research

Should we screen diabetic patients using biguanides for megaloblastic anaemia?

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BACKGROUND Patients taking biguanides on a continuous basis sometimes develop vitamin B_{12} deficient megaloblastic anaemia. The prevalence of this side effect has not been estimated.
METHODS We screened 600 patients with type 2 diabetes treated with biguanides (phenformin or metformin) for a mean of 11.8 years (SD: 3.6 years) with complete blood counts, red cell indices and red cell morphology. If this showed macrocytosis, we measured total serum vitamin B_{12} and antiparietal cells antibodies (APCA). Patients with macrocytosis and low serum vitamin B_{12} levels were treated with cyanocobalamin 1 mg injection daily for seven days.
RESULTS Fifty-four (9%) of the patients had megaloblastic anaemia with low serum total vitamin B_{12} levels, only three (0.5%) also had abnormally raised APCA. All 54 patients responded to cyanocobalamin with a reticulocyte increase within 10 days.
CONCLUSION Annual screening for megaloblastic anaemia in patients on long term treatment with biguanides may be worthwhile. The anaemia is easily remediable and does not necessitate withdrawal of the drug.

The biguanides, metformin and phenformin, were introduced in 1957 as oral antihyperglycemic agents to treat noninsulin dependent diabetes mellitus.[1] Approximately 10% of patients taking metformin continuously have reduced B_{12} absorption[2] with those using phenformin less affected.[3] The exact mechanism of this effect has been unclear. Some evidence implicates bacterial overgrowth[4,5] perhaps by delaying absorption of glucose.[6]

The aim of this observational study was to estimate the prevalence of megaloblastic anaemia among ambulatory diabetic patients on long term treatment with biguanides.

Methods

Patients with type 2 diabetes (a total of 600: 275 men and 325 women) using biguanides long term, alone or in combination with a sulfonylurea, were followed as outpatients in the diabetes centre of the general hospital 'G. Gennimatas' in Athens, Greece. Most of the 574 patients (96%) used metformin, the remaining 26 (4%) used phenformin. Men had an age range of 42–85 years, mean age 61.8 years (SD: 7.8) and women 46–87 years, mean age 63.1 years (SD: 7.2). They had used biguanides for a mean of 11.8 years (SD: 3.6 years). We excluded those with a history of alcohol or other drug abuse, psychiatric disease, liver disease, chronic renal failure, cardiopulmonary disease, bowel surgery, stomach or bowel disease, or cancer.

Every patient completed a questionnaire with informed consent, including sociodemographic data and medical history. They were tested with complete blood counts, red cell indices and red cell morphology. Total serum vitamin B_{12} and antiparietal cells antibodies (APCA) were performed on those with macrocytosis. Anaemia was defined as haemoglobin level <14.0 g/dL (men) and <12.0 g/dL (women). Macrocytosis was defined as MCV >94 (men) and >99 (women). Blood films were evaluated for macrocy-

tosis and hyper-segmented neutrophils. Patients with macrocytosis and serum total B_{12} levels <200 pg/mL were treated with cyanocobalamin 1 mg by injection daily for seven days.

Results

Megaloblastic anaemia was discovered in 54 out of the 600 patients on long term biguanides with a prevalence of low serum total vitamin B_{12} levels of 9% (95% CI: 6.8–11.6%), 26 men and 28 women (mean HG: 11.0, SD: 0.8) (mean HG: 12.7, SD: 0.9). Only three patients (0.5%) had a pathologically high APCA. All responded to cyanocobalamin treatment with a reticulocyte rise within 10 days.

Discussion

We have confirmed previous research on the prevalence of megaloblastic anaemia among patients on long term biguanides[2,3] and gone on to show this is easily reversible with cyanocobalamin treatment.

Severe B_{12} deficiency may result in peripheral nerve damage, which of course is easily confused with the peripheral neuropathy of diabetes. This misdiagnosis could lead to permanent nerve loss of a potentially reversible condition.

Therefore, perhaps annual screening for megaloblastic anaemia in patients on long term treatment with biguanides is worthwhile because the complication is remediable and does not necessitate withdrawal of the drug.[7]

Implications of this study for general practice

- Diabetic patients on long term biguanides are at risk of developing B_{12} deficient megaloblastic anaemia.
- Annual screening for megaloblastic anaemia may be worthwhile.
- Treating the anaemia with cyanocobalamin does not mandate withdrawal of the biguanide.

Conflict of interest: none declared.

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