobin count was observed [9, 12]. We also noticed hematological benefits of treatment, such as increasing platelets count during GCV therapy.

In randomized trials (Kimberlin et al.) observed neutropenia was dose dependent [9]. According to dose dependent neutropenia our results not correlate with other studies [9, 12]. We observed neutropenia occur-

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**Fig. 4. Platelet count before and after GCV treatment**

**Fig. 5. Haemoglobin concentration before and after GCV treatment**
rence only in 27.5% of patients in comparison with more than a half of GCV treated patients in existing randomized control trials. In all patients in our study group observed neutropenia wasn’t dose dependent.

Thrombocytopenia is a common manifestation of CMV disease at birth. Although one can expect positive effects of therapy on all symptoms the dose dependent thrombocytopenia is quite often observed in adults and children treated with GCV. In our study no GCV related thrombocytopenia was observed. As a result of treatment with GCV we observed increasing platelets count in all newborns. There was no correlation between dose or duration of GCV therapy and platelets count. Farther studies are necessary to explain these discrepancies.

Treatment with GCV influenced hemoglobin concentration. We observed anemia in all patients, but we must remember that during treatment several blood samples were collected and it might had crucial influence on anemia occurrence. After GCV treatment we observed increased reticulocyte count. We can conclude that bone marrow function during GCV treatment was not repressed. If hemoglobin concentration decreased reticulocyte count increased.

It is obviously known that during GCV therapy there is large interpatient variability in pharmacokinetic parameters [13]. We suggest that if the individual doses of GCV are used, the drug is well tolerated in newborns [14]. The doses of GCV in our study were individually determined and were higher then doses used in adults (the mean daily dose of GCV during treatment was 11.1 ± 5.1 mg/kg/day).

The mean serum concentration of GCV was 6.62 ± 1.49 at 0 h and 1.91 ± 0.81 mcg/ml 4.5 hour after the end of GCV infusion. If the serum concentration exceeded expected limits (0.5-8.0 mcg/ml) at this time point the dose and/or frequency of administration was modified. Therefore in 25 (62.5%) newborns GCV was administered every 8 hours (instead of initial 12 h) to obtain appropriate therapeutic levels in the blood. Our observations suggest, that drug monitoring using HPLC method may be useful in estimating appropriate levels of the drug in serum to obtain the efficacy and safe of treatment. Possibly, precisely monitored drug administration, individualized according to serum concentration of GCV is responsible for good results according to neutrophils and platelets count in our study.

GCV eliminates CMV excretion in body fluids within seven to eight days in most patients [15]. Most authors suggest that GCV should be administered minimum within 3 weeks to ensure benefits of treatment. Results of randomized control trials with GCV show that during GCV treatment the amounts of CMV excreted to urine was decreased, but viruria returned when the therapy was stopped. Anyway therapy with ganciclovir transiently reduces virus shedding and may lessen the consequences of congenital cytomega ly in some infected infants [9, 16-18]. In randomized control trials GCV was administered intravenously within 6 weeks and observed side effects were dose related [9, 12]. In our study GCV related side effects also occurred. There was no correlation between duration of therapy and observed side effects (neutropenia, anaemia).

It may suggest that prolonged therapy with GCV using therapeutic drug monitoring may be useful in successful inhibition of replication of virus with minimum side effects.

No newborn had severe side effects during therapy. We can conclude that GCV is well tolerated in majority of newborns and observed short-term safety of treatment is promising.

Conclusions

1. GCV is well tolerated in newborns if serum concentration monitoring and the individual doses are used.
2. There in no correlation between individual dose used, prolonged therapy of GCV and observed side effects.
3. Neutropenia and anemia are the most frequent observed side effects during GCV treatment.

References

Effects of ganciclovir therapy on selected hematological parameters


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