COMMENT ON FLORY ET AL.

Reports of Lactic Acidosis Attributed to Metformin, 2015–2018. Diabetes Care 2020;43:244–246

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Flory et al. (1) analyzed cases of lactic acidosis (LA) reported to the U.S. Food and Drug Administration's Adverse Event Reporting System (FAERS) for 2015–2018 to evaluate whether changes to the U.S. metformin label in 2016 altered the reporting rate of LA.

LA is rare, and large electronic databases are useful in studying its incidence. The Originator Pharmacovigilance (PV) Database (Merck KGaA) includes all individual case study reports on all metformin tablets manufactured by Merck, from patients, health care practitioners, health authorities, and the literature. The EudraVigilance Data Analysis System (EVDAS) and FAERS collect cases from marketing authorization holders, health authorities, and the literature in the European Union and U.S., respectively.

A new EVDAS system requirement (November 2017) requires manufacturers to pull all LA cases in their countries of marketing authorization from the system into their respective company PV database. This increased the number of reports from, for example, France in the Merck PV database, as few identify the manufacturer of the product in EVDAS. The new requirement subsequently created a spillover to FAERS for all companies with marketing authorizations and respective case reporting obligation in the European Union and U.S.

The reporting rates for metformin-associated LA (MALA) have fluctuated quite significantly between 2015 and 2019 (Table 1). Cases from the literature are prone to duplication and latency; e.g., 28 cases in a publication in 2018 (2) resulted in 54 cases in EVDAS in 2018, causing a spike in reporting (Table 1*B*). Reporting rates are more stable if literature-derived cases are excluded (Table 1*D*).

Table 1—Number of LA case reports with metformin as suspect or concomitant drug (MALA) in several PV databases by year of entry

Database	Case origin	2015	2016	2017	2018	2019
A. FAERS	All MALA cases	521	717	892	1,939	—
	U.S.	111	171	189	243	—
	Italy	59	99	245	553	—
	France	33	91	65	344	—
B. EVDAS	All MALA cases	526	1,069	767	902	911
	% all metformin cases	20.0	29.6	17.0	18.1	16.3
	U.S.	30	128	109	116	89
	% all metformin cases	4.6	14.9	10.1	13.1	13.4
	Italy	68	50	170	208	120
	% all metformin cases	20.1	28.4	28.9	36.7	20.8
	France	182	295	168	144	300
	% all metformin cases	52.3	62.2	42.6	28.0	40.0
C. Merck PV	All MALA cases	276	315	275	573	481
	% all metformin cases	6.1	5.6	5.3	8.7	5.8
	U.S.	12	20	21	25	27
	% all metformin cases	2.6	4.4	6.4	8.8	7.9
	Italy	62	63	66	104	25
	% all metformin cases	18.1	29.6	24.5	30.4	12.3
	France	37	56	32	134	209
	% all metformin cases	24.3	32.9	18.3	30.7	40.6
D. EVDAS, literature cases excluded	All MALA cases	359	543	442	506	620
	% all metformin cases	13.6	15.0	9.8	10.1	11.1
	U.S.	17	24	49	35	14
	% all metformin cases	2.6	2.8	4.5	4.0	2.1
	Italy	47	33	70	113	111
	% all metformin cases	13.9	18.8	11.9	19.9	19.2
	France	136	198	141	139	295
	% all metformin cases	39.1	41.8	35.8	27.0	39.4

Data are numbers of cases unless otherwise indicated.

In the U.S., the percentage of all reported cases is low, but it is much higher in Italy and, especially, France, where MALA is a topic of health authority interest and where physicians are encouraged to report cases. Other biases are also at play.

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For example, an ongoing PhD thesis in northern France increased reporting of MALA in 2018–2019, again causing a reporting spike for that period (Table 1*B*–*D*).

Social media is used increasingly by health care practitioners and patients to identify adverse events (AE) (3), with further potential for bias and nocebo effects. For example, a high frequency of reports of muscle AE with statins in observational data, news media, and social media has not been substantiated in randomized controlled trials (4,5).

Thus, reporting of AE to PV databases is subject to multiple sources of distortion and bias, and caution is needed when using these reports to interpret changes in AE incidence. We recommend that two or more PV databases should be used in such studies.

Duality of Interest. K.B. is a full-time employee of Merck KGaA, the originator of metformin hydrochloride (Glucophage), and this reply was created in line with ongoing Merck analyses on the quality of MALA case reports (see IDF 2019 abstract BU-04319). A medical writer (Dr. Mike Gwilt, GT Communications) provided editorial assistance, funded by Merck KGaA. No other potential conflicts of interest relevant to this article were reported.

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