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ORIGINAL PAPER

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Coumarin embryopathy in an extremely low birth weight infant associated with neonatal hepatitis and ocular malformations

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Abstract Coumarin embryopathy (CE) is a well-documented sequelae of prenatal exposure to vitamin K antagonists. We report on a female premature infant (25 weeks' gestation) born to a mother who had received phenprocoumon during pregnancy following mechanical heart valve replacement. The infant presented with impaired coagulation, intraventricular and minor parenchymal cerebral haemorrhages and midface hypoplasia typical of CE. In addition, there was hepatopathy with conjugated hyperbilirubinemia, elevated liver enzymes and repeated episodes of hypoglycemia upon attempts to discontinue glucose supplementation, all lasting for 4 months. There was corneal opacity with anterior segment dygenesis in the left eye, and persistent pupillary membrane, cataract and persistent hyperplastic primary vitreous in the right eye. While liver disease is an uncommon but serious side effect of vitamin K antagonists, this is the first report describing neonatal hepatopathy as part of CE. In anticoagulation of pregnant women with mechanical heart valves, vitamin K antagonists should be used with utmost restraint.

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Abbreviations CE: Coumarin embryopathy · INR: International normalised ratio

Introduction

Coumarin embryopathy (also known as fetal warfarin syndrome or warfarin embryopathy) following prenatal exposure to vitamin K antagonists was first reported in 1966 by DiSaia [7]. In a recent overview, Van Driel et al. summarised 63 cases of CE (55 liveborn, five stillbirth and three elective abortions) reported since 1959 [21]. About 6% of all newborns exposed to coumarins throughout pregnancy suffer from CE; of these, 80% develop skeletal anomalies (e.g. midfacial hypoplasia, epiphyseal calcifications), 45% have central nervous malformations (e.g. midline structure defects) and 10% show signs of intracranial haemorrhage. As coumarins readily cross the placenta and subsequently affect fetal coagulation, there is a persistent risk for intracranial bleedings until birth. The rate of spontaneous abortion in women treated with coumarins throughout pregnancy has been estimated to be as high as 30%.

Liver disease following treatment with vitamin K antagonists is a rare but potentially serious complication which normally resolves upon discontinuation of the medication [5, 6, 11, 12, 16, 18, 19]. Here, we report on a very preterm infant exposed to phenprocoumon in utero who developed long-lasting hepatopathy in addition to signs of classical CE.

Case report

The 28-year-old mother had been treated with phenprocoumon (Marcoumar; Roche Pharma, Switzerland) because of mechanical mitral valve replacement following bacterial endocarditis. Upon becoming pregnant, she was

advised to continue oral anticoagulation because of the high risk situation for thrombo-embolic events. She received 1.5–3 mg phenprocoumon per day, resulting in International Normalised Ratios (INR) of 2.1–3.2. At 24 weeks' postmenstrual gestational age, she had vaginal bleeding, and anticoagulation was changed to subcutaneous low-molecular-weight heparin (dalteparin, Fragmin; Pfizer, Switzerland). Ultrasound showed minor cerebral parenchymal bleeding and enlarged ventricles of the fetus. The mother received steroids to induce fetal lung maturation. At 25 4/7 weeks, a cesarean was performed because of protracted fetal heart rate decelerations, and a female infant was born with Apgar scores of 0/3/5, birthweight of 780 g (P25–50), head circumference of 22.7 cm (P10) and a length of 33 cm (P25–50). As phenprocoumon is characterised by a long biological half-life time in vivo, the infant's INR was measured on the first day of life and found to be 3.6. Lasting INR normalisation was achieved after repeated administration of fresh frozen plasma during the first 3 days of life. The infant had respiratory distress, which was treated with surfactant replacement, mechanical ventilation (35 days), continuous positive airway pressure (20 days) and prolonged supplemental oxygen. A patent ductus arteriosus closed following several rounds of ibuprofen and indomethacin. She had four rounds of anti-infectious medications (amoxicillin+clavulanic acid, ceftazidime, amikacin and amphotericin B).

The infant showed midfacial hypoplasia with depressed nasal bridge and a high-arched palate typical of CE (Fig. 1). There were no epiphyseal calcific stipplings. Magnetic resonance imaging showed small residual intraparenchymal bleedings in the left frontal lobe, hypoplasia of the cerebellum with a normal-sized fourth ventricle, an infracerebellar arachnoid cyst, hypoplastic pontine structures and normal images of other midline structures. Because of neonatal seizures she was treated with phenobarbital from the first day of life and additionally with phenytoin from the 22nd until the 75th day of life.

