Reports of Lactic Acidosis Attributed to Metformin, 2015–2018

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OBJECTIVE

In 2016, the U.S. Food and Drug Administration (FDA) revised metformin's label to permit use in patients with mild-moderate chronic kidney disease. We sought to determine whether this change was associated with increased reports of metformin-associated lactic acidosis (MALA) to the FDA's Adverse Event Reporting System (FAERS).

RESEARCH DESIGN AND METHODS

Publicly available FAERS reports were analyzed.

RESULTS

MALA reports increased from 521 in 2015 to 1,939 in 2018. After restriction to U.S. reports, absolute and relative increase in MALA reports was less, from 111 to 243. The proportionate reporting ratio (PRR), a measure adjusted for rates of other adverse event reports, was stable.

CONCLUSIONS

The increased reports deserve attention, but the PRR's stability and FAERS's known limitations, including lack of a denominator or control group, do not permit the conclusion that U.S. MALA rates have increased. Further study with more robust data sources is needed.

In April 2016, the U.S. Food and Drug Administration (FDA) revised the labeled contraindication to metformin use in chronic kidney disease to permit metformin's use, with some restrictions, in patients with an estimated glomerular filtration rate (eGFR) between 30 and 60 mL/min/1.73 m^2 (1). This change was based on emerging realization that lactic acidosis (LA), the feared complication of metformin use in chronic kidney disease, was a rare event that typically occurred in the setting of another likely cause, such as cardiovascular collapse, with an unlikely contribution from metformin (2,3). We sought to determine whether this change in FDA policy was associated with changes in the volume of reports of LA with metformin use (metformin-associated LA [MALA]) to the FDA's Adverse Event Reporting System (FAERS).

RESEARCH DESIGN AND METHODS

We used publicly available FAERS reports from 2015 to 2018, which are accessible both through a web-based querying tool and as downloadable files (4,5). MALA reports during this period are described after stratification by the year that they were initially reported to the FDA. Initial analyses included reports of international

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origin. After inspection of the data, the decision was made to limit primary analysis to reports of events occurring in the U.S.

The total annual number of adverse event reports (with or without LA) for metformin was calculated, as were both total and LA reports for a comparator group comprising other diabetes drugs (sulfonylureas, DPP-4 inhibitors, thiazolidinediones, GLP-1 receptor agonists, SGLT2 inhibitors, and insulin). Reports were restricted to those in which metformin or the comparator drugs were flagged as "primary suspect" rather than merely incidentally present. Proportional reporting ratios (PRRs) for each year were calculated as: ([number of LA reports for metformin]/[total number of reports for metformin])/([number of LA reports for comparator drugs]/[total number of reports for comparator drugs]) (6). The PRR is commonly used to enhance signal detection in surveillance databases, although it lacks epidemiologic interpretability and does not necessarily eliminate reporting bias or confounding.

Sensitivity analyses included dropping the requirement that drugs be the "primary suspect" and calculating PRRs for additional comparison groups, including for all nonmetformin drugs and for each diabetes drug class listed above.

Data processing and analysis were conducted using R 3.4.4.

RESULTS

A preliminary query, using the web-based tool, for reports of LA associated with metformin (MALA reports) showed an increase from 567 reports in 2015 to 2,231 in 2018. When downloadable files were used and analysis restricted to reports with metformin as "primary suspect," the increase was from 521 in 2015 to 1,939 in 2018 (Table 1). Over the same period, overall reports of any adverse event for metformin increased from 4,913 to 8,733. The percentage of MALA reports originating in the U.S. fell from 23% to 12%.

Table 1—Characteristics of LA case reports with metformin present as either primary suspect or incidental drug

	Year			
	2015	2016	2017	2018
All cases				
N	521	717	892	1,939
Country				
Britain	14 (2.7)	27 (3.8)	20 (2.2)	60 (3.1)
France	33 (6.3)	91 (12.7)	65 (7.3)	344 (17.7)
Germany	52 (10.0)	77 (10.7)	26 (2.9)	142 (7.3)
Italy	59 (11.3)	99 (13.8)	245 (27.5)	553 (28.5)
Other non-U.S.	252 (48.4)	252 (35.1)	347 (38.9)	597 (30.8)
Domestic (U.S.) cases only				
N	111	171	189	243
Age, years, mean (SD)	46.4 (21.9)	60.6 (15.2)	59.5 (15.1)	47.6 (20.3)
Sex				
Not recorded	24 (21.6)	41 (24.0)	21 (11.1)	31 (12.8)
Female	42 (37.8)	28 (16.4)	104 (55.0)	84 (34.6)
Male	45 (40.5)	102 (59.6)	64 (33.9)	128 (52.7)
AKI also reported	30 (27.0)	39 (22.8)	46 (24.3)	104 (42.8)
Sulfonylurea concomitant use	1 (0.9)	3 (1.8)	26 (13.8)	31 (12.8)
DPP-4i concomitant use	3 (2.7)	4 (2.3)	5 (2.6)	4 (1.6)
TZD concomitant use	0 (0.0)	2 (1.2)	1 (0.5)	1 (0.4)
GLP-1RA concomitant use	1 (0.9)	1 (0.6)	3 (1.6)	2 (0.8)
SGLT2i concomitant use	0 (0.0)	1 (0.6)	1 (0.5)	2 (0.8)
Insulin concomitant use	7 (6.3)	12 (7.0)	13 (6.9)	6 (2.5)
LA reports/all reports	0.05	0.06	0.08	0.11
Nonmetformin diabetes drugs				
LA reports, *n*	21	26	18	28
LA reports/all reports	0.0004	0.0009	0.0006	0.0007
PRR compared with metformin	144	74	139	145

Data are *n* (%) unless otherwise indicated. AKI, acute kidney injury; DPP-4i, DPP-4 inhibitor; GLP-1RA, GLP-1 receptor agonist; SGLT2i, SGLT2 inhibitor; TZD, thiazolidinedione.

