Liver damage associated with minocycline use in acne: a systematic review of the published literature and pharmacovigilance data

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Authors' objectives
To identify and characterise reported cases of hepatotoxicity associated with minocycline.

Searching
MEDLINE, CINAHL, Cochrane Library, EMBASE, Current Contents and TOXLINE were searched from database inception to December 1998. Search terms included 'liver diseases (fatty liver, liver failure, liver function tests, liver transplantation, hepatic dysfunction)', 'hepatitis (hepatitis, autoimmune hepatitis, chronic hepatitis, chronic drug-induced hepatitis, toxic hepatitis)' and 'jaundice'. Papers published in English, French, German, Swedish and Spanish were eligible for inclusion. Reference lists of retrieved articles were searched for additional studies. A citation search was carried out using BIDS for those papers recognised to be particularly pertinent to the subject. The authors state that grey literature was also acquired for the review but do not report how this was identified. Data reported on adverse drug reactions were supplied by John Wyeth and Brother Ltd. (UK). Additional data on adverse events, which were provided by the World Health Organization (WHO), were reviewed separately from other data.

Study selection
Study designs of evaluations included in the review
The authors state that original studies of any design were eligible for inclusion in the review; however, only case reports were included.

Specific interventions included in the review
Oral minocycline; studies of intravenous minocycline were not included in the review. Doses ranged from 50 to 200 mg/day.

Participants included in the review
Patients with acne. Patients taking minocycline for reasons other than acne were excluded, as were those for whom there were no details of their age and gender. The age of participants ranged from 14 to 73 years, with the majority of cases in their teens or early 20s.

Outcomes assessed in the review
Liver damage. Studies reporting findings of laboratory investigations indicating liver dysfunction, or where a specific reference was made by the authors to liver dysfunction, were included.

How were decisions on the relevance of primary studies made?
The studies were assessed for inclusion by consensus.

Assessment of study quality
No formal assessment of quality was undertaken.

Data extraction
Patient details and medical histories were entered into a database (Access). The interpretation and recording of details was further reviewed by two independent researchers to ensure accurate assessment of clinical symptoms and/or investigations from the data. All case reports were compared by age, gender, country of domicile and year of occurrence to identify duplicate publications.
Methods of synthesis
How were the studies combined?
A narrative synthesis was presented. Cases were classified into one of the following three groups: autoimmune hepatitis, hypersensitivity reactions and unspecified hepatitis.

How were differences between studies investigated?
Differences between the studies were discussed narratively.

Results of the review
Sixty-five case reports were included in the review.

Autoimmune hepatitis (n=29).
Cases were generally associated with a prolonged course of minocycline therapy (the median was 365 days for females and 730 days for males), the presence of autoantibodies (90%) and symptoms of arthritis and/or arthralgia (72%). Recovery on complete cessation of the drug was apparent for all patients in a mean of 14 days (range: 4 - 38). Five patients experienced a recurrence of symptoms in response to re-challenge with minocycline.

Hypersensitivity reactions (n=16).
The condition was typically associated with eosinophilia (69% of patients) and desquamation of the skin (63%). The duration of treatment with minocycline before onset was less than 35 days in all cases. Three patients died from what appeared to be a hypersensitivity reaction, and one patient received a liver transplantation and survived.

Unspecified hepatitis (n=20).
The duration of treatment with minocycline ranged from 8 to 360 days for females and 9 to 840 days for males. One patient died and another received a liver transplantation and survived. One case experienced a resumption of symptoms on re-exposure to minocycline.

WHO data.
The WHO has recorded 8,025 reactions to minocycline overall, 6% of these involved the liver. The outcome of these reactions was reported in less than half the cases. Three deaths were evident.

Authors' conclusions
This review has indicated that minocycline therapy has been implicated in several instances of severe hepatic dysfunction, including four deaths. Severe cases of minocycline-associated hepatotoxicity appear to be a hypersensitivity reaction, and this occurs within a few weeks of commencing therapy. An autoimmune hepatitis usually presents after exposure to minocycline for at least one year, is more common in women, and is sometimes associated with lupus-like symptoms.

CRD commentary
This was a good review of the area given the authors' objective of identifying and characterising cases of hypertoxicity associated with minocycline. An extensive literature search was conducted which included attempts to locate unpublished data, and it is therefore likely that the majority of case reports were identified. The inclusion criteria were clear with the exception of study design. The authors stated that 'original studies' were included, although only case reports were included in the review. It should, therefore, be noted that this review only provided an indication of cases of minocycline-associated liver damage; it gives no information on the incidence of these cases or of whether minocycline has a more severe side-effect profile than other similar drugs. Adequate details of the review process and of the cases included were presented. A formal quality assessment was not conducted, but as this review was limited to case reports this would not have been practical. The synthesis provided was appropriate given the data, and the authors' conclusions are supported by the data. However, the limitations of case reports should be considered when interpreting...
the results.

Implications of the review for practice and research
Practice: The authors state that physicians should not prescribe tetracyclines to patients in whom an adverse reaction has been suspected previously. A genetic predisposition to hypersensitivity reactions has previously been suggested and this may be important to consider when prescribing minocycline.

Research: The authors did not state any implications for further research. [A: A study of the comparative rates of hepatitis in people exposed to minocycline compared with those not exposed is required]

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