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Pregnancy during lamivudine therapy in chronic hepatitis B – case report

The introduction of prophylactic vaccinations against hepatitis B virus (HBV) infections in the nineties of the 20th century markedly decreased the incidence of acute infections with HBV in Poland. Up till now, however, chronic hepatitis B remains to be an important epidemiological, clinical and therapeutic problem, which, along with hepatitis C virus (HCV) infection, belongs to one of the biggest health threats.

The aim of treatment in chronic hepatitis B is to eliminate hepatocytes where HBV replicates, to stop the inflammatory course of the disease and the hepatic necrosis, as well as to prevent the development of primary hepatocellular carcinoma. Suppression of virus replication favours better cell-mediated response and that is why the antiviral therapy is the basic method of controlling the HBV infection course. Therapeutic intervention, according to present-day, well established standards, involves treatment of chronic hepatitis B with lamivudine and/or interferon alpha (IFN alpha).

We have noticed that in clinical practice the monitoring of antiviral therapy in chronic hepatitis B in women of reproductive age is becoming especially important.

It is widely known that in case of a pregnancy in a patient infected with HBV there is a risk of intrauterine fetus infection, which rises significantly with the serological profile of positive hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg) and in the presence of HBV DNA in serum. There is also a potential vertical transmission from mother to child during parturition. At the same time no teratogenic influence of HBV has been found, even in cases with proven neonatal infections (1, 3, 5).

The possibility of pregnancy in patients being in reproductive age and taking lamivudine cannot be excluded, especially that the therapy can last a few months or even longer and can be carried out in ambulatory conditions. With the present knowledge it is difficult to predict if the lamivudine may have an influence, and of what kind, on the course of pregnancy and the fetus itself.

Below we present the case of woman with chronic hepatitis B infection who became pregnant during lamivudine monotherapy and with positive HBV replication markers.

CASE REPORT

A patient of 19 years of age was treated against chronic hepatitis B infection in the Department of Infectious Diseases of the Medical University of Lublin. The diagnosis was based on anamnesis,

clinical features, biochemical tests, serological tests and histopathological results of liver biopsy. The third generation enzyme-linked immunosorbent assay tests (Elisa, Abbot, Abbott Laboratories, 100 Abbott Park Rd., Abbott Park, Illinois) proved the presence of HBsAg, HBeAg and total antibody to hepatitis B core antigen (anti-HBc) in the serum.

Anti-HBc IgM and antibody to hepatitis C virus (anti-HCV) were not detected. Marking of HBV DNA in the serum was done (Digene Hybrid Capture System: Murex Diagnostica GmBH, Amplicor Roche), assuming a positive result at the level of more than 5.0 pg/mL, as instructed. The serum HBV DNA was 6615 pg/mL.

The serum biochemical results showed an elevated activity of alanine aminotransferase (ALT) ranging from 82 to 131 IU/L, with the normal level of bilirubin and total proteins (TP). No abnormalities in blood cell count were found, the results being haemoglobin (HGB) – 14 g/L, haematocrit (HCT) – 40.3 %, red blood count (RBC) – 4.48 M/mL and white blood count (WBC) – 7.1 k/mL. There were no antinuclear, antimitochondrial and anti-smooth muscle antibodies found.

Histological grading results of liver biopsies showed a significant degree of inflammatory process intensification (grade III) and clear cirrhosis features (stage III) according to the Knodell score system. Tissue reaction against HBsAg was observed in some hepatocytes. The therapy with interferon alpha (Roferon; Roche, F. Hoffmann–La Roche S.A. Bale-Suisse) was started with a dose of 3 MU 3 times a week. As the high HBV replication activity was present, after 12 weeks of treatment, lamivudine (Zeffix, Glaxo Welcome Group, Priory Street, Ware, UK) was started with the dose of 100 mg once a day. Normalisation of serum ALT levels at 30 IU/L and undetectable HBV DNA in serum were achieved after 3 months of this combined therapy. There was no seroconversion from HBeAg to anti-HBe, though. The control results showed the presence of HBsAg and HBeAg in the serum.

