

**CLINICAL REVIEW**

# MALAdaptive: Do We Avoid Metformin Unnecessarily?

*Chris Terpening, PhD, PharmD, BCACP*

**Convention holds that the use of metformin is contraindicated in many patients secondary to concerns about lactic acidosis. However, current evidence suggests that metformin-associated lactic acidosis is at most idiosyncratic. Awareness of the current evidence should permit broader use of this valuable medication. (J Am Board Fam Med 2014;27:136–141.)**

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Treatment of type 2 diabetes is one of the most common challenges encountered by the family physician. The percentage of people diagnosed with diabetes in the United States has risen from <1% in the 1950s to 7% in 2010.<sup>1</sup> In response to this increase, the pharmaceutical industry has developed a wide array of treatment options, with 29 individual agents, not including combinations, currently approved and marketed in the United States to help control blood glucose levels. Of all these agents, the one drug that has come to be recognized by multiple organizations as the preferred agent for initial treatment of diabetic patients is metformin.<sup>2,3</sup>

Metformin is a biguanide that exerts its blood glucose-lowering effects through reducing insulin resistance, in particular in the liver, where it inhibits gluconeogenesis. Its efficacy at reducing hemoglobin A1c is unsurpassed among oral antidiabetic agents, and there is a very low incidence of hypoglycemia if it is used as a monotherapy. Metformin reduces microvascular disease to a extent similar to other antidiabetic treatments.<sup>4,5</sup> Moreover, there is

some suggestion that its use can reduce macrovascular events in diabetic patients.<sup>4,5</sup>

From a practical standpoint, the most problematic adverse effects of metformin are gastrointestinal: mainly diarrhea, cramping, upset stomach, and vomiting. Most patients develop a tolerance to these effects early in therapy, although a measurable proportion can only tolerate reduced doses, if any. For this latter population, it is altogether reasonable to substitute other antidiabetic medications to help achieve improved blood glucose control. However, many people either never try metformin or have metformin discontinued because of the presence of specific warnings.<sup>6</sup> Other than the ubiquitous “hypersensitivity” contraindication that appears in every package insert, all the warnings (eg, renal impairment, hepatic failure) are regarding the concern that metformin may increase the risk of lactic acidosis, resulting in the condition known as metformin-associated lactic acidosis (MALA).

Lactic acidosis is indeed a serious medical condition, with a high associated mortality sometimes exceeding 80%.<sup>7,8</sup> It is characterized by reduced pH (<7.35), elevated serum lactate levels (>5 mmol/L), anion gap elevations, and an increased lactate-to-pyruvate ratio. Lactic acidosis can result from a wide array of different conditions, including sepsis, cardiogenic shock, hypovolemia, severe pulmonary disease, and end-stage liver disease. This article examines the data addressing whether metformin contributes to lactic acidosis and therefore whether the current contraindications are appropriate.<sup>9–13</sup>

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From the Departments of Family Medicine and Clinical Pharmacy, West Virginia University, Charleston.

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Corresponding author: Chris M. Terpening, PhD, PharmD, BCACP Departments of Family Medicine and Clinical Pharmacy, West Virginia University, 3110 MacCorkle Ave SE, Charleston, WV 25304 (E-mail: cterpening@hsc.wvu.edu).

## Metformin Serum Concentrations and Lactic Acidosis

For metformin to contribute to lactic acidosis, one must assume that its use would increase circulating lactate levels. Chronic renal impairment is listed as a contraindication to metformin use because metformin is exclusively renally cleared. Therefore, impaired renal function should increase metformin levels, which might increase the risk of lactic acidosis. However, the evidence that metformin raises serum concentrations of lactate in a clinically significant manner is minimal. The most recent Cochrane review of the subject reported that, based on aggregate data from 123 trials, baseline lactate levels rose from  $1.13 \pm 0.25$  to  $1.24 \pm 0.31$  mmol/L in patients treated with metformin.<sup>14</sup> This change was not significantly different from baseline (weighted mean difference, 0.12 mmol/L; 95% confidence interval [CI], -0.01 to 0.25) or from other non-biguanide comparators (weighted mean difference, 0.04 mmol/L; 95% CI, 0.00–0.13). Furthermore, even when serially measured in 24 patients with chronic kidney disease, lactate levels were not elevated (1.7 mmol/L) and did not correlate with either metformin dose or measured metformin serum concentration.<sup>15</sup>

