Rifampicin in the treatment of severe intrahepatic cholestasis of pregnancy

Victoria Geenes a, Jenny Chambers b, Rshmi Khurana c, Elisabeth Wikstrom Shemer d, Winnie Sia c, Dalvinder Mandair e, Elwyn Elias e, Hanns-Ulrich Marshall f, William Hague g,  Catherine Williamson a,∗

aWomen’s Health Academic Centre, King’s College London, London, United Kingdom
bWomen’s Health Research Centre, Imperial College London, London, United Kingdom
cRoyal Alexandra Hospital, University of Alberta, Edmonton, Canada
dDepartment of Women’s and Children’s Health, Akademiska Hospital, Uppsala University, Uppsala, Sweden
eLiver Unit, University of Birmingham Trust Hospital, Birmingham, United Kingdom
f Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
g Robinson Research Institute, University of Adelaide, Adelaide, South Australia, Australia

A R T I C L E   I N F O

Article history:
Received 9 October 2014
Received in revised form 23 February 2015
Accepted 19 March 2015

Keywords:
Bile acids
Pregnancy
Obstetric cholestasis
Ursodeoxycholic acid
Rifampicin

A B S T R A C T

Objective: To describe the use of combined ursodeoxycholic acid (UDCA) and rifampicin treatment in intrahepatic cholestasis of pregnancy (ICP).

Study design: A questionnaire survey of 27 women with 28 affected pregnancies identified via the UK and International Obstetric Medicine forum. The clinical case notes of women with ICP treated with combined UDCA and rifampicin therapy were reviewed, and data regarding maternal and perinatal outcomes extracted.

Results: Serum bile acids remained high whilst taking UDCA as monotherapy. In 14 pregnancies (54%) serum bile acids decreased following the introduction of rifampicin. In 10 pregnancies (38%), there was a 50% reduction in serum bile acids. There were no adverse effects reported with either drug.

Conclusions: This is the first report of the use of rifampicin in ICP. The data suggest that combined treatment with UDCA and rifampicin is an effective way of treating women with severe ICP who do not respond to treatment with UDCA alone.

© 2015 Elsevier Ireland Ltd. All rights reserved.

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific liver disease, associated with an increased risk of adverse fetal outcomes, including preterm delivery, meconium staining of the amniotic fluid and stillbirth [1,2]. It is characterised by maternal pruritus and elevated transaminases and serum bile acids. The most sensitive and specific biochemical marker for the diagnosis and monitoring of ICP is the concentration of serum bile acids. Recent studies have shown an increased risk of adverse perinatal outcomes in women with severe ICP (i.e. in those with serum bile acids >40 μmol/L) [1,2]. ICP is commonly treated with ursodeoxycholic acid (UDCA), which has been shown to improve pruritus and serum biochemistry, including serum bile acid levels [3–5]. The mechanisms of action of UDCA are not fully understood, but are proposed to include improved bile acid transport and detoxification [6]. Evidence from in vitro studies of the developing fetal heart and the placenta suggest that UDCA may also have a direct protective effect on the fetal compartment in ICP [7]. However, not all women treated with UDCA have a biochemical response or an improvement in symptoms.

Rifampicin has been used in the treatment of several cholestatic liver diseases. In primary biliary cirrhosis it has been shown to reduce bilirubin, enhance hepatic efflux of organic anions, including serum bile acids, and improve pruritus. The mechanisms of its action in such diseases are complementary to those of UDCA, and include enhanced bile acid detoxification and elimination [6]. Combination therapy with rifampicin and UDCA might therefore be more effective than UDCA treatment alone, but there have been no reports of the use of rifampicin in ICP. The aim of this study was...
to evaluate the impact of the addition of rifampicin to UDCA in the treatment of ICP.

Materials and methods

Women diagnosed with ICP and treated with a combination of ursodeoxycholic acid (UDCA) and rifampicin were identified via the UK and International Obstetric Medicine Discussion Forum, an online organisation for obstetricians and physicians with a specialist interest in Obstetric Medicine. Between 2009 and 2012 consultants with an interest in maternal medicine were asked to submit the details of any woman in their care with severe ICP treated with these drugs. ICP was diagnosed in women presenting with pruritus and elevated liver enzymes, including raised serum bile acids. Women with other causes of pregnancy-specific liver dysfunction, including pre-eclampsia, the HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome and acute fatty liver of pregnancy, were excluded. Clinical case notes were reviewed and data regarding drug treatment, serum biochemistry, pregnancy and fetal outcomes collated in an anonymised database. Blood test results from the 24-h period before either treatment was started were used for analysis. Blood tests were performed according to local hospital policy, and further information regarding whether individual women were fasted or not is not available. Statistical analysis was performed using Stata (StataCorp, Texas).