On 29 June, 2000 IFN alpha was stopped and the treatment was continued with only lamivudine at the dose of 100 mg once a day. After 3 months of this therapy HBV DNA level reached 25.46 pg/ml, with HBsAg and HBeAg also present in the serum. The therapy was continued until 28 November, 2000 when, during check-up, the patient told us that the date of her last menstruation had been 6 October, 2000 and the pregnancy test was positive. The gynaecological examination confirmed pregnancy. The patient had been exactly informed of the necessary use of contraceptives during the whole therapy period but in spite of those recommendations she became pregnant for the first time in her life.

There were no medical problems during the whole pregnancy period. Gynaecological and a few ultrasound examinations did not show any abnormalities. On 29 June, 2001, in the 38th week of pregnancy the patient gave birth to a healthy child. The labour was spontaneous, completed with vacuum extractor because of the prolonged second stage. Her baby boy weighed 3995 g and was given 9 points in the Apgar scale. The paediatric examination revealed no abnormalities. The child was given the combined active-positive prophylaxis (Hepatitis B Gamma globulin; Engerix B, Smithkline Beecham Biologicals, Rue De l' Institut 89, 1330 Rixensart, Belgium).

DISCUSSION

The safety of lamivudine use in the first trimester of pregnancy in women infected with HBV has not yet been proven (2). Most of the available data regarding pharmacokinetics of lamivudine in pregnancy has been obtained in studies in HIV infected mothers. According to Guidelines for the Use of Antiretroviral Agents in human immunodeficiency virus (HIV) infected patients prepared by National Institutes of Health (NIH) Panel to Define Principles of Therapy of HIV Infection, in these subjects lamivudine should be given together with zidovudine mainly after 10–12 weeks' gestation (4). Preclinical research on animals has confirmed a potential risk of fetus injury and therefore Food and Drug Administration (FDA) has classified lamivudine as a category C drug.

The presented case shows that lamivudine used in a daily dose of 100 mg in our patient during the first 6 weeks of pregnancy did not cause any fetus injury. However, we believe that this one case is insufficient to establish the safety of lamivudine therapy in chronic hepatitis B in pregnant women.

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SUMMARY

In case of a pregnancy in a patient infected with hepatitis B virus there is a risk of intrauterine fetus infection, which rises significantly with the serological profile of positive hepatitis B surface antigen, hepatitis Be antigen and in the presence of HBV DNA in serum. Therefore, in clinical practice the monitoring of antiviral therapy in chronic hepatitis B in women of reproductive age is becoming especially important. The safety of lamivudine use in pregnant women infected with hepatitis B virus has not yet been proven. In this case, the patient became pregnant during the treatment with lamivudine and when hepatitis B virus replication markers were present in the serum (hepatitis B surface antigen, hepatitis Be antigen, hepatitis B virus DNA). Treatment with lamivudine lasted through the first 6 weeks of pregnancy, which was complicated by a possibility of intrauterine hepatitis B virus infection, did not cause any fetus injury.

Ciąża u pacjentki z przewlekłym zapaleniem wątroby typu B, leczonej lamiwudyną

Ciąża u pacjentki z przewlekłym zapaleniem wątroby typu B (pzw B) wiąże się z ryzykiem wewnątrzmacicznej infekcji płodu, które wzrasta przy obecności HBsAg, HBeAg oraz HBV DNA w surowicy krwi. Monitorowanie terapii antywirusowej w pzw B u kobiet w wieku rozrodczym w praktyce klinicznej jest szczególne ważne. Nie potwierdzono bezpieczeństwa stosowania lamiwudyny u ciężarnych kobiet zakażonych wirusem zapalenia wątroby typu B. W prezentowanym opisie pacjentka zaszła w ciążę w czasie terapii lamiwudyną oraz przy obecnych markerach replikacji w surowicy krwi (HBsAg, HBeAg, HBV DNA). Terapia lamiwudyną trwała przez pierwsze sześć tygodni ciąży, zagrożonej możliwością wewnątrzmacicznej infekcji, nie spowodowała żadnych uszkodzeń płodu.