That being said, there are many reports of intentional metformin overdose in which lactate levels rose in the absence of other confounding comorbidities. In the largest of these, Wills et al<sup>16</sup> reported on a chart review of cases from a poison center. They found 14 cases of lactic acidosis from among 398 metformin overdoses (3.5%). In those patients, a median intake of 15 g of metformin (interquartile range, 9–40 g) resulted in a median lactate level of 7.0 mmol/L (interquartile range, 6.5–12.4 mmol/L) and a pH of 7.25 (interquartile range, 7.00–7.32). However, the remaining 384 cases (96.5%) did not show alterations in either lactate or pH, although median metformin exposures were lower (median, 2.8 g; interquartile range, 0.7–11 g). This interquartile range is worth noting because it means that many patients did not develop lactic acidosis despite metformin intake exceeding 11 g. The inconsistent nature of the relationship between metformin overdose and lactate also was demonstrated by Lalau and coworkers.<sup>17</sup> In a case series of 13 metformin overdoses, 7 developed lactic acidosis, all of whom ingested multiple substances in addition to metformin. Of the 3

patients with overdoses solely of metformin, none developed lactic acidosis, despite ingesting 25.5 to 51 g of the drug. When viewing all 13 patients, there was no significant correlation between serum metformin levels and serum lactate levels. Thus, even with an overdose, the development of lactic acidosis seems to be idiosyncratic.

An argument could be made that metformin may only increase lactate levels in susceptible individuals. If so, a correlation between metformin and lactate or pH should be clearer in those with reported MALA. However, the vast majority of case series have failed to establish any correlation between metformin levels and either lactate or pH.<sup>18–21</sup> In terms of outcomes, the connection potentially becomes even more paradoxical. While not universally observed,<sup>21,22</sup> several case series have reported an inverse relationship between metformin concentration and mortality, with survivors having markedly higher metformin levels than those who did not survive.<sup>18,19,23</sup> Furthermore, rates of surviving MALA, especially when severe, are markedly better than surviving lactic acidosis of other origins.<sup>21,24</sup> Thus it is possible that metformin could be protective in lactic acidosis.

If the correlation between metformin and lactate is so unclear, why are there so many case reports in the literature? This can be attributed in part to the very definition of MALA. It is typically defined as any lactic acidosis in a patient *thought to be* taking metformin. While the name implies some element of contribution by metformin to the lactic acidosis, the definition clearly includes cases of “metformin-coincident lactic acidosis” where there is no impact of the presence of metformin. The majority of case reports historically have not included measurements of metformin levels because this is not a commonly available lab test. Instead, they make an assumption that all patients are compliant with metformin therapy.<sup>25,26</sup> When measured, however, there are many cases in which metformin levels are normal to nonexistent.<sup>18,23,27</sup> As such, it would be inappropriate to implicate metformin in those circumstances.

## Population Studies

Independent of discussions of serum concentrations, if one is to argue for a causative role of metformin in lactic acidosis, one should be required to demonstrate a higher rate of lactic acido-

sis among metformin users than among nonusers. Even if one accepts an idiosyncratic role of metformin in overdose, an increase in incidence during typical therapeutic use has proven difficult to demonstrate. Brown and colleagues<sup>28</sup> reported a rate of lactic acidosis among diabetic patients in a large health maintenance organization of 9.7 of 100,000 patient-years, during years when no biguanide was available in the United States. As such, most regard this as the “baseline” rate for this rare event. There have been attempts to prospectively measure MALA. A phase 4 trial mandated by the US Food and Drug Administration (FDA) and specifically designed to study adverse events of metformin use did not identify any cases from among 7227 patients.<sup>29</sup> The most recent Cochrane review pooled data from 347 prospective trials, providing >70,000 patient-years of metformin use, and found no cases of lactic acidosis.<sup>14</sup> Using Poisson statistical analysis, the authors calculated an upper limit of 4.3 cases per 100,000 patient-years of exposure. The package insert from the manufacturer, using both clinical trials and cases of it reported, estimates an incidence of 3 per 100,000 patient-years.<sup>6</sup>