Results

Twenty-eight ICP pregnancies treated with both UDCA and rifampicin were identified in twenty-seven women (one woman had two pregnancies during the study period). Two pregnancies were excluded from subsequent analysis as rifampicin had been started before UDCA, based on the woman’s previous history of severe ICP responding to rifampicin (see Table 1 and supplementary Figure 1). Of the remaining 26 pregnancies, two (8%) were twin gestations. 14 (54%) of the women had a previous history of ICP, and four (15%) had a history of stillbirth associated with ICP. Two women (8%) had a history of gallstones and six (23%) had a history of pruritus when taking the combined oral contraceptive pill. The mean gestational age at onset of pruritus was 21.6 weeks (Interquartile range [IQR] 13 to 28 weeks) and at diagnosis 24.5 weeks (IQR 18.8 to 30 weeks). Further clinical details can be found in Table 1.

The mean gestational age at which UDCA treatment was commenced was 26.4 weeks (IQR 22.9 to 31.1 weeks) and the starting dose of UDCA ranged from 500 to 1500 mg in divided doses daily. The maximum doses of UDCA ranged from 1500 to 3500 mg in divided doses daily. The mean gestational age at which rifampicin treatment was added was 30.2 weeks (IQR 29.4 to 34.0 weeks), and the doses used ranged from 300 to 1200 mg in divided doses daily. The mean number of weeks which women received combined UDCA and rifampicin treatment for was 2.7 weeks (IQR 0.6 to 6.3 weeks). Further details regarding doses and duration of treatment with each drug are given in Table 1. No adverse side
effects were reported by women for either treatment. None of the women in this study received any other treatments specifically for ICP. However, six women (23%) received vitamin K, four women (15%) received an antihistamine, and 10 women (38%) were given steroids (either betamethasone or dexamethasone) to promote fetal lung maturity.

The serum biochemistry values for women before commencing UDCA treatment, before commencing rifampicin treatment and prior to delivery are shown in Figs. 1–3. In all women, serum bile acids remained high following the commencement of UDCA therapy (Fig. 1). In 14 (54%) women, serum bile acids reduced following the commencement of rifampicin treatment (Fig. 1). Ten women (38%) had a 50% or greater reduction in serum bile acids following the introduction of rifampicin. Subgroup analysis of these women did not identify any clinical or biochemical factors that could be used to predict a response to rifampicin treatment (Table 2). In particular, compared with women who did not respond to rifampicin treatment, women who responded were not more likely to have a history of pruritus when taking the oral contraceptive pill (30%, 3/10 vs. 19%, 3/16), nor a previous history of ICP (80%, 8/10 vs. 43%, 7/16). Furthermore, there was no difference in the dose of rifampicin used or in the number of weeks of treatment (1–4 weeks) (IQR 0 to 3 weeks) vs. 2–3 weeks (IQR 1 to 5 weeks). Of note, the two women with a history of gallstones both had a greater than 50% reduction in serum bile acids following the introduction of rifampicin.

The biochemical response to rifampicin for the other markers of liver dysfunction was less clear (Figs. 2 and 3). 15% (4 women) had a 50% or greater reduction in serum ALT, and 12% (3 women) had a 50% or greater reduction in serum bilirubin. Similar reductions were seen in serum AST (23%, 4 of 17 women) and GGT (4.5%, 1 of 22 women) (data not shown). Clinical case notes were reviewed for evidence of a subjective improvement in symptoms. Of the 15 pregnancies in which comment on symptoms was made in the clinical notes, 10 recorded a reduction in pruritus following the introduction of rifampicin.

The mean gestational age at delivery was 34±4 weeks (IQR 33–35 weeks) (Table 1). 16 (62%) women had vaginal deliveries, of whom 14 (54%) had labour induced for worsening serum biochemistry and/or symptoms. Of the ten women who required caesarean section, seven (27%) were delivered electively and three (12%) were delivered as an emergency procedure. There were no post-partum haemorrhages reported. Twelve babies (46%) were admitted to the neonatal unit, mainly for prematurity. Meconium staining of the amniotic fluid was reported in 8 cases (31%). There were no stillbirths or congenital abnormalities.

