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Do contraindications to metformin therapy deprive type 2 diabetic patients of its benefits?

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Abstract

Background: Metformin is considered to be the drug of choice in overweight, newly diagnosed type 2 diabetes. Lactic acidosis is stated to be the most serious side effects of metformin therapy. Current available guidelines contain so many ambiguous terms in describing the contraindications to metformin use that they do little to assist in addressing this problem. Moreover, these ambiguous contraindications may deprive many diabetic patients from the benefit of metformin. **Objectives:** The aim of the current study was to evaluate the safety of metformin use in the presence of "standard" contraindications to its use. **Research design and methods:** This was a cross sectional study that involved type 2 diabetic patients who were on chronic treatment with metformin. A fasting blood sample was taken from each subject to determine levels of serum creatinine levels, bicarbonate, fasting blood sugar, lactate, insulin, C-Peptide, and metformin plasma concentration. **Results:** 106 patients were recruited in the study with 68 (64%) females. The mean age was 58 ± 13 years. The results illustrate that metformin has been prescribed for patients who are listed in the guidelines as having standard contraindications to its use. There were 30 (28%) patients with impaired renal function (Clcr < 60ml/min.) and five with Clcr < 30ml/min. Moreover, 30 (28%) had ischemic heart disease, six (5%) patients were diagnosed as having congestive heart failure, five (4%) with chronic obstruction pulmonary disease, and three (2%) with peripheral vascular disease. Although the numbers of those patients were not large enough to establish and confirm the safety of metformin in the presence of these standard contraindications and precautions, there were no cases of lactic acidosis observed. **Conclusions:** This study along with other studies has revealed that there is vagueness in the available guidelines in prescribing metformin, which led to the different observed practices. This study revealed that metformin is still prescribed to patients with listed contraindications. Clearer guidelines are needed for prescribing metformin with more specific contraindications. For example it would be more beneficial if the degree of heart failure, classified according to the New York Heart Association is specified.

Key words: *Diabetes, metformin, lactic acidosis, creatinine clearance, guideline, contraindications*

Introduction

Metformin is a biguanide (1, 1-dimethylbiguanide) used as an oral hypoglycaemic agent in the treatment of type 2 diabetes mellitus (DM).[1,2] It improves insulin sensitivity, as shown by a reduction in hepatic glucose production. [1,3] It undergoes rapid renal excretion through active secretion.[4,5]

According to United Kingdom Prospective Diabetes Study (UKPDS) [1] metformin is now considered to be the drug of choice for the treatment of overweight in newly diagnosed type 2 diabetic subjects. Two factors limit the use of metformin, with both factors relating to its adverse effects. The first is its gastrointestinal adverse effect. [6,7] However, in order to minimize this effect, metformin should be taken with meals and, as the symptoms are dose related, metformin should be started at a lower dose. More than half of the patients can tolerate the maximal dose, but about 5% cannot tolerate any dose of metformin. [5,8] The second effect is rare but potentially fatal lactic acidosis.[9] The true incidence of metformin associated lactic acidosis is unknown.[10] The Food and Drug Administration (FDA) has estimated the rate of fatal or non-fatal lactic acidosis to be five cases per 100,000 persons treated with metformin over the course of one year.[11] However, almost all of the reported cases of lactic acidosis associated with metformin therapy have occurred in the presence of other conditions, which can themselves potentially precipitate lactic acidosis, such as renal impairment, congestive heart failure and sepsis.[12,13]

Despite this low incidence, guidelines are still using ambiguous terms in describing contraindications and precautions for metformin use. Moreover, these terms are not absolutely matching, which might result in depriving a significant number of diabetics of its use. Table 1 shows the

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Table 1: Descriptions of terms in different guidelines

Contraindications	Manufactured (package insert), 2005	AMH [15]	IDF [16]	NICE [14]
Impaired renal function	Clcr<60ml/min	Clcr<30ml/min	eGFR<60ml/min	Clcr<30ml/min
Heart Failure	Yes	Yes	Not stated	Not stated
Severe liver dysfunction	Yes	Precaution	Not stated	Not stated
Elderly	Not stated	Precaution	Not stated	Not stated
Alcohol misuse	Yes	Precaution	Not stated	Not stated