However, it can be argued that using patients from clinical trials potentially introduces a selection bias because they may exclude patients at high risk. Thus, population-based studies might prove to be more accurate. A nested case-control analysis from the United Kingdom identified a total of 6 potential cases of lactic acidosis in >50,000 patient-years, yielding a crude incidence of 3.3 per 100,000 patient-years among those taking metformin.<sup>30</sup> This incidence was statistically similar to the incidence among users of sulfonylureas (4.8 per 100,000 patient-years). Furthermore, all the cases had potential comorbidities that could have independently caused the lactic acidosis. In a similar vein, the Fremantle Diabetes Study, a long-term observational study, identified 3 potential cases from among 5228 patient-years of metformin use.<sup>31</sup> This resulted in a crude incidence of 57 per 100,000 patient-years, much higher than other estimates. Once again, however, the incidence was not statistically different from the incidence in patients not taking metformin (28 per 100,000 patient-years;  $P = .4$ ), and all 3 cases had confounding comorbidities. A Canadian study found 2 cases from among 22,296 patient-years of exposure, for a crude incidence of 9 per 100,000 patient-years.<sup>32</sup> As with the others, both cases had comorbidities

that could independently explain the lactate levels. Finally, a group in the Netherlands identified 16 cases of MALA and used local population data to extrapolate this to an estimated rate of 47 per 100,000 patient-years.<sup>19</sup> However, they did not attempt to estimate rates of lactic acidosis among those not taking metformin for comparison. Furthermore, 9 of the 16 cases had normal levels of metformin when measured, and each of the 16 cases had a potentially confounding comorbidity. With all these reports, the comorbidities represent the usual contraindications from the metformin package insert, that is, renal impairment, severe hepatic disease, severe coronary events, and other hypoxic conditions. These comorbidities have been chosen because of their independent risk for lactic acidosis. It is interesting that, while chronic renal impairment often is regarded as the most common risk factor for MALA, acute kidney injury also seems to be a strong contributor. Three different hospital groups looking at all cases of lactic acidosis at their institutions, whether or not metformin was involved, reported that acute renal impairment was a risk factor for lactic acidosis but metformin ingestion was not.<sup>33–35</sup> As such, many of the reports of MALA reputedly in the absence of risk factors<sup>36,37</sup> do have a major risk factor.

### Contraindications

One might argue that the reason MALA is so rare is that the contraindications work and are being followed. The data, however, do not support this argument. In the Fremantle Diabetes Study mentioned earlier, more than a third of the patients receiving metformin had a formal contraindication, most commonly chronic renal impairment and heart failure, yet lactic acidosis incidence did not change compared with other treatments.<sup>31</sup> A retrospective cohort from Scotland reported that 24.5% of patients receiving metformin had a contraindication to its use. Of these patients, the most common contraindications included use of a loop diuretic, renal impairment, and admission to a hospital for cardiac failure. The single case of lactic acidosis out of 4600 patient-years of exposure occurred in a patient with a large acute myocardial infarction who rapidly developed renal failure and died the same day.<sup>38</sup> In Thailand, 266 of 1458 diabetic patients taking metformin had a contraindication, most often chronic renal impairment (203

patients), yet none developed lactic acidosis over an average treatment duration of 4 years.<sup>39</sup> These studies and others<sup>11,40,41</sup> paint a picture of the frequent use of metformin outside of proscribed limits, yet reports of lactic acidosis remain rare.

Rachmani and colleagues<sup>42</sup> took an alternate route by randomizing 393 patients with one or more contraindications to metformin to either continue or discontinue metformin therapy. The most common contraindications were renal impairment, advanced heart failure, and advanced chronic obstructive pulmonary disorder. After 4 years, lactic acid levels were not statistically different between groups (1.63 mmol/L for those discontinued vs 1.66 mmol/L for those still taking metformin), and no cases of lactic acidosis occurred in either group. However, the group who discontinued metformin gained more weight than the continuation group (+3.6 vs +0.9 kg;  $P < .002$ ) and had a greater increase in hemoglobin A1c (+0.5% vs +0.2%;  $P < .01$ ). There were no differences in mortality or macrovascular endpoints. These results suggest that discontinuing metformin “just to be safe” does not seem to improve safety and may worsen certain conditions. The whole point of contraindications is to help practitioners avoid use in inappropriate patients to reduce the risk of an event in the future. It is not clear that avoiding metformin in patients with contraindications alters the risk of lactic acidosis at all.

