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Letter to the Editors

Updated study on risk of cholestatic liver disease and flucloxacillin

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Since the first two cases of intrahepatic cholestasis associated with flucloxacillin use were reported from Sweden in 1985 [1], flucloxacillin has been repeatedly associated with cholestatic liver disease [2–7]. The liver disease is characterized by painless jaundice with predominant elevation of alkaline phosphatase and bilirubin within 1 to 5 weeks after stopping drug therapy [4]. Because of concern over adverse hepatic reactions in association with the use of flucloxacillin the Australian Department of Human Services and Health restricted flucloxacillin use to severe infections and all advertising by the manufacturer was stopped in 1994. Subsequently flucloxacillin prescription dispensing decreased by about 30% between June 1994 and December 1995 [8]. Although the United Kingdom (UK) Medicines Controls Agency published a warning concerning this association as early as 1992 [9], flucloxacillin (including Co-fluampicil) has remained a first-line therapy for *Staphylococcus aureus* infections and between 1991–2006 was increasingly used in primary care settings in the UK [10].

Using the UK population-based General Practice Research Database (GPRD) we found a consistent risk of cholestatic liver disease in the 45 days after first-time use of flucloxacillin: 7.6 per 100 000 users (95% confidence interval [CI] 3.6, 13.9) between January 1985 and July 1991 [4], 6.5 per 100 000 users (95% CI 2.7, 15.1) between August 1991 and October 1992 [5], and 8.5 per 100 000 users (95% CI 5.4, 12.6) between November 1992 and 2002 [7].

We have updated these study results in the GPRD to include another 346 072 people who used flucloxacillin for the first time from January 1 2003 to the end of data collection in 2007 in comparison with 1 179 360 first-time penicillin V users. We used the same criteria as those in our previous studies [4, 5, 7] to identify cases of cholestatic liver disease of uncertain origin. Briefly, we went through all the electronic records of potential cases, excluding subjects where a causal relationship was unlikely, such as cases with another apparent cause of liver disease other than the drug under study including gallstones, alcohol abuse, viral hepatitis and cancer. We then validated cases by reviewing the original clinical records for a random sample of cases where computer-recorded data were consistent with the characteristics of drug-induced cholestatic liver disease. Among 346 072 first-time users of flucloxacillin we identified a total of 21 cases with apparent idiosyncratic cholestatic hepatitis within 1–45 days after a prescription for flucloxacillin (yielding an incidence estimate of 6.1 per 100 000 users [95% CI 3.8, 9.3]). In comparison, we identified four cases out of 1 179 360 first-time users of penicillin V (yielding an incidence estimate of 0.3 per 100 000 users [95% CI 0.1, 0.9]). The risk of flucloxacillin-associated cholestatic liver disease is consistent with those reported in our earlier studies while the risk for penicillin V is low.

To evaluate whether Co-fluampicil, a combination of flucloxacillin and ampicillin, also induces cholestatic liver disease, we investigated the independent risk of cholestatic liver disease associated with the use of this combination therapy. Among 159 215 first-time users of Co-fluampicil recorded after January 1 1988, there were six patients who developed a liver illness which was consistent with idiopathic cholestatic hepatitis within 45 days after a prescription (estimated incidence of 3.8 per 100 000 users [95% CI 1.4, 8.2]).

The current results regarding flucloxacillin in relation to cholestatic liver disease are in close agreement with those previously reported. Users of a combination of flucloxacillin and ampicillin had a risk of developing cholestatic hepatitis of about 4 per 100 000 users. These risks are substantially higher than the risk found in users of penicillin V (0.3 per 100 000 users).

Competing interests

None declared.

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