Diabetologia (1983) 24: 16–18

Diabetologia

Malabsorption of Vitamin B_{12} and Intrinsic Factor Secretion During Biguanide Therapy

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Summary. In a survey of 46 randomly selected diabetic patients on biguanide therapy, 30% had malabsorption of vitamin B_{12}. Withdrawal of the drug resulted in normal absorption in only half of those with malabsorption. In most patients with persistent malabsorption, the results of absorption tests with exogenous intrinsic factor suggested the diagnosis of coincidental intrinsic factor deficiency. Further considerations, however, led to the concept that biguanides can induce malabsorption by two different mechanisms. One of these is temporary and unrelated to intrinsic factor secretion and the other is permanent and mediated by depression of intrinsic factor secretion.

Key-words: Biguanides, phenformin, metformin, vitamin B_{12}, intrinsic factor deficiency, malabsorption.

Malabsorption of vitamin B_{12} is a well-known complication of biguanide therapy. Any disease causing malabsorption may, however, occur in diabetic patients and an interesting feature of studies of vitamin B_{12} absorption in diabetic patients on biguanides is the apparent rarity of such conditions. As we had formed an impression that anaemias not related to biguanide therapy occurred more often than might be expected, we decided to test this by a study of the absorption of vitamin B_{12} by diabetic patients on biguanides and extended this to the effects of metformin on the gastric secretory capacity of normal subjects.

Subjects and Methods

Subjects

Forty-six diabetic patients on biguanide therapy were selected randomly for a survey of the capacity to absorb vitamin B_{12}. Thirty-eight were female (aged 40–72 years, average 58 years) and eight were male (aged 45–72 years, average 59 years). The ratio of males to females is representative of the sex distribution of obese non-insulin-dependent diabetic patients attending the clinic. The average age of onset of diabetes was 50 years in males (range 38–67 years) and 51 years in females (range 32–75 years).

Twenty-eight patients (24 males, four females) were studied on metformin 13 (three males, ten females) on phenformin and five (one male, four females) while on both drugs at different times. The dose of metformin ranged from 1 to 3 g daily, and the duration of treatment at the time of study was from 1 to 6 years; the dose of phenformin was 50 mg twice daily and the duration of treatment ranged between 3 months and 6 years.

Methods

The capacity to absorb vitamin B_{12} was measured with a scanning type whole body monitor utilising six sodium iodide detectors each 15.2 cm diameter and 10.2 cm thick housed in a custom built room with 15 cm thick steel walls. The statistical accuracy of a result is ± 5% (i.e.: 5 ± 5%, 20 ± 5%, etc.) and the mean coefficient of variation between results is 26%. A control series absorbed between 26% and 89% (mean ± SD: 50.6 ± 14.7%) of 1 μg radioactive cyanocobalamin and for routine purposes absorption of < 30% is regarded as subnormal. After preliminary scanning, oral doses of 1 μg, 0.25 μCi, ^{57}Co or ^{58}Co cyanocobalamin were given after a 12-h fast which was continued for a further 3 h, the patient being monitored immediately after dosing and again 14 days later to give a measure of the amount absorbed. Patients who retained < 30% of the dose were regarded as having malabsorption and in these cases further measurements were made with intrinsic factor (200 mg hog gastric mucosal concentrate, Armour Pharmaceuticals, Eastbourne, UK) and 3 weeks after drug withdrawal. The gastric acid secretory response to pentagastrin and serum vitamin B_{12} levels were also measured in some patients with malabsorption persisting after drug withdrawal.

