JYP

Revisiting Metformin: Annual Vitamin B12 Supplementation may become Mandatory with Long-Term Metformin Use

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ABSTRACT

Monitoring of adverse drug reactions of a drug is a continuous process and runs through-out the life of a drug. Many rare adverse effects of a drug are documented after years of use; when a single case (signal generation) is reported leading subsequently to reporting of more cases. Deficiency of Vitamin B12 (vit B_{12}) is a known sequel of prolonged metformin therapy. It was recommended to have annual measurement of serum vit B_{12} levels in patients on long term metformin therapy way back in 1970 itself. After more than 50 years of use of metformin, we have come to know that metformin induced vit B_{12} deficiency can cause neuropathy; forcing to change the recommendation from annual screening of vit B_{12} levels to annual supplementation of vit B_{12}.

Key words: Metformin, neuropathy, type 2 diabetes

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INTRODUCTION

Not all hazards of a drug are known before marketing. Some adverse effects of drugs come to fore only after years of use. That is why constant post-marketing monitoring is necessary and why clinicians are expected to report all adverse effects to the regulatory/monitoring agencies. A single case reported in the medical literature can also lead to the generation of a signal, and subsequently more cases are reported. This forms the core of pharmacovigilance.[1] In recent times, rare adverse effects due to long-term metformin therapy have been reported, thus necessitating revision of recommendations.

Metformin, a biguanide, was introduced in the United Kingdom in 1958, in Canada in 1972, and in the United States in 1995. It is the drug of first choice for the treatment of type 2 diabetes, particularly in overweight and obese people and those with normal kidney function.[2] As of 2009, metformin is one of the only two oral antidiabetics in the World Health Organization Model List of Essential Medicines.[3] Due to this, metformin, either used as monotherapy or as combination therapy with other oral antidiabetic agents or insulin, has become the most widely used antidiabetic drug. Due to widespread use, much is known about its side effects (SEs). The most dreaded SE of biguanides, lactic acidosis, is never a problem with judicious use of metformin.[4] Gastrointestinal SEs of metformin can be overcome by initiating metformin therapy at a low dose and slowly increasing the dose, by giving metformin after meals, or by utilizing a slow-release metformin preparation.[5]

ADVERSE EFFECTS OF METFORMIN

One well-documented SE of metformin is malabsorption of vitamin B_{12} (vit B_{12}) and consequently low serum levels

of the vitamin. Within the first 10–12 years after it came into use, it became evident that long-term metformin therapy causes vit B_{12} malabsorption. Prevalence of vit B_{12} malabsorption was found to be 30% in patients taking long-term metformin therapy, and low serum levels of vit B_{12} were found in approximately 20% of patients having vit B_{12} malabsorption.[6] In another study, low serum levels of vit B_{12} were reported in 17.5% of patients using 2 g of metformin daily for at least 2 years.[7]

The first case of vit B_{12} deficiency–induced megaloblastic anemia due to long-term metformin was reported in 1980. The patient developed megaloblastic anemia after 8 years of metformin use.[8] Subsequently, more cases were reported. In 2007, case of hyperhomocysteinemia-induced deep vein thrombosis was reported, where the hyperhomocysteinemia was apparently caused by long-term metformin therapy–induced vit B_{12} deficiency.[9] Recently, the first case of peripheral neuropathy due to metformin-induced vit B_{12} deficiency was reported.[10] So, what had been feared by early researchers in the field of metformin-induced malabsorption – that metformin can cause subacute combined degeneration of the cord, which can be easily mistaken as diabetic neuropathy – has proved true.[6,7]

REVISTING METFORMIN

Annual measurement of serum vit B_{12} levels in patients on long-term metformin therapy was recommended way back in 1970s.[6-8] However, given the present setup of primary care centers in developing countries, with the lack of adequate laboratory facilities, it is doubtful that such monitoring will be possible in all diabetic patients.[11,12] In any case, this is hardly the routinely-followed method in patients on metformin therapy. Moreover, cost-effectiveness of annual measurement of vit B_{12} levels will also need to be considered, given that the incidence of type 2 diabetes is on the rise. Also, it must be remembered that vit B_{12} deficiency–induced neuropathy precedes the appearance of megaloblastic anemia. While the anemia of vitamin B_{12} deficiency is reversible, the progress of the neuropathy is only arrested and not reversed with initiation of vit B_{12} therapy. Even after measurement of low vit B_{12} levels, the differential diagnosis from other causes of vit B_{12} deficiency will be difficult to make. The fact that the symptoms of diabetic neuropathy resemble metformin-induced neuropathy will add to the confusion.

Thus, annual injections of vit B_{12} (in a dose of 1 mg) given to every patient on long-term metformin therapy will be a more practical and cost-effective method. This method will ensure replenishment of vit B_{12} stores for at least 1 year. It will also obviate the need for annual screening of vit B_{12} levels.

REFERENCES

1. Clark JA, Klincewicz SL, Atang PE. Overviw- Spontaneous Signalling. In: Mann RD, Andrews EB, editors. Pharmacovigilance. Chichester, England: John Wiley and Sons Ltd; 2002. p. 247-71.
2. American Diabetes Association. Standard of Medical care in diabetes-2009. Diabetes Care 2009;32:S13-61.
3. World Health Organization. WHO Model List of Essential Medicines. 16th ed. Geneva: WHO; 2009. p. 24. Available from: http://www.who.int/medicines/publications/essentialmedicines/en/index.html [last cited on 2010 May 2].
4. Tomkin GH. Malabsorption of vitamin B12 in diabetic patients treated with phenformin: A comparison with metformin. Br Med J 1973;3:673-5.
5. Bailey CJ, Wilcock C, Scarpello JH. Metformin and the intestine. Diabetologia 2008;51:1552-3.
6. Tomkin GH, Hadden DR, Weaver JA, Montgomery DA. Vitamin-B12 status of patients on long term metformin therapy. Br Med J 1971;2:685-7.
7. Stowers JM, Smith OA. Vitamin B12 and metformin. Br Med J 1971;3:246-7.
8. Callaghan TS, Hadden DR, Tomkin GH. Megaloblastic anaemia due to vitamin B12 malabsorption associated with long-term metformin treatment. Br Med J 1980;280:1214-5.
9. Lin HY, Chung CY, Chang CS, Wang ML, Lin JS, Shen MC. Hyperhomocysteinemia, deep vein thrombosis and vitamin B12 deficiency in a metformin-treated diabetic patient. J Formos Med Assoc 2007;106:774-8.
10. Bell DS. Metformin-induced vitamin B12 deficiency presenting as a peripheral neuropathy. South Med J 2010;103:265-7.
11. World Health Organization. Quality assurance in health laboratory services. New Delhi: WHO Regional Office for SE Asia; 2003. Available from: http://www.searo.who.int/LinkFiles/BCT_Reports_HLM-354.pdf [last cited on 2010 May 2].
12. Snehlatha C. Quality control and quality assurance in laboratory research. Int J Diabetes Dev Ctries 1998;18:44-5.

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