Table 2: The baseline characteristics of patients who completed the study (Results are mean+/-SD)

N = 106	Mean ± SD
Age (years)	58 ± 13
Female (n)	68
Male (n)	38
Metformin Dose (Met dose) (mg/day)	1592 ± 566
Metformin Concentration (Met conc.)(mg/l)	0.56 ± 0.44
Lactate (mmol/l)	1.5 ± 0.55
Clcr† (ml/min)	83 ± 44

† Clcr= Creatinine Clearance

Table 3: The prevalence of medical illness along with type 2 DM in the patients n= 106

Medical condition	Number of subjects (%)
Ischemic heart disease	30 (28%)
Impaired renal function	30 (28%)
CHF*	6 (5%)
COPD†	5 (4%)

* CHF = Congestive heart failure
† COPD = Chronic obstructive pulmonary disease

Table 4: Characteristics of CHF patients

Patients #	Age (years)	Metformin dose (MG/DAY)	Metformin concentration (MG/L)	CLCR* (ML/MIN)
1	66	1000	0.98	28
2	43	2000	0.25	107
3	77	2000	1.70	66
4	77	1000	0.64	37
5	83	2000	1.59	45
6	70	1000	1.79	30

* Clcr = creatinine clearance

contraindications and precautions of metformin as given by National Institute for Clinical Excellence (NICE) guidelines,[14] Australian Medical Handbook (AMH),[15] manufacturers, and International Diabetes Federation (IDF).[16] As shown, the guidelines are not consistent in describing contraindications to metformin use. For example, in case of impaired renal function, the manufacturers package insert specified creatinine clearance (Crcl) of <60ml/ min as a contraindication versus < 30ml/ min in Australian Medical Handbook (AMH). Moreover, the guidelines employ undefined and confusing terms in describing metformin use. For example, almost all available guidelines contraindicate metformin use in congestive heart failure (CHF) patients without specifying the degree of heart failure as classified by the New York Heart Association (NYHA).[17]

Clearer guidelines for metformin use and contraindications are recommended. As an example, it would be more useful for prescribing practitioners to be provided with detailed dosage adjustment in certain subgroups, particularly in conditions such as renal impairment.

The aims of this study were to assess risks and benefits of metformin use in diabetics with various clinical backgrounds, and to determine the degree of lactic acidosis, if detected.

Methods

The study was conducted at Fremantle Hospital and Health Services (FHHS), which is part of South Metropolitan Health Service in Western Australia and at the Fujairah Hospital in United Arab Emirates (UAE). The Human Research Ethics Committee of the Curtin University of Technology, South Metropolitan Health Service and Fujairah Hospital Ethical Committee approved this study. Written informed consent was obtained from all participating subjects.

Study design

The study was a prospective cross-sectional study. In-patients with type 2 diabetes mellitus on long term treatment with oral metformin (at least seven days to ensure steady state metformin concentrations) were invited to participate in the study. Patients were excluded from the study if they refused to give consent for any reason, and if they were unable to give informed consent, including patients with cognitive dysfunction or language barriers.

A fasting blood sample was collected from eligible patients and investigated for fasting plasma glucose, venous lactate, and creatinine. Data on the past medical history, current medications, demographic data (age, weight, height, and sex), and duration of diabetes were collected from patient medical files.

For this study, renal function was classified into three groups dependent on the degree of renal impairment.

- Group one: patients with Clcr > 60 mL/min.

- Group two: patients with Clcr > 30 ml/min and ≤ 60 mL/min.
- Group three: patients with Clcr ≤ 30 ml/min.

The normal fasting serum lactate has a range: 0.4−1.2 mmol/l, [18] with lactic acidosis defined as a metabolic acidosis in which the arterial blood lactate is ≥5mmol/l and the arterial pH is ≤7.35 [19,20]. Therefore, any lactate level above 1.2 mmol/l was considered to favour hyperlactataemia. All metformin levels measured were trough levels. For the purpose of the current study, therapeutic concentrations of 0.1 to 1.1mg/l were considered as a reference range for the metformin plasma level [4,21]. Any concentration above that was considered to favour the accumulation of metformin.

