Lactic acidosis in metformin therapy: searching for a link with metformin in reports of 'metformin-associated lactic acidosis'

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Authors' objectives
To review all reports of lactic acidosis in metformin-treated patients published since May 1995, to try to establish the link between metformin and the onset of lactic acidosis.

Searching
BIOSIS Previews, MEDLINE, EMBASE, Pascal and a Derwent database were searched for literature published in any language from May 1995 to January 2000. The search terms were not reported.

Study selection
Study designs of evaluations included in the review
The authors seem to have searched for single case reports and case series.

Specific interventions included in the review
Metformin therapy given at a dose ranging from 0.5 to 2.85 g/day (where reported) for a duration of 1 week to 15 years (where reported).

Participants included in the review
People receiving metformin therapy for a range of indications. The people included in the review had the following conditions: asthma, chronic cardiac and renal failure, end-stage liver failure, pneumonia, acute renal failure, chronic dialysis therapy, postsurgical shock syndrome, severe heart failure, and intestinal occlusion. The mean age of the included participants was 60.9 years.

Outcomes assessed in the review
Recorded cases of 'metformin-associated lactic acidosis' were sought. Reports of lactic acidosis secondary to metformin overdosage or contrast media-induced renal failure in metformin-treated patients were excluded. From the publications reviewed, the link between metformin and lactic acidosis was assessed according to the following criteria: lactic acidosis, metformin accumulation, and the presence of concurrent pathologies.

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
Validity does not seem to have been assessed, although the authors reported whether the included articles gave brief or full details of the case. 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 authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

Data were extracted into the following categories: brief or full details provided; age; metformin dose, duration and last intake delay; blood parameters, i.e. lactate (mmol/L), pH, metformin (mg/L) and creatinine (mg/dl); and whether the blood creatinine was greater than 1.5 mg/dL (before admission and after admission). The link between metformin and lactic acidosis was assessed using three questions.
1. Are the criteria of lactic acidosis (blood lactate greater than 5 mmol/L and pH less than or equal to 7.35) met?

2. Are the criteria of metformin accumulation (plasma metformin concentration or serum creatinine primarily increased) met?

3. Are there concurrent pathologies present which may have precipitated lactic acidosis?

**Methods of synthesis**

How were the studies combined?
The results of the reports were summarised narratively.

How were differences between studies investigated?
Differences between the patients were discussed in the narrative summary.

**Results of the review**

There were 21 reports including 26 patients. The criteria of lactic acidosis were not met in 4 patients (therefore, n=22).

Metformin concentration was determined in only 4 of the 22 included patients, and one of these 4 patients had a normal value. The authors state that in the 18 patients with lactic acidosis where plasma metformin concentration data were unavailable, the presence of primary renal failure was absent or unlikely in 6 patients, uncertain in 2, and likely or proven in 14; however, there appears to be a discrepancy in these numbers since they total 22 and not 18. With regard to the 14 patients with likely or proven primary renal failure, the precipitating factor was metformin in 12 patients (in the context of renal failure, either chronic or acute) and intercurrent pathologies in 2 others. Overall, lactic acidosis was either absent (n=4), precipitated by concurrent pathology (n=8), precipitated by metformin without apparent associated pathology (n=12) or of uncertain origin (n=2). Death occurred 10 times but only once in the 12 patients with metformin-induced lactic acidosis; this was unrelated to metformin.

**Authors' conclusions**

While the term 'metformin-associated lactic acidosis' is commonly used to depict all situations of lactic acidosis in metformin therapy, true metformin-associated lactic acidosis, i.e. one which refers to metformin and concurrent pathologies as co-precipitating factors, was never observed in the reports studied. As there was no mortality due to metformin alone, it is important that physicians are familiar with the range of other risk factors that contribute to lactic acidosis in patients treated with metformin.

**CRD commentary**

This seemed to be a systematic review of published case reports, although the review question and the study selection criteria were not very clear, particularly in relation to study design. The literature search included several electronic databases and there were no language restrictions. However, the search terms were not given and there was no apparent attempt to find unpublished data. The validity of the primary studies does not appear to have been assessed. Details of the included reports were adequate and the summary of the data seemed appropriate.

The authors' conclusions seem to follow from the results of their review, although it should be borne in mind that published case reports do not represent the true incidence of any condition or complication.

**Implications of the review for practice and research**

Practice: The authors state that it is important that physicians are familiar with the factors that contribute to lactic acidosis in patients treated with metformin. They should not lay the blame for lactic acidosis on metformin unnecessarily, neither should they inappropriately limit the use of metformin.

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