Ophthalmologic examination showed bilateral abnormalities. In the left eye, there was a cloudy cornea with deep vascularisation and a shallow anterior chamber with pupillary deformation, suggestive of anterior segment dysgenesis. In the right eye, there was a persistent pupillary membrane, and the posterior pole was hard to visualise. After resorption of the membrane, follow-up examinations showed cataract and persistent hyperplastic primary vitreous.

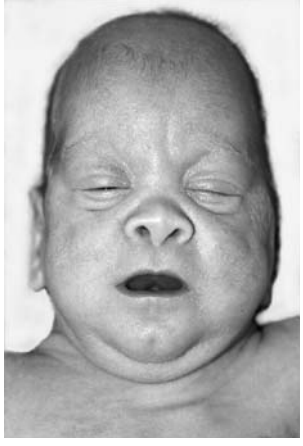

Fig. 1 Photograph of face with midfacial hypoplasia at age 3 months

Soon after birth, the infant developed hepatomegaly and persistent jaundice with conjugated hyperbilirubinemia (peak: 112 μ*M* at day 13 of life) and elevated liver enzymes (peak ASAT: 151 U/l on day 96 of life; peak γGT: 256 U/l on day 124 of life). Until 4 months of age, there was recurrent hypoglycemia unless the infant received glucose in addition to regular meals. Thereafter, symptoms of hepatic dysfunction receded. Investigations into possible infectious, metabolic, anatomic and endocrinological reasons for the liver dysfunction observed yielded negative results. No liver biopsy was performed.

Discussion

Anticoagulation of pregnant women has been a matter of debate between various experts [1, 2, 4, 8, 9, 15, 17, 20] The European Society of Cardiology 2003 guidelines state that continuation of vitamin K antagonist during the first trimester of pregnancy is the safest therapeutic option for the mother and that low-molecular-weight heparin should not be recommended in patients with heart valve prostheses during pregnancy. This recommendation is based on a presumed mortality between 1 and 4% mainly due to valve thrombosis while on heparin therapy [20]. In contrast, the American College of Chest Physicians (ACCP) 2004 guidelines recommend dose-adjusted low-molecular-weight heparin throughout pregnancy in women with prosthetic heart valves [2]. The case reported here serves to document the grave consequences for the fetus exposed to phenprocoumon in utero and, consequently, supports the ACCP-2004 stance. In addition to CE-related midfacial hypoplasia and sequelae of preterm birth, the baby girl had long-lasting hepatopathy and is factually blind.

While eye anomalies, including congenital cataracts, have been described as part of CE earlier, this is only the second report [13] linking complex eye malformations to intrauterine phenprocoumon exposure. The effect of coumarins on the developing eye and central nervous system may be indirect due to (micro)haemorrhages, or direct, through an interference with normal development during organogenesis between 6–9 weeks of gestation. The most recent investigations reveal that cartilage, bone and the developing nervous system contain vitamin K-dependent proteins [21]. The complications of coumarins seem to be to dosage-dependent [22]. While the mother described herein had received moderate doses, the protracted depression of the newborn infant's INR 11 days after cessation of phenprocoumon suggests that the fetus had been functionally overdosed.

Moreover, the premature born girl presented here appears to be the first case of phenprocoumon-related neonatal hepatitis. Hepatotoxicity is a rare but sometimes serious adverse effect of coumarin medication [5, 6, 11, 12, 14, 16, 18, 19]. Whereas phenprocoumon seems to induce

what appears to be a hepatitis-like alteration, warfarin and acenocoumarol are thought to have more cholestatic effects [6, 12]. The degree of liver damage ranges from asymptomatically elevated liver enzymes to jaundice [6, 11, 19] or rarely severe hepatic failure necessitating liver transplantation [5, 16]. Symptoms of liver damage appear between 10 weeks and 8 months after initiation of the drug, and the recovery of hepatic function occurs during the period 1 to 5 months after cessation [12, 18] This time course is well in line with the clinical course of the baby presented here. Clavulanic acid might have aggravated the liver damage observed [3, 10], while phenytoin was administered only after evidence of liver damage was apparent.

