Mei 2003

Increased use of metformin and lactic acidosis

Introduction

Metformin (e.g. Glucophage®) is a biguanide used in the treatment of diabetes mellitus. Since February 1999 according to the practice guidelines of the Dutch College of General Practitioners [1], metformin is the drug of first choice for the treatment of obese patients with diabetes mellitus. This was based on the results of the UKPDS study[2]. Since then there is a gradual increase in the number of dispensed Defined Daily Dosages (DDD= 2g) of metformin in the Netherlands (Figure 1) [3].

Metformin causes lowering of the blood glucose and improve blood lipids in the diabetic by inhibition of the active transport of glucose in the intestinal mucosa, an absent activation of glucose transporters, inhibition of gluconeogenesis, inhibition of fatty acid oxidation and of lipid synthesis which [4]. Metformin is approved in the Netherlands since 1967 for *the treatment of non-insulin-dependent diabetes mellitus (NIDDM), especially in obese patients, when the blood glucose cannot be regulated by dietary measurements or sufficient physical exercise alone*[5]. The most frequent adverse events include gastrointestinal complaints (15-25%) like nausea, vomiting, diarrhea, abdominal pain and anorexia. More rarely, dysgeusia may occur[4]. Early symptoms of lactic acidosis, generally defined as an accumulation of lactic acid more rapidly than it can be metabolised, include nausea, vomiting and diarrhea. Since these adverse events may also occur as such, differential diagnosis with the initial stages of lactic acidosis may be bothersome.

Reports

The Netherlands Pharmacovigilance Centre Lareb has received seven reports concerning lactic acidosis associated with the use of metformin (table 1).

The reports concerned three females and four males. The mean age was 61.3 years (range 50-77). Four patients died. Five reports were submitted by specialist doctors.

One report has been submitted to Lareb before adaptation of the referred guidelines, and six reports have been received afterwards. The relative number of reports of lactic acidosis in respect to reports on other ADRs associated with metformin is not statistically significant higher after adaptation of this guidelines (odds ratio 6.4 (95% confidence interval 0.8-54.6). However, the increase in the use of metformin will also cause an increase in the number of cases of lactic acidosis.

Other sources of information

Literature

Other biguanides like phenformin and buphormin, have been withdrawn from the market in the 1970s in many countries because of the risk of lactic acidosis[4]. Lactic acidosis, associated with the use of metformin, however, is a rare event and may occur with an average incidence rate of 3 per 100,000 patient-years [6-8] Lactic acid accumulations, may especially occur in the presence of predisposing conditions like superimposed shock, renal insufficiency, concurrent heart failure, liver disease or alcohol abuse. A study by Horlen showed that 22 percent of the patients did have one or more contraindications[9]. Also in all patients, reported to Lareb, there were known risk factors for developing a lactic acidosis.

Table 1. Reports of lactic acidosis in suspected association with metformin

Patient, Sex, age	Dose	Source	Concomitant medication	adverse drug reaction	Additional risk factors	Time to onset; outcome; remarks
A M, 77	850 mg 1dd1	pharmacist	furosemide triamterene verapamil digoxin bisacodyl	lactic acidosis	chronic heart failure	time to onset unknown recovered
B M, 51	500 mg 2dd1	specialist	amitryptiyline bromhexine susp insulin nadroparin	lactic acidois hepatic insufficiency	hepatic insufficiency?	2 weeks recovered Not clear if hepatic insufficiency is cause or result of lactic acidosis.
C M, 50	850 mg 3dd1	specialist	acenocoumarol digoxin benzbromarone furosemide enalapril	lactic acidosis multiple organ failure	chronic heart failure?	unknown
D F, 52	850 mg 3dd	hospital pharmacist	tolbutamide venlafaxin acamprosaat	lactic acidosis	alcohol abuse, hepatic cirrhosis.	time to onset unknown Patient died Case report published[10]
E M, 75	500mg, 2dd	specialist	morphine acarbose atenolol Ferro sulfate	lactic acidosis	renal insufficiency,	time to onset unknown patient died
F M, 65	500mg 2dd2	specialist	amlodipine atenolol enalapril/ hydrochlorothiaz. glimepiride	lactic acidosis	Pyelonephri-tis, septic shock	time to onset unknown patient died
G, F, 59	850 mg 2dd	specialist	simvastatin glimepiride chlortalidone atenolol irbesartan domperidone	lactic acidosis	renal insufficiency	five years after start patient died

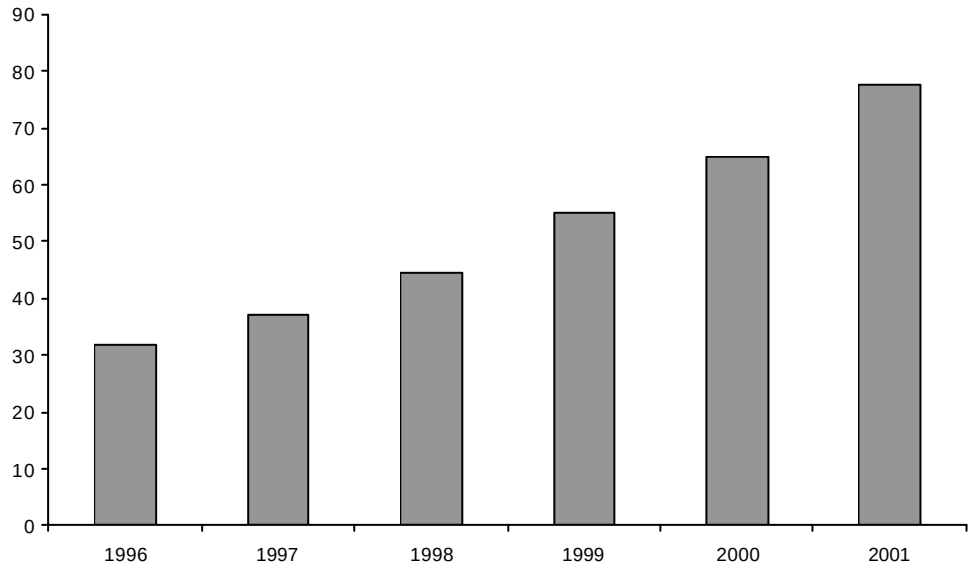

Figure 1. The number of dispensed Defined Daily Dosages (DDD=2g) for metformin from 1996 till 2001[3].

Databases

The WHO database contains over 2251 reports on lactic acidosis associated with the use of metformin which makes this association is exceptionally disproportional present in the database (ROR 572 (95% CI 524-624)). There is no clear relationship between the annual number of reports submitted to the WHO and the publication of the UKPDS study.

Mechanism

Serum lactate concentrations are usually not clinically important and less then 2 meq/L with metformin therapy[6]. Additional factors may cause an accumulation of lactic acid, like renal insufficiency leading to high plasma levels of metformin or diseases associated with an impaired tissue perfusion, like concurrent heart failure. Finally, a liver disorder or alcohol abuse may cause increase lactic acid plasma levels due to a decrease in the lactate utilization.

Conclusion

Lareb received seven reports of lactic acidosis in association with metformin, including six cases reported since metformin is the first choice of treatment and increased dispension.
Four patients died. Our reports suggest that, possibly neglected risk factors contribute to this adverse drug reaction. Moreover, risk factors may evolve or aggravate during therapy.
Lareb is concerned about the increasing lactic-acidosis-associated morbidity and mortality due to increased prescription, despite proper recommendations in the SPC.

References

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