The effects of metformin on gastric acid and intrinsic factor secretion were studied in seven healthy volunteers before and after taking 2 g metformin daily for 14 days. On each occasion, after an overnight fast, a nasogastric tube was passed and the basal secretion collected for a period of 30 min. Pentagastrin (6 μg/k body weight) was then given IM and the secretion for the ensuing hour collected by constant suction. The acid output was measured by titration against sodium hydroxide using phenol red as an indicator. An aliquot was then adjusted to pH 10 with 5 N sodium hydroxide and, after 10 min, to pH 7 with 5 N hydrochloric acid before storage at − 20 °C pending measurement of intrinsic factor by radioimmunoassay [1] using a pH 7.0

0012-186X/83/0024/0016/$01.00

Table 1. Malabsorption of vitamin B_{12} during biguanide therapy in 14 diabetic patients

Patient No.	Age (years)	Sex	Biguanide therapy	Dose of vitamin B_{12} absorbed (%)			
				During drug therapy		After drug withdrawal	
				B_{12} alone	B_{12} + intrinsic factor	B_{12} alone	B_{12} + intrinsic factor
Transient malabsorption							
1	66	F	Metformin 2.0 g/day 2 years	8	16	54	57
2	64	F	Metformin 1.5 g/day 3 years	16	–	27	30
3	69	F	Metformin 2.5 g/day 1 year	16	21	73	71
4	51	F	Metformin 2.0 g/day 1 year	19	26	52	–
5	58	F	Metformin 2.5 g/day 4 years	22	22	51	36
6	61	M	Metformin 2.0 g/day 2 years	23	–	46	45
7	48	F	Metformin 2.5 g/day 3 years	25	24	40	–
Mean				18	22	49	48
Persistent malabsorption and others							
8	63	M	Phenformin 0.1 g/day 2 years	15	40	5	47
9	61	F	Metformin 2.0 g/day 10 years	5	43	3	39
10	65	F	Metformin 2.0 g/day 4 years	18	54	7	34
11	66	F	Phenformin 0.1 g/day 3 years	27	–	–	–
12	60	F	Metformin 3.0 g/day 3 years	21	41	–	–
13	62	F	Metformin 2.0 g/day 2 years	15	12	13	–
14	74	F	Metformin 1.0 g/day 9 months	16	62	17	71
Normal values on metformin (n = 21, range 30–71)				52			
Normal values on phenformin (n = 16, range 30–70)				49			

Table 2. Gastric secretory function in normal subjects before and after metformin 2 g daily

Subject No.	Age (years)	Sex	Before metformin			After 2 weeks metformin		
			Volume (ml)	Acid (mmol/l)	Intrinsic factor (ng units)	Volume (ml)	Acid (mmol/l)	Intrinsic factor (ng units)
1	27	F	298	28.4	5276	254	28.7	8022
2	30	F	194	6.2	5528	183	7.2	6081
3	26	M	270	26.6	5528	276	31.0	12763
4	25	M	316	34.5	16308	188	1.1	0
5	26	F	171	9.1	3523	108	1.7	0
6	27	F	128	10.6	3279	127	9.8	0
7a	26	F	180	30.9	4590	178	21.7	0
7b	26	F	203	22.3	1456	186	19.5	1663
Average (excluding 7b)			222	20.9	6290	188	14.5	3867
Average (including 7b)			220	21.1	5686	187	15.1	3591

Subject 7 had two periods of drug ingestion at an interval of 4 weeks

phosphate buffer medium and separating bound and free cobalamin by 2.5% (w/v) albumin coated Norit OL charcoal (Hopkins & Williams, Chadwell Heath, UK). The statistical accuracy of a result is ± 2% and the mean coefficient of variation between samples is 15%. The extent of any interference by metformin in concentrations of 1.0 and 6.0 mg/ml neutralised gastric juice was examined as was the effect of any destruction in vitro of intrinsic factor by metformin in the same concentrations at 20 °C for periods of 0.5, 1, 2, 4 and 24 h and at − 20 °C for 1 week.

Results

In the series of 46 patients, 14 (30%) had malabsorption of vitamin B_{12} on one or other biguanide (Table 1). The incidence was higher in those on metformin, 12 with malabsorption out of 33 patients (36%) than in those on phenformin, two with malabsorption out of 18 patients (11%). None of the five patients who had both drugs at different times developed malabsorption while on phenformin, but four did so while on metformin (Nos. 1, 2, 3 and 14).

