increases the risk of gestational diabetes. In women who weighed less than 3500 g at birth, weight for gestational age may provide additional predictive information on risk. No other birth characteristics were predictive of gestational diabetes. The non-significant raised risk in women weighing 4500 g or more at birth could indicate undiagnosed or unrecorded maternal diabetes. Low birth weight and low weight for gestational age may be common risk factors for gestational diabetes and non-insulin dependent diabetes. The results are compatible with the fetal origins of disease hypothesis. Future studies combining birth information with risk factors in adulthood may improve predictive models for identifying women at risk of gestational diabetes.

Barbro Mork Emblem was instrumental in linking the generational birth information and in setting up the generational analytical database.

Contributors: GE had the idea for the study, conducted analyses, and wrote the report. RS provided guidance in using the registry, discussed core ideas and study design, and edited the report. LI supervised data collection, discussed core ideas and study design, and edited the report. All authors are guarantors of the paper.

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Drug points

Prolonged cholestasis associated with irbesartan

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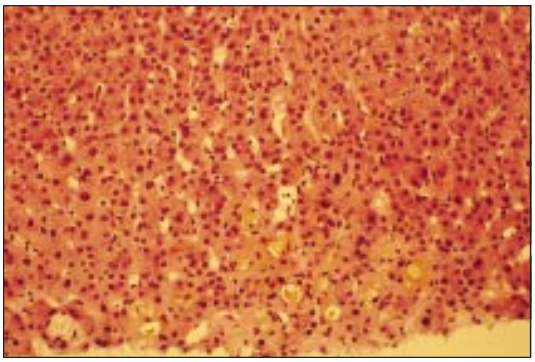
A 62 year old woman was admitted with a week's history of jaundice. Examination showed deep icterus and hepatomegaly. She had no history of liver disease, blood transfusion, alcohol or drug misuse, or travel abroad. She had been hypertensive for 15 years and took atenolol 50 mg daily. Treatment had been changed to irbesartan (Aprovel, Bristol-Myers Squibb, Hounslow) 300 mg daily one month before admission.

Liver function tests showed concentrations of albumin 240 g/l (normal range 360-520 g/l), bilirubin 403 µmol/l (0-17 µmol/l), alkaline phosphatase 3193 IU/l (20-125 IU/l), γ-glutamyltransferase 1924 IU/l (10-50 IU/l), and aspartate aminotransferase 177 IU/l (0-40 IU/l). Serology for hepatitis A, B, and C, cytomegalovirus, Epstein-Barr virus, and autoimmune screen gave negative results. Tests for haemochromatosis and α_1 antitrypsin deficiency gave normal results. An ultrasonogram and computerised tomogram were normal.

Irbesartan was stopped one week after admission and substituted with amlodipine and atenolol. The patient remained jaundiced, with a bilirubin concentration of 324 µmol/l after two months. A liver biopsy sample obtained on two different occasions showed notable portal tract expansion with minimal inflammation, ectatic bile ductules, and cholestatic rosettes (figure). These features were more pronounced in the second biopsy sample. Endoscopic retrograde cholangiopancreatography gave normal results. Her condition gradually improved and the bilirubin concentration returned to normal in about 16 weeks. She continues to be anicteric at more than one year's follow up.

The temporal profile of her cholestatic jaundice in relation to the irbesartan and the lack of an alternative cause for liver dysfunction suggests a drug reaction. The diagnosis also fulfils the international consensus criteria for drug induced hepatotoxicity.[1]



Parenchymal cholestasis with "cholestatic rosettes" and ballooning degeneration of hepatocytes in liver biopsy sample (haematoxylin and eosin × 20)

A review of hepatotoxicity with angiotensin converting enzyme inhibitors showed that a cholestatic pattern was present in the liver of eight out of 13 patients.[2] There have been reports of severe acute hepatic injury as well as 80 reports of minor liver injury in association with losartan.[3–5] The manufacturers of irbesartan were, however, previously unaware of any association between this drug and severe hepatic dysfunction.

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