Comment

This is the first report of the use of combined UDCA and rifampicin treatment in ICP. This study shows that rifampicin may be a useful adjunct to treatment in pregnant women with increasing serum bile acids despite maximal UDCA therapy. Following the addition of rifampicin, over half of women had some improvement in bile acids, and in 38% of women there was a reduction of greater than 50%. There were no adverse effects reported from either treatment and there were no stillbirths. This study is that it is the first report of its kind, although rifampicin has been used with good effect in other cholesstatic liver disorders, including primary biliary cirrhosis and childhood cholestatic syndromes [8–14]. In primary biliary cirrhosis it has been shown to improve both pruritus and serum biochemistry, including serum bile acids [8,12]. It is therefore biologically plausible that it would have a similar effect in ICP. Rifampicin has
also been extensively used in the treatment of tuberculosis, including in the treatment of pregnant women, and there are encouraging safety data relating to its use in pregnancy.

The mechanism of action of rifampicin in cholestasis is not fully understood, but a study of the use of rifampicin in pre-operative patients with gallstones showed that it enhances bile acid detoxification, bilirubin conjugation and bilirubin excretion [6]. In the same study, these effects were complemented by the up-regulation of bile acid export pathways in the liver by UDCA [6].

Table 2

<table>
<thead>
<tr>
<th>Maternal medical history</th>
<th>Responder (N=10)</th>
<th>Non-responder (N=16)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of gallstones</td>
<td>2 (20%)</td>
<td>0 (0%)</td>
<td>ns</td>
</tr>
<tr>
<td>History of pruritus with oral contraceptives</td>
<td>3 (30%)</td>
<td>3 (19%)</td>
<td>ns</td>
</tr>
<tr>
<td>History of ICP</td>
<td>8 (80%)</td>
<td>7 (43%)</td>
<td>ns</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis of ICP</th>
<th>Gestation at onset of pruritus</th>
<th>Gestation at diagnosis of ICP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>26±1 (14±15 to 29±9)</td>
<td>27±0 (19±1 to 31±5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biochemistry at diagnosis</th>
<th>Serum bile acids (μmol/L)</th>
<th>Alamine transaminase (IU/L)</th>
<th>Aspartase transaminase (IU/L)</th>
<th>Bilirubin (μmol/L)</th>
<th>Gamma glutamyl transferase (IU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>33 (17–70)</td>
<td>103.5 (62.5–194.5)</td>
<td>52 (26–154.5)</td>
<td>11 (8.5–23.5)</td>
<td>20 (16.5–36.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biochemistry at commencement of UDCA</th>
<th>Serum bile acids (μmol/L)</th>
<th>Alamine transaminase (IU/L)</th>
<th>Aspartase transaminase (IU/L)</th>
<th>Bilirubin (μmol/L)</th>
<th>Gamma glutamyl transferase (IU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>58.5 (26.5–121.2)</td>
<td>184 (92–443.5)</td>
<td>110.5 (40–216)</td>
<td>13.5 (8–24)</td>
<td>25.5 (21–40)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biochemistry at commencement of rifampicin</th>
<th>Serum bile acids (μmol/L)</th>
<th>Alamine transaminase (IU/L)</th>
<th>Aspartase transaminase (IU/L)</th>
<th>Bilirubin (μmol/L)</th>
<th>Gamma glutamyl transferase (IU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>258 (115–388)</td>
<td>237 (43.5–415)</td>
<td>107.5 (34.5–192)</td>
<td>14 (8.5–19.5)</td>
<td>24.5 (18.5–34)</td>
</tr>
</tbody>
</table>

The implications of the study are that treatment with rifampicin may be considered in women with ICP who do not have an adequate clinical or biochemical response to UDCA alone. Anecdotaly, it is known that not all women with ICP have a clinical or biochemical improvement with UDCA treatment. Although the reasons for this are not known, the data presented here suggest that a sub-group of these women will respond to combined therapy with rifampicin. Given that there were no adverse effects reported in the study and that there is a well established safety profile for both drugs in pregnancy, it is reasonable to consider combined therapy in women with severe ICP who have not responded to treatment with UDCA alone.

Future research is needed to determine genetic or metabolomic features that will predict which women with ICP will respond to UDCA alone, or to UDCA in combination with rifampicin, so that treatment can be tailored to individuals. Furthermore, the data presented here warrant further investigation in the form of a prospective randomised and preferably placebo-controlled trial to assess whether combined treatment with UDCA and rifampicin is safe and effective in the management of severe cholestasis of pregnancy.

In summary, rifampicin may be a useful adjunct to the treatment with UDCA in women with severe ICP, and should be used in combination with UDCA, given that the two drugs act in a complementary fashion to enhance bile acid detoxification and increase bile acid excretion.

Conflict of interest

The authors have no conflict of interest to declare.

Role of funding source

This study was supported by the National Institute for Health Research (NIHR) Biomedical Research Centres based at Kings College London (grant number: guysbrc-2012-1) and Imperial College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health NIHR or the Department of Health. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgements

Paul Seed for help with statistical analysis.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejogrb.2015.03.020.

References