Results

Overall 106 type 2 diabetic patients were recruited in the study. 64% were female. The mean metformin concentration was 0.56 ± 0.44mg/l. The mean lactate level of the patients was 1.5 ± 0.55mmol/l with a maximum level of 3.33 mmol/l and minimum value of 0.60mmol/l. Table 2 illustrates the baseline characteristics of the patients recruited.

Patient's medical conditions

Most of the patients had a concurrent medical illness along with type 2 DM, such as, hypertension, ischemic heart disease, CHF, renal impairment. As evident from Table 3 there were six patients who had CHF. All of the six patients were on diuretic treatment. Table 4 shows the details of CHF patients identified in the study.

Discussion

Classically, lactic acidosis is subdivided into two groups: type A or anaerobic is due to hypoxia from the hypoperfusion of tissues, whereas type B or aerobic is due to metabolic conditions such as liver disease, sepsis or DM. Both lead to lactic acid overproduction and/or defective excretion in the aerobic state. [22] Metformin was classified to cause type B lactic acidosis. However, data from one study [21] indicated that pure type B lactic acidosis occurs only in exceptional cases and that most metformin-treated patients present with a mixed (A + B) lactic acidosis (i.e. metformin accumulation with concurrent disease).[13] As mentioned before, the true incidence of metformin-associated lactic acidosis is not known. [10] However, most of the reported cases have occurred in patients with severe conditions, such as renal failure, that could in themselves have caused the lactic acidosis. [6,11,23,24] As shown in Table 1, guidelines provides a list of contraindications and cautions for metformin use but the terms used are still confusing to prescribing doctors. Consequently, this led to different clinical practice for metformin use.

In United Kingdom [25] it has been shown that doctors tend not to comply with the listed contraindications for metformin use, believing that these have been developed from experience with phenformin. Therefore, it has been argued that metformin contraindications are overzealous.[10]

The results of the current study illustrate, that metformin has been prescribed for patients who are listed in the guidelines as having standard contraindications for its use but the number of those patients was not enough to establish and confirm the safety of metformin in the presence of these stated contraindications. There were some cases of hyperlactataemia but no cases of lactic acidosis were observed. Nevertheless, if the recommendations and precautions listed in the available guidelines were followed regarding metformin use, a decision would be made to discontinue metformin in 34 % of the recruited patients.

In order to weigh the risk and benefit of metformin use with contraindications, several clinical studies have evaluated the safety of continued use of metformin in patients with contraindications to metformin. In a meta-analysis study, Salpeter et al [10] observed that out of 164 prospective studies 156 (95%) studies allowed for the inclusion of patients with at least one contraindication to metformin. Sixteen percent of all participants were estimated to be older than 65 years with no adverse effects observed among those groups. This study, along with other studies, [10,25-27] revealed that there is an imprecision in the available guidelines in prescribing metformin, which has led to different observed practices. The results of the current study support the need to review those guidelines by establishing clearer terms in describing contraindications to metformin use.

However, this study has limitations. Since medical files were the main source in retrieving the medical and current histories of the patients, these may not always be reliable, especially with newly admitted patients for whom records were not complete and definitive diagnosis was not reached (e.g. "query CHF" and "query renal failure"). Moreover, only one blood sample was taken to estimate Clcr, which may not always be a reliable indicator of potential metformin accumulation especially in patients with moderate renal impairment.

Conclusion

The incidence of metformin-associated lactic acidosis is not known. Almost all of the reported cases of lactic acidosis associated with metformin therapy have occurred in the presence of other contraindications or conditions which themselves precipitate lactic acidosis, such as, renal impairment. In this study, no cases of lactic acidosis were observed, and it was shown that in clinical practice, the prescribing patterns do not conform to the guidelines, and the available guidelines appear to be misleading which explains the differences observed. Therefore, it is strongly recommended that the contraindications to metformin as stated in the guidelines should be reviewed, and clearer guidelines are needed for metformin prescription with more specific contraindication. This would minimize unnecessary avoidance of the drug in patients with type 2 diabetes who could benefit from treatment.

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