Authors' objectives
To evaluate whether the administration of therapeutic doses of paracetamol cause hepatic injury in the alcoholic patient.

Searching
MEDLINE (from 1966 to November 1999), Best Evidence and the Cochrane Database of Systematic Reviews were searched. The MEDLINE search was limited to the headings of ‘adverse event’, ‘poisoning’ and ‘toxicity of paracetamol in humans’. The reference lists of the included papers were also examined for additional relevant studies. Articles written in any language were considered.

Study selection
Study designs of evaluations included in the review
The inclusion criteria stated that experimental study designs would be included.

The review included randomised placebo-controlled trials (RCTs), non-randomised open-label trials, open-label comparative trials, and case reports.

Specific interventions included in the review
Therapeutic use (single or repeated ingestion) of paracetamol in doses not exceeding 4 g/day. The measurement of blood levels of paracetamol was not a requirement. The included dosages ranged from 1 g to 4 g/day. Studies without these dosage levels were excluded from the review.

Participants included in the review
Alcoholic patients were included. The case reports listed ages of patients between 27 and 67 years.

Outcomes assessed in the review
The authors did not pre-define the outcome measures.

The included studies looked for hepatic injury, measured by signs of clinical disease or laboratory abnormalities (levels of aspartate transaminase, alanine transaminase or INR).

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors did not perform a validity assessment. However, the studies were classified according to their methodology, in order to assess their validity. A common classification was used: Class I, properly controlled randomised and blinded clinical trials; Class II, prospective non-randomised or non-blinded clinical trials, cohort, or well-designed case-control studies, dramatic results in uncontrolled studies, and volunteer studies; and Class III, retrospective case series, and case studies. The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Data extraction
The principal author extracted data for the review. Data were extracted for the following categories: methodology, age,
gender, history of alcohol and paracetamol use, dose and duration of paracetamol use, concomitant medications, pertinent medical history, maximum aspartate transaminase achieved, and co-morbid conditions.

Methods of synthesis
How were the studies combined?
The studies were combined in a narrative review.

How were differences between studies investigated?
The authors do not state a method for assessing any differences between the studies.

Results of the review
Twenty-seven studies were included in the review: 7 Class I or II studies, and 20 Class III case reports for 25 patients.

Class I data (2 RCTs, n=260) showed that, compared with a placebo group, the repeated ingestion of a therapeutic dose of paracetamol over 48 hours by patients with severe alcoholism did not produce a deterioration on liver function tests nor any clinical manifestations.

Class II data (prospective, non-randomised trials, n=55) revealed that therapeutic doses of paracetamol have been administered to patients with an array of liver diseases (alcoholic, primary biliary, postnecrotic, or unspecified cirrhosis or alcoholic, acute viral, chronic active, or other infectious hepatitis) for periods up to 14 days without an adverse effect. In several further studies, a 1 to 2 g single dose of paracetamol was administered to alcoholic patients to study metabolism, again without any adverse effects.

Class III data (retrospective case reviews and case reports) described hepatic injury after repeated paracetamol ingestion with therapeutic intent, although usually not at therapeutic doses. The information from these studies was often incomplete and contradictory.

Authors' conclusions
All the methodologically sound studies available indicated that the therapeutic dosing of paracetamol to the alcoholic patient was not associated with hepatic injury. There was no change in hepatic aminotransferase enzymes, prothrombin time, or other biochemical parameters when compared with a placebo group in well-designed trials. Unless stronger evidence of a potentially dangerous interaction emerges, the use of paracetamol in the alcoholic patient is reasonable.

CRD commentary
This systematic review stated a clear research question, although some of the inclusion and exclusion criteria were not predefined by the authors. The literature search was limited and could have looked at additional databases. While there were no language restrictions on the search, the authors did not assess publication bias or search for unpublished literature.

The studies were assessed for quality using a grading system rather than a scoring of methodological quality. Apart from the data extraction, the authors did not state who performed the study selection or validity assessment processes for the review. It would appear that only one author extracted the data, and the data were not checked by any of the other authors.

The results were combined in a narrative review since the data for a statistical meta-analysis were unavailable. There was very little discussion of the differences between the studies, although the quality was incorporated into the discussion of the included studies.

Overall, the authors' conclusions appear to follow from the data presented. Readers should take note of the different outcomes from the more reliable findings in the Class I and II studies, compared with the lower-quality non-randomised and non-controlled Class III case reports.
Implications of the review for practice and research

Practice: The authors state that during chronic treatment of pain, paracetamol may be preferred in the compliant alcoholic patient owing to the adverse effects associated with long-term use of non-steroidal anti-inflammatory agents.

Research: The authors did not state any implications for further research.

Bibliographic details

PubMedID
11319580

Indexing Status
Subject indexing assigned by NLM

MeSH
Acetaminophen /adverse effects; Alcoholism /complications; Analgesics, Non-Narcotic /adverse effects; Clinical Trials as Topic; Fever /drug therapy; Humans; Liver /drug effects; Pain /drug therapy

AccessionNumber
12001003800

Date bibliographic record published
30/04/2003

Date abstract record published
30/04/2003

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.