In seven of the 14 with malabsorption withdrawal of the biguanide was followed by a normal absorption test and these patients were regarded as having transient malabsorption. In this group the introduction of intrinsic factor did not significantly augment absorption during or after drug therapy.

Investigations could not be completed in the other seven patients because of intercurrent illness but there

was evidence of malabsorption persisting after drug withdrawal in five (Nos. 8–10, 13 and 14). In four of these patients (Nos. 8–10 and 14), the effect of intrinsic factor was to normalise absorption both during and after drug therapy and these patients all had pentagastrin fast achlorhydria and serum vitamin B_{12} level between 70 and 90 ng/l. Normalisation of absorption during drug therapy was also observed in one patient (No. 12) who was not studied after drug withdrawal and malabsorption uninfluenced by intrinsic factor during drug therapy and persisting after drug withdrawal was observed in a further patient (No. 13).

The results of the study of gastric secretory function in volunteers on metformin are shown in Table 2. As judged by the Wilcoxon matched-pairs signed-ranks test there was no significant difference between group mean values before and during metformin ingestion ($p > 0.05$). There was, however, a marked individual variation in response with absence of intrinsic factor during drug ingestion in four subjects. One of these subjects was re-studied with a negligible difference between the results on the second occasion. There was no evidence of interference by metformin in the radioimmunossay system nor of any destruction in vitro of intrinsic factor by metformin.

Discussion

The accepted criteria for the diagnosis of biguanide-induced malabsorption of vitamin B_{12} are malabsorption during drug therapy and remission on drug withdrawal. This pattern was seen in seven patients. The mechanism of the effect is not clear but while competitive inhibition or inactivation of enzymes involved in absorption [2] and small intestinal bacterial overgrowth [3] have been postulated, the lack of effect of exogenous intrinsic factor seen in this and other series suggests that depression of intrinsic factor secretion is not involved [2, 4, 5].

When malabsorption is corrected by intrinsic factor during drug therapy and the malabsorption persists after drug withdrawal and is again corrected by intrinsic factor, it is difficult to avoid the conclusion that the drug is unrelated to the malabsorption and that the malabsorption is due to coincidental disease. When this pattern is accompanied by achlorhydria and a low serum vitamin B_{12} level (as in patients 8–10 and 14), a diagnosis of spontaneous failure of intrinsic factor secretion appears unavoidable. To find four such cases, and another with malabsorption corrected by intrinsic factor during drug therapy in a series of 46 patients, was unexpected and the pattern of events in one patient suggests an alternative explanation to coincidental spontaneous failure of intrinsic factor secretion.

Patient 14, with persistent malabsorption, had two normal absorption tests during phenformin therapy lasting 3½ years and a further normal test in the subsequent year on dietary control. Metformin was then introduced and 9 months later and 17 months after the last normal absorption test, she was found to have malabsorption corrected by intrinsic factor. This persisted in spite of drug withdrawal and oral antibiotic therapy and was corrected by intrinsic factor on three out of four tests in the year after drug withdrawal. The short time scale of development of intrinsic factor deficiency seemed more in keeping with a drug effect than a spontaneous event and the studies in normal volunteers were initiated to study the effect of metformin on gastric secretion. While there was no significant change in acid output, disagreeing with a previous report of augmentation [6] of intrinsic factor output, there were striking individual responses with dramatic falls in intrinsic factor output in four subjects.

It is clear from our results that it is unwise to assume that malabsorption of vitamin B_{12} during biguanide therapy will invariably remit on drug withdrawal and the practical implications of this are obvious. Whether persistent malabsorption is due to spontaneous failure of intrinsic factor secretion or, as we suspect, to a permanent effect of biguanides on intrinsic factor secretion, is a matter for further study.

Acknowledgements. We are grateful to Rona Laboratories for financial support and to the volunteers for their help.

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Received: 9 March 1982
and in revised form: 13 August 1982

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