Rifampin is safe for treatment of pruritus due to chronic cholestasis: a meta-analysis of prospective randomized-controlled trials

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CRD summary
The authors concluded that the results suggest that rifampin, for a short duration, is a safe and effective treatment for pruritus associated with chronic cholestasis. The authors' conclusions are likely to be reliable, however, the majority of participants had primary biliary cirrhosis and thus generalisation to other patient groups may not be possible.

Authors' objectives
To determine the efficacy and safety of rifampin for pruritus associated with cholestasis due to chronic liver disease.

Searching
MEDLINE, PREMEDLINE, the Cochrane Database of Systematic Reviews, ACP Journal Club, DARE, the Cochrane Controlled Trials Register and EMBASE were searched for trials published between 1965 and 2004; the search terms were reported. The references of relevant articles were also checked and investigators contacted. Abstracts from conference proceedings were screened.

Study selection
Prospective randomised controlled trials (RCTs) were eligible for inclusion. All of the included trials were crossover RCTs. Studies that compared rifampin with placebo or an alternative pharmacological treatment for pruritus were eligible for inclusion. The comparator of interest was placebo in all but one trial, which compared rifampin with phenobarbitalone. The mean dose of rifampin ranged from 300 to 600 mg/day, and was 10 mg/kg per day in paediatric populations. Treatment duration was 14 days in most of the included studies; in one the duration was 7 days. Where reported, the washout period ranged from 7 to 30 days before treatment initiation. The use of cholestyramine for the control of pruritus was allowed in one trial. Studies of patients with pruritus associated with chronic cholestasis were eligible for inclusion. In most participants the aetiology of the liver disease was primary biliary cirrhosis. The mean age of the participants ranged from 5 to 57 years. The primary outcomes were improvement of pruritus and side-effects. The severity of pruritus was assessed using a pruritus scoring scale or visual analogue scales.

Two reviewers independently selected studies for inclusion in the review, and any disagreements were resolved by discussion.

Assessment of study quality
The methodological quality of the included trials was assessed using a previously validated questionnaire (Poynard 1988). The criteria used focused on description of the population and statistical methods. A total score was given to each study; the highest possible score was 26 and the lowest possible score was -2.

Two reviewers independently evaluated the quality of the included trials, and any disagreements were resolved by consensus.

Data extraction
Data were extracted for a number of factors, including indication for treatment, co-administration of other medication, side-effect profile, and methods to identify and confirm clinical outcomes. The odds ratio (OR) and corresponding 95% confidence interval (CI) were calculated for each outcome.

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.
Methods of synthesis
The studies were combined in a meta-analysis using both fixed-effect and random-effects models. Summary estimates were reported as ORs with their corresponding 95% CI. Heterogeneity was assessed using the Breslow Day test or the corrected Mantel-Haenszel \( \chi^2 \) test.

Results of the review
Five crossover RCTs (N=61) were included in the review.

The overall quality of the included trials was considered to be adequate.

Compared with placebo or alternative treatment, rifampin was found to increase the odds of resolution of pruritus symptoms (OR 15.2, 95% CI: 5.2, 45.6, p=0.001). A similar effect was found with a random-effects model. No evidence of significant statistical heterogeneity was found.

Four participants were reported to have suffered side-effects to treatment with rifampin: two reported nausea and decreased appetite (300 mg/day), one reported an allergic reaction (600 mg/day), and one developed haemolytic anemia and renal failure. None of the participants developed hepatotoxicity.

Authors' conclusions
The results suggest that treatment with rifampin for a short duration is safe and effective for pruritus associated with chronic cholestasis. It also suggests that the use of rifampin for a short duration is associated with a low risk of hepatotoxicity.

CRD commentary
The review question was supported by clear inclusion criteria and a number of relevant sources were searched for potential papers. Methods undertaken to select studies for inclusion in the review and evaluate methodological quality were likely to minimise the possibility of reviewer error or bias. Results on individual criteria for validity were reported for each study. The studies were pooled using standard quantitative methods, and heterogeneity was assessed. Results for the planned sensitivity analysis and publication bias check were not reported. Given differences in the studies with regard to population and the inclusion of adult and paediatric patients, it might have been useful to separate out these groups. The majority of participants had primary biliary cirrhosis, thus generalisation to other patient groups may not possible. The authors' conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that longer term studies with larger samples are need to clarify the safety and efficacy profile of rifampin.

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