Hydroxyurea for the treatment of sickle cell disease

CRD summary
The review investigated the evidence surrounding the efficacy, effectiveness and toxicity of hydroxyurea in the treatment of sickle cell disease. The authors found that hydroxyurea was efficacious, but that there was insufficient evidence regarding effectiveness and toxicity. The review was well conducted, but it was based on only two randomised studies and generally moderate to low quality observational studies, so the results may be unreliable.

Authors' objectives
To summarise the published literature on the efficacy, effectiveness and side effects of hydroxyurea in patients with sickle cell disease, and to review the barriers to its use.

Searching
Electronic searches of MEDLINE, EMBASE, TOXLINE and CINAHL (to June 2007) were conducted. Search terms were reported in the review. Handsearches of bibliographies were performed. The authors discussed the search results with experts in the field. All searches were restricted to papers published in English.

Study selection
Randomised controlled trials (RCTs), cohort studies with a control population and before-after studies with at least 20 patients in the intervention group were eligible for inclusion. To investigate toxicity, studies of under 20 patients were eligible, as well as case reports (with adequate description of dose and duration of intervention) and case series of over 100 patients. In the included studies, the longest follow-up times in observational studies ranged from 36 to 45 months (where stated).

Studies of patients treated with hydroxyurea were eligible for inclusion. Dosage regimens for each study were given in the review, but were generally similar across studies, with most starting at 15 mg/kg or 20 mg/kg and titrating upward by 5 mg/kg at intervals (ranging from every four weeks to every six months). Control interventions were placebo or cognitive behavioural therapy (CBT) in one study.

No outcome inclusion criteria were stated. In the included studies of efficacy/effectiveness, reported outcomes were: death; fetal haemoglobin (Hb F) level (%); haemoglobin (Hb) level (g/L); mean corpuscular volume (fL); reticulocyte count (cellx10^9 /L); pain episodes; acute chest syndrome; stroke; blood transfusions; hospital admission; weight gain; exercise; and clinical severity score.

Studies of patients with sickle cell disease were eligible for inclusion. To investigate toxicity, studies of patients without sickle cell disease who had been treated with hydroxyurea were also included. In the included studies, the majority of patients had Hb Sβ thalassemia. In the included studies of efficacy/effectiveness, the patients' mean age ranged from 1.3 to 33 years (where stated), and the proportion of men ranged from 40 per cent to 74 per cent. Details of the patients' genotypes and haplotypes were also reported in the review.

Two reviewers independently reviewed titles, abstracts and full articles for relevance. Disagreements at the level of title review led the abstract to be checked. Disagreements at the level of abstract review were resolved by discussion. Disagreements at the level of article review were resolved through consensus.

Assessment of study quality
Quality of RCTs was assessed on the Jadad scale. The authors developed their own scale for assessing the quality of observational studies. The quality of surveys was assessed based on a scale developed by Ratanawongsa. Paired reviewers independently assessed the quality of all studies. In the case of RCTs, disagreements were resolved by a third reviewer. In the case of observational studies, the quality score was averaged.

Data extraction
Mean/ median scores and magnitude of effect were reported for all outcomes of interest. In addition, intervention studies were categorised as indicating "improvement", "potential improvement", "partial improvement", "no improvement" and "detrimental". Relating to adverse events reported in case reports, causality was assessed using the World Health Organisation's causality assessment instrument.

One reviewer extracted the data and a second reviewer checked the completeness and accuracy of the extraction. Disagreements were resolved by consensus.

**Methods of synthesis**

The studies were described using a narrative synthesis, then combined using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) grading scheme, as modified in the Evidence-based Practice Center Manual. This method is based on consistency, directness and precision to give an overall assessment of the strength of the evidence. The evidence from the case reports was graded according to the WHO Collaborating Center for Drug Monitoring. It was performed by two reviewers, then discussed and agreed on by all reviewers.

**Results of the review**

One high quality RCT involving adults (299 participants) and one moderate quality RCT involving children (25 participants) were included in the review of effectiveness/efficacy. Thirty seven observational studies (nine retrospective, two cross-sectional and 26 prospective studies) were included in the review. Eight of the observational studies were considered high quality.

**Efficacy/effectiveness in children:** one RCT found that treatment with hydroxyurea was associated with a non-significant increase in Hb levels (0.4mg/dL change from baseline) and increase in Hb F levels (10.7 per cent, \( P<0.001 \)). Treatment with hydroxyurea was associated with lower rate of hospitalization (1.1 versus 2.8 admissions) and number of days hospitalised per year (7.1 versus 23.4) compared to placebo. Observational studies of children found hydroxyurea treatment was associated with higher Hb and Hb F levels and fewer hospital admissions and transfusions. There was no evidence of treatment being associated with pain crises, mortality or neurological events.

