A case-series of metformin-associated lactic acidosis in the German spontaneous reporting system – time to remember this serious adverse drug reaction!

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Background

Metformin is the first-line drug in the treatment of type 2 diabetes mellitus. In Germany, prescriptions have increased substantially since 1990 (Figure 1), with the highest rates of increase in patients > 75 years (Figure 2). An increase of spontaneous reports of metformin-associated lactic acidosis (MALA) since 1990, with a cluster in 2012, has prompted us to reassess reports from recent years (Figure 3).

Objective

To investigate patient characteristics, outcome and possible risk factors in spontaneous reports of MALA.

Methods

We included cases from the German spontaneous reporting database from 2001–2012 with available original reporting documents (report form, medical letters, laboratory findings). We reviewed data on patient characteristics, medical history, laboratory findings and outcome.

Results

99 of 221 reports of MALA were eligible. 5 reports were excluded because neither pH nor serum lactate was documented, or pH was > 7.35. Table 1 displays the clinical characteristics of the remaining 94 cases. The distribution of the reports to different age groups is shown in Figure 4.

The reported data on duration of metformin medication to diagnosis of lactic acidosis were highly variable ranging from a few days to several years. In roughly half of the cases the initiation of metformin administration is unknown.

Discussion

Our data suggest that an age above 70 years and concomitant cardiovascular or renal disease are risk factors for MALA. Since metformin is prescribed increasingly for older patients, this might in part explains the observed increase of reports in Germany. Acute renal failure (ARF) was identified as the possible trigger for MALA in the majority of our cases. However, we cannot clearly distinguish between vomiting/diarrhea as a cause for dehydration and ARF inducing MALA or a symptom of beginning lactic acidosis. Nevertheless, gastroenteritis in elderly patients treated with metformin should be considered as a potential risk factor for MALA. Regular monitoring and informing of patients and caregivers about the risks of metformin in acute illness seems crucial, especially in patients at high risk of renal function deterioration. The benefit-risk profile of metformin in elderly patients requires further studies.

References

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