In conclusion, vitamin K antagonist-based anticoagulation of pregnant women poses a considerable risk to the fetus and as such warrants a search for a safer approach, such as low-molecular-weight heparin.

References

1. ACOG committee opinion (1999) Anticoagulation with low molecular weight heparin during pregnancy. Int J Gyn Obstet 65:89–90
2. Bates SM, Greer IA, Hirsh J, Ginsberg JS (2004) Use of antithrombotic agents during pregnancy: the seventh ACCP conference on antithrombotic and thrombolytic therapy. Evidence based guidelines. Chest 126:627S–644S
3. Cauli C, Fenu L, Perra A, Marongiu F (2004) Amoxicillin-clavulanic acid and oral anticoagulants: a possible dangerous association. Ann Ital Med Int 19:276–279
4. Chan WS, Anand S, Ginsberg JS (2000) Anticoagulation of pregnant women with mechanical heart valves a systematic review of the literature. Arch Intern Med 160:191–196
5. de Man RA (1993) Phenprocoumon-induced liver failure. Neth J Med 43:91
6. de Man RA, Wilson JPH, Schalm SW, ten Kate FJW, Van Leer E (1990) Phenprocoumon-induced hepatits mimicking non-A, non-B hepatitis. J Hepatol 11:318–321
7. DiSaia PJ (1966) Pregnancy and delivery of a patient with a Starr-Edwards mitral valve prosthesis. Obstet Gynecol 28: 469–472
8. Ginsberg JS (1999) Thromboembolism and pregnancy. Throm Haemost 82:620–625
9. Ginsberg JS, Kowalchuk G, Hirsh J (1989) Risk to the fetus of anticoagulant therapy during pregnancy. Arch Intern Med 149:2233–2236
10. Gresser U (2001) Amoxicillin-clavulanic acid therapy may be associated with severe side effects – review of the literature. Eur J Med Res 6:139–149
11. Hautekeete M, Holvoet J, Hubens H (1995) Cytolytic hepatitis related to the oral anticoagulant phenprocoumon. Gastroenterol Clin Biol 19:223–224
12. Höhler T, Schnütgen M, Helmreich-Becker I, Mayet WJ, Mayer zum Bueschenfelde KH (1994) Drug-induced hepatitis: a rare complication of oral anticoagulants. J Hepatol 21:447–449
13. Kaplan LC (1985) Congenital Dandy Walker malformation associated with first trimester warfarin: a case report and literature review. Teratology 32:333–337
14. Lee WM (1995) Drug-induced hepatotoxicity. N Engl J Med 333:1118–1127
15. Montalescot G, Polle V, Collet JP (2000) Low-molecular-weight heparin after mechanical heart valve replacement. Circulation 101:1083–8106
16. Mix H, Wagner S, Böker K, Gloger S, Oldhafer KJ, Behrend M, Flemming P, Mann MP (1999) Subacute liver failure induced by phenprocoumon treatment. Digestion 60:579–582
17. Sanson BJ, Lensing AWA, Prins MH (1999) The use of low-molecular-weight heparin in pregnancy. Thromb Haemost 81:668–672
18. Schimanski CC, Burg J, Möhler K, Höhler T, Kanzler S, Otto G, Galle PR, Lohse AW (2004) Phenprocoumon-induced liver diseases range from mild acute hepatitis to (sub-) acute liver failure. J Hepatol 41:67–74
19. Slagboom G, Loeliger EA (1980) Coumarin-associated hepatitis. Arch Intern Med 140:1028–1029
20. Task Force on the Management of Cardiovascular Diseases During Pregnancy of the European Society of Cardiology (2003) Expert consensus document on management of cardiovascular diseases during pregnancy. Eur Heart J 24:761–781
21. Van Driel D, Wesseling J, Sauer PJJ, Touwen BCL, Van Der Veer E, Heymans HSA (2002) Teratogen update: fetal effects after, in utero exposure to coumarins, overview of cases, follow-up findings, and pathogenesis. Teratology 66:127–140
22. Vitale N, De Feo M, De Santo LS, Pollice A, Tedesco N, Cotrufo M (1999) Dose-dependent fetal complications of warfarin in pregnant women with mechanical heart valves. J Am Coll Cardiol 33:1637–1641