Journal of Diabetes and Its Complications 29 (2015) 1261–1265

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Adverse event notifications implicating metformin with lactic acidosis in Australia

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ARTICLE INFO

Article history:
Received 13 April 2015
Received in revised form 1 June 2015
Accepted 2 June 2015
Available online 9 June 2015

Keywords:
Metformin
Diabetes
Lactic acidosis
Adverse effect
Pharmacovigilance

ABSTRACT

Objective: To summarise the reported lactic acidosis cases associated with metformin from the Australian Therapeutic Goods Administration (TGA) and estimate the incidence of metformin-associated lactic acidosis (MALA) in Australia.
Method: All "lactic acidosis" cases associated with metformin and reported to the TGA between January 1971 and October 2014 were included. Data extracted included patient demographics, medical history and co-existing conditions, metformin dosage and relevant pathology results.
Result: A total of 152 cases of suspected MALA were included in this study. For 20 patients the outcome was unknown. There were 23 patients (n = 132, 17.4%) reported as deceased. Plasma lactate levels were higher in non-survivors (p = 0.02). Thirty-five patients (n = 132, 26.5%) were reported to have at least one pre-existing contraindication to the use of metformin; this proportion was not different between patients who died or survived. Renal impairment was the most common contraindication. Approximately 75% of patients were reported to have at least one clinical condition which might cause acidosis. Metformin dosage, plasma lactate and serum creatinine were not correlated. Based on the cases reported to the TGA, the incidence of MALA in Australia was estimated to be 2.3 (95% CI, 1.5–3.1) cases per 100,000 patient–years between 1997 and 2011.
Conclusion: Pre-existing clinical conditions, such as renal impairment, and acute illnesses associated with lactic acidosis were frequently reported in the cases of MALA. The estimated incidence of MALA was lower than in most previous studies in other countries, probably due to the nature of spontaneous reports to the TGA.

1. Introduction

Metformin is recommended as the first-choice for pharmacological treatment of type 2 diabetes mellitus (T2DM) in Australia (General practice management of type 2 diabetes —2014–15, 2014) and many other countries (Inzucchi et al., 2012; Anonymous). A wide array of benefits has been attributed to metformin. These include attenuation of abnormal glucose metabolism, weight loss, improvement in components of the metabolic syndrome, lipid lowering properties and cardiovascular protection (Anonymous, 1998; Rocha, Almeida, Santos, & Carvalho, 2013; Wulffele, Kooy, de Zeeuw, Stehouwer, & Gansevoort, 2004; Bailey & Turner, 1996). A common clinical conundrum facing practitioners treating patients with T2DM is the potential risk of lactic acidosis (LA), which has a mortality rate of 30%–50% (Kirpichnikov, McFarlane, & Sowers, 2002; Lalau & Race, 1999a). The incidence of metformin-associated lactic acidosis (MALA) has been estimated in the United States (U.S.) and European countries (Bodmer, Meier, Krahenbuhl, Jick, & Meier, 2008; Kamber, Davis, Bruce, & Davis, 2008; Stang, Wysowski, & Butler-Jones, 1999; Wiholm & Myrhed, 1993), but there is limited data in Australia. The reported incidence of MALA has varied, ranging from 1.5 to 530 cases per 100,000 patient–years; in comparison, LA has been reported with an incidence of 9.7 to 16.7 per 100,000 patient–years in individuals with diabetes not taking metformin (Bodmer et al., 2008; Stang et al., 1999; Wiholm & Myrhed, 1993; van Berlo-van de Laar, Vermeij, & Doorenbos, 2011; Scott, Martin, & Inder, 2010; Misbin et al., 1998). Given the benefits of metformin and the relatively rare incidence of MALA, many recent publications have supported its expanded use, even in cases where it would be officially contraindicated, particularly as the available data suggest that lactate levels and the risk of LA do not differ appreciably in patients taking this drug versus other glucose-lowering agents (Salpeter, Greyber, Pasternak, & Salpeter, 2010; Tahrani, Varughese, Scarpello, & Hanna, 2007; Holstein & Stumvoll, 2005; Stades, Heikens, Erkelens, Holleman, & Hoekstra, 2004).

In Australia, adverse effect (AE) reporting is one of the main pathways for the Therapeutic Goods Administration (TGA) to monitor the safety of medicines. All reports are analysed and checked by

Funding sources: None.
Conflicts of interest: None.
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http://dx.doi.org/10.1016/j.jdiacomp.2015.06.001
1056-8727/

medical experts before becoming publicly accessible. These AE cases are reported mostly by pharmaceutical companies, as well as voluntarily by hospitals, general practitioners, State and Territory Health Departments, consumers and community pharmacists. The objective of this study was to: i) summarise the cases of LA related to metformin usage reported to the TGA and evaluate other medications and clinical conditions reported in these cases; and ii) estimate the incidence of MALA in Australia.

2. Methods

The terms "metformin" and "lactic acidosis" (defined by the Medical Dictionary for Regulatory Activities; MedDRA (Medical Dictionary for Regulatory Activities - MedDRA, 2013)) were used to search the medication AE reports from the TGA. All cases reported from 1971 to October 2014 were obtained.

Data extracted included patient demographics, medical history including risk factors for LA, metformin daily dosage, other medications including documented therapy for acidosis (inotropes, mechanical ventilation and renal replacement therapy), relevant pathology results (e.g. lactate level, pH and creatinine) and description of the AE (the medical conditions or AEs were defined by MedDRA).

According to the Cohen and Woods (1976) classification, metformin is implicated with type B_2 LA, a form of LA caused by drugs or toxins with no clinical evidence of insufficient tissue oxygen delivery. The medicines implicated in drug-induced LA were identified according to the Cohen and Woods classification type B_2 (Cohen & Woods, 1983; Mizock & Falk, 1992). The following medicines were included: isoniazid, linezolid, theophylline, valproate, spironolactone, beta-agonists, and anti-retroviral agents.