On the other side of the coin, the benefits of metformin have been demonstrated to be maintained in those with classic contraindications. Observational and case-control studies demonstrated a reduction in all-cause mortality with metformin use in patients with diabetic heart failure compared with the use of alternate diabetes medications.<sup>40</sup> In accordance with this, the FDA removed heart failure as a contraindication in 2006. Expanding on this, investigators with the Reduction of Atherothrombosis for Continued Health (REACH) Registry assessed the impact of metformin in patients with diabetes and established atherosclerotic disease.<sup>43</sup> Overall, metformin use was associated with a 24% reduction in mortality ( $P < .001$ ). In a subgroup analysis, benefits were observed in those with heart failure (31% reduction;  $P = .006$ ), age 65 to 80 years (23% reduction;  $P = .02$ ), and moderate renal impairment (creatinine clearance, 30–59 mL/min/1.73 m<sup>2</sup>; 36% reduction;  $P = .003$ ). A more recent assessment of data from >51,000

patients in the Swedish National Diabetes Register observed a similar mortality benefit.<sup>44</sup> After propensity analysis, all-cause mortality was 13% less in those taking metformin monotherapy than in those taking other oral antihyperglycemics ( $P = .032$ ) and 34% less than those taking insulin monotherapy ( $P < .001$ ). Furthermore, these benefits were observed even in patients with estimated glomerular filtration rate (GFR) of 45 to 60 mL/min/1.73 m<sup>2</sup>, with a 13% reduction in all-cause mortality compared with any therapy (hazard ratio, 0.87; 95% CI, 0.77–0.99). Those with a GFR of 30 to 45 mL/min/1.73 m<sup>2</sup> did not see the same benefit, but neither did they observe any increase in risk (HR, 1.02; 95% CI, 0.84–1.24). There were 6 documented cases of lactic acidosis among patients taking metformin, which the authors felt was too few for convincing statistical analysis. However, they did evaluate any acidosis or serious infection as an endpoint, which would include any cases that might have been inadvertently missed. These rates were lower in metformin users than in comparator groups among those with a GFR of  $\geq 60$  mL/min/1.73 m<sup>2</sup> (HR, 0.91; 95% CI, 0.84–0.98) and in those with a GFR of 45 to 60 mL/min/1.73 m<sup>2</sup> (HR, 0.85; 95% CI, 0.74–0.97). Those with a GFR of 30 to 45 mL/min/1.73 m<sup>2</sup> were not different from other comparators (HR, 0.98; 95% CI, 0.79–1.21). Viewed as a whole, it is quite possible to conclude that discontinuing or failing to try metformin may deprive patients of significant benefits.

## Conclusions and Recommendations

While there are cases of metformin overdose resulting in lactic acidosis in the absence of confounders, even these situations seem to be idiosyncratic. Current contraindications do not seem to alter the incidence of lactic acidosis and simply serve to deny many patients the clear benefits of metformin. While the data may support an “all metformin, all the time” approach, simple pragmatism suggests a more cautious approach. Instructing patients to interrupt metformin therapy whenever they have a significant acute illness is rational and encouraged. If the illness is severe enough to require hospitalization, insulin can be substituted in a closely monitored fashion. It is, however, imperative to make sure that a temporary illness does not become a permanent bar to metformin use. The practitioner should make sure to restart metformin

at the earliest opportunity, no later than discharge from the hospital. In terms of the most common contraindication, chronic renal impairment, any GFR cutoff seems arbitrary because the risk has not been clearly defined. However, there seems to be evidence of safety with GFRs as low as 30 mL/min. Several nations (eg, the United Kingdom, Australia, the Netherlands) already have adopted that as a recommendation. The joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes states that "use down to a GFR of 30 mL/min, with dose reduction advised at 45 mL/min . . . appear[s] very reasonable."<sup>2</sup> Given this wide level of support, one may hope that the FDA will alter the contraindications in the package insert accordingly. Until such time, the current listed contraindications should not be regarded as absolute, but instead the practitioner should take the entire risk/benefit picture into account.

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