When the data set was restricted to reports from the U.S., annual MALA reports doubled from 111 to 243, while the number of metformin reports for any adverse effect increased from 2,168 to 2,321. The percentage of metformin reports that were for LA, as opposed to other adverse events, increased from 5.2% to 10.5% ($P < 0.001$). For comparator drugs, LA reports increased from 21 to 28, while the total number of adverse event reports declined from 59,200 to 38,679. The percentage of reports for comparator drugs that were for LA rose from 0.04% to 0.07% ($P = 0.04$). Relative to the comparator, the PRRs for metformin and LA ranged from 74 to 145 (Table 1), with no statistically significant upward trend over time.

Demographic and clinical data were limited. Age was recorded for 83.6% of MALA cases and sex for 81.5%. Metformin daily dose was recorded for 27.4%, with a median of 2,000 mg. eGFR and serum creatinine were unavailable, although the percentage of LA reports with acute kidney injury concomitantly reported rose from 27.0% to 42.8% ($P < 0.01$).

Results were not materially altered by sensitivity analyses (data not shown), except that the PRR and its trend varied by comparison group. For instance, when GLP-1 receptor agonists were the comparator, PRR declined from 441 to 263. For SGLT2 inhibitors, PRR showed no trend, varying from 32.6 in 2015 to 35.3 in 2018.

CONCLUSIONS

Metformin is the most widely used type 2 diabetes drug, so any plausible safety concern for metformin deserves evaluation. The increase in MALA reports after the less-restrictive FDA label change is striking. However, we feel that these data should not prompt immediate concern to U.S. prescribers.

First, the increase in MALA reports when all FAERS data are analyzed is attenuated after restriction to U.S. cases. Even if the increase in international reports reflected a real increase in MALA rates, this would suggest the increase is less likely related to U.S. regulatory changes or to affect U.S. stakeholders.

The international trends are also difficult to interpret because FAERS

international reports largely consist of obligatory reporting from manufacturers. Metformin has multiple manufacturers, each obligated to report concerns with metformin, so that a single MALA case publicly reported either in the literature or in another nation's adverse events database might oblige several manufacturers to report the same case to FAERS, which does not automatically de-duplicate reports.

This issue potentially affects both domestic and international FAERS entries, and it is not possible to establish using public data whether a given case in FAERS is a duplicate. Yet, examination of the 10-fold increases seen in some European countries suggests that duplication may have significantly contributed. For example, one published series of 28 MALA cases at an Italian hospital between 2000 and 2014 was cited as the source of 91 Italian FAERS reports in 2018 (R. Ball, personal communication). Further, in 2017, the European Medicines Agency launched a new safety report database, which manufacturers are required to monitor and may have stimulated additional duplicate FAERS submissions (R. Ball, personal communication, and ref. 8).

Second, while the doubling in annual U.S. MALA reports is statistically significant and deserves attention, the lack of an upward trend for the PRR versus plausible comparators illustrates that the increase does not clearly stand out from background fluctuations in adverse event reporting. Further, FAERS data are subject to "notoriety" reporting bias, in which an increase in the number of cases reported can be driven by greater public awareness of an adverse effect. Increased discussion of LA in the wake of the FDA label change or a reduction in fear of litigation resulting from reports could stimulate such reporting.

FAERS data have limitations that make it challenging to address these concerns through further analyses. These include lack of a denominator (the number of patients in the population exposed to metformin), any true control group, or data regarding key covariates. Accordingly, further research on trends in MALA rates should use more robust methods, such as cohort studies using data from large health systems.

Despite their limitations, these data serve as a reminder that metformin should not be assumed safe in all circumstances. In particular, metformin's safety is not fully established at eGFR $<$45 mL/min/1.73 m^2 (9–11). Clinicians should exercise caution when prescribing metformin in that group, especially in patients with unstable renal function. We believe that prescribers should limit the maximum dose of metformin to 1,000 mg daily when eGFR is 30–45 mL/min/1.73 m^2, given that metformin is renally cleared (12).

In conclusion, annual MALA cases reported to FAERS in the U.S. increased since the 2016 FDA label change. After standard adjustments for concurrent reports of other adverse events and drugs, any increases largely disappear. Given this finding, as well as the inherent limitations of FAERS, we find no convincing evidence of increased MALA rates in the U.S. subsequent to the label change. However, our study highlights the need for further monitoring using methods less susceptible to bias. Caution remains necessary in patients with compromised renal function, for whom both dose adjustment and frequent monitoring of serum eGFR are recommended.

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Duality of Interest. J.H.F. reports a consultant role with Boehringer Ingelheim and Eli Lilly and Company. S.H. is a consultant to the Medullary Thyroid Carcinoma Registry Consortium funded by Novo Nordisk, AstraZeneca, Eli Lilly and Company, and GlaxoSmithKline. S.E.I. reports clinical trial leadership or consultant roles with Boehringer Ingelheim, AstraZeneca, Novo Nordisk, Sanofi/Lexicon, Zafgen, vTv Therapeutics, and Eisai Inc. (TIMI) and has given lectures for Merck and Boehringer Ingelheim. No other potential conflicts of interest relevant to this article were reported.

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