The data were summarised and analysed using Microsoft Access 2010 and the IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). Independent t-tests or Mann–Whitney U tests were performed for comparing the continuous variables between patients who died and survived. Spearman tests were used to explore the possible correlation between metformin daily dosage and plasma lactate level, plasma pH and serum creatinine. Pearson chi-square tests or Fisher's exact tests were performed for the categorical variables. An alpha of <0.05 was considered statistically significant.

The estimated incidence of MALA was calculated using the average annual number of cases reported to the TGA from 1997 to 2011 (the annual numbers of community prescriptions of metformin reported in the Australian Statistics on Medicines were only available for this period), divided by the estimated annual number of patients taking metformin in these 15 years. The estimated patient number was calculated using the annual numbers of community prescriptions (i.e. subsidised and non-subsidised) of metformin reported in the Australian Statistics on Medicines (Australian Statistics on Medicines, 1997–2011) divided by twelve, assuming each patient had one prescription each month based on the standard dosage and pack quantities subsidised through the Australian Pharmaceutical Benefits Scheme.

3. Results

A total of 152 cases of LA potentially associated with metformin use were reported to the TGA during the study period. The median age of patients reported in the case reports was 68 years (IQR: 63–74 years, $n = 150$ where age was documented), and 42.8% were men. Patients had been treated with metformin in a mean (standard deviation, SD) daily dose of 2124 ($\pm$966) mg ($n = 134$; six patients had a dose more than 3000 mg/day, including intentional overdose). The mean lactate level was 12.0 ($\pm$6.0) mmol/L, which was reported in 74 patients; the pH was reported in 51 cases (47 of these cases had noted lactate level).

The annual numbers of community prescriptions of metformin reported in the Australian Statistics on Medicines increased gradually from 1997 to 2011, while the reported number of MALA cases varied each year. Overall, the estimated incidence of MALA was 2.3 (95% CI, 1.5–3.1) cases per 100,000 patient–years (ranged between 0.5 and 6.8 cases per 100,000 patient–years) between 1997 and 2011.

For 20 patients the outcome was unknown. There were 23 patients ($n = 132$, 17.4%) reported as deceased. Plasma lactate levels were higher in patients who died ($p = 0.02$, Table 1), but there was no significant difference found in age, plasma pH, serum creatinine or metformin daily dosage. Metformin daily dosage, plasma lactate, plasma pH and serum creatinine were not correlated, except for the plasma lactate and pH ($p < 0.01$, Spearman $r = -0.66$).

Of the 152 cases, 78 cases (51.3%) reported metformin as the only medication being taken. The most commonly prescribed anti-diabetic medications in addition to metformin were sulfonylureas (39.5%, Table 2). Ten medications associated with Type B_2 LA were identified in 29 cases ($n = 152$, 19.1%; some cases had more than one medication associated with Type B_2 LA). Four cases ($n = 152$, 2.6%) reported metformin use with a contrast medium.

Of the cases, 35 cases ($n = 132$, 26.5%) were reported to have at least one contraindication to the use of metformin according to the medical history (Table 1), and this proportion was not significantly different between patients who survived and died ($p = 0.32$). Renal impairment was the most common contraindication.

Overall, 98 cases ($n = 132$, 74.2%) reported at least one clinical condition which might cause acidosis (some cases had more than one condition, Table 1); acute renal failure (in 56 patients; $n = 98$, 57.1%) was most common. Ten patients ($n = 98$, 10.2%) had documented cardiac failure or circulatory collapse.

4. Discussion

The present study analysed a total of 152 LA cases associated with metformin usage from the national pharmacovigilance database in Australia. The mortality in this present study was approximately 17%, which was lower than reported rate in the previous literature (Bailey & Turner, 1996; Renda et al., 2013). It is possible that the severity of the cases was different (i.e. the plasma lactate levels in this present study were typically lower than in previous studies) (Renda et al., 2013; Vecchio et al., 2014; Kajbaf & Lalau, 2013). For instance, Renda et al. (Renda et al., 2013) recently reported a mortality rate of 25.4% of MALA by reviewing the LA cases between 2001 and 2011 in the National Pharmacovigilance Network of the Italian Medicines Agency, noting a mean lactate level of 15.2 mmol/L in all the patients (vs. 12.0 mmol/L in this present study). Kajbaf and Lalau reported the mortality rate associated with MALA fell steadily from around 50% to 25% since the 1960s, based on a worldwide pharmacovigilance database (Kajbaf & Lalau, 2014), suggesting that it might reflect the change in the outcome of systemic pathologies present in metformin-treated patients. The worldwide database used in their study included cases from different countries, in which adverse event reporting systems might be different; this may explain the difference of mortality rate from our estimation. Also, improvements in clinical management over the years might have been important in lowering the mortality (Keller et al., 2011; Panzer, Kluge, Kreymann, & Wolf, 2004).

The cases of MALA in this present study frequently reported the presence of pre-existing contraindications and other risk factors of LA, so it might be true that metformin is often unfairly implicated as a cause of LA (Juurlink & Roberts, 2014). We observed that more than one-quarter of patients had conditions contraindicating the use of metformin. Similar findings of metformin frequently being prescribed, disregarding the contraindications, have been reported (Huang, Castelino, & Peterson, 2014; Emslie-Smith et al., 2001). The incidence of LA in patients receiving metformin with contraindications has apparently not increased (Holstein & Stumvoll, 2005; Stades et al., 2004; Scheen & Paquot, 2013). For instance, renal impairment may lead to the accumulation of metformin as it is excreted through the kidney. However, a recent cohort study of more than 77,000 patients