**Efficacy/effectiveness in adults:** one RCT found that patients treated with hydroxyurea had fewer painful crises per year than those treated with placebo (2.5 compared to 4.5 events per year, \( p=0.001 \)) and a longer time to first painful crisis (three months versus 1.5 months, \( P<0.01 \)). They also had higher levels of fetal Hb (8.6 per cent versus 4.7 per cent, \( p<0.001 \)), higher number of fetal Hb cells (0.48 versus 0.35, \( p<0.001 \)) and a higher Hb level (91 versus 85 g/L, \( p<0.001 \)). Although mortality rates in the seven-year follow-up were lower in the group treated with hydroxyurea than those treated with placebo, an intention-to-treat analysis revealed no difference in mortality rates (3.1 versus 3.6 per 100 person-years). There was no difference between the two groups in terms of quality of life.

In the six observational studies that reported haematologic outcomes, fetal Hb and Hb were both higher in patients while being treated with hydroxyurea. Of the three studies that reported painful crises outcomes, one reported no change in frequency of crises while on treatment, one reported a significant decrease in crises and one reported fewer crises in patients treated with hydroxyurea compared to those treated with CBT. Of the three studies that reported change in rates of hospitalisations, two reported significant decreases in hospitalisations while on therapy. There was no difference in hospitalisation rate in patients treated with hydroxyurea compared to those treated with CBT.

The GRADE summary evidence concluded that there was high evidence of efficacy/effectiveness of hydroxyurea in the treatment of sickle cell disease to i) increase fetal Hb in children and adults, ii) reduce pain crises in adults, iii) reduce frequency and duration of hospitalisations in children and adults and iv) reduce transfusion frequency in adults. There was moderate evidence of a beneficial effect on increases in Hb in children and a reduction of pain crises in children. There was low grade evidence of an effect on mortality in adults or an effect on neurologic events in children, and insufficient evidence of reduction in neurologic events in adults or transfusion frequency in children.

In the two RCTs, hydroxyurea was associated with lower neutrophils counts (adults) and white cell counts (children). Other than this, there was no evidence of differential rates of side effects between treated and placebo groups. Case reports of patients with various outcomes who were being treated with hydroxyurea are described in the review.

The GRADE summary evidence for toxicity concluded that there was high evidence supporting no increased risk of
leg ulcer and low evidence suggesting an increased risk of leukaemia or spermatogenesis defects in adults. There was insufficient evidence regarding outcomes in children and, in adults, the following outcomes: skin neoplasms, secondary cancers and adverse pregnancy outcomes associated with hydroxyurea treatment.

Barriers to use: there was high quality evidence to support the observation that negative provider attitudes and poor provider knowledge was a barrier to use of pain medication. There was moderate evidence that a patient’s sex is not a barrier to use. There was low evidence regarding whether the following factors were related to use of therapy: patient/family knowledge; number of hospital visits; and patient’s age.

Cost information
In the one RCT included in the review, annualised total costs were similar in the group treated with hydroxyurea compared to those treated with placebo, but costs for hospitalisation for pain were lower in the hydroxyurea group (p<0.05).

Authors’ conclusions
Hydroxyurea was an efficacious treatment in patients with sickle cell disease. There was insufficient data from studies in usual practice or studies with long-term follow-up to make conclusions regarding effectiveness or toxicity.

CRD commentary
The research questions to be addressed were stated clearly. The search strategy was comprehensive, but was limited to English language publications, so it is possible that some papers or unpublished data were excluded, leading to publication bias. Inclusion criteria for study design, interventions and patients were clearly stated. No outcome inclusion criteria were stated. Since the authors appeared to include any possible outcomes, this would not have led to bias in the selection process. The reviews attempted to minimise errors and bias in the process of identifying relevant papers and abstracting the data by having two reviewers independently performing these functions.

Given the heterogeneity of the study designs and outcomes included, a narrative synthesis was appropriate.

The results of the review were based heavily on one RCT each in adults and children, and the observational studies were generally not of very high quality, bringing their reliability into question.

The authors' conclusions relating to efficacy (that hydroxyurea was efficacious in patients with SCD) may not be reliable, given the moderate to low quality of the included studies. The conclusion relating to safety seemed appropriately cautious.

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

Research: the authors suggested several areas of further research, including study of subgroups of patients who were under-represented in the review, such as those with Hb SC and those with HIV/AIDS. Further study of various doses of hydroxyurea was required, as was longer term follow-up to determine toxicity. The authors highlighted several other outstanding research questions in the review.

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