The Perioperative Management of Metformin for the Oral and Maxillofacial Surgery Patient: Risks and Recommendations

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In 2015 it is estimated that 250 million people will have diabetes mellitus (DM). The growing epidemic of diabetes, particularly among young children, has found its way into the office of the oral and maxillofacial surgeon more than ever before. Metformin (Glucophage; Bristol-Myers Squibb, New York, NY) is an oral hypoglycemic often used solely or as an adjunct in the treatment of type 2 diabetes mellitus. The complication of lactic acidosis is indeed uncommon, but with a potentially fatal outcome, its importance cannot be ignored. To date, there has been a paucity in the literature for the perioperative management of metformin. Many surgeons and anesthesiologists are unaware of the potential dangers and how they can be avoided. This article will review the evidence, and we will attempt to put forth guidelines in the management of this commonly used drug in the perioperative period, focusing on the oral and maxillofacial surgeon.

What Is Metformin?

Metformin (dimethylbiguanide) is an oral hypoglycemic agent that has become one of the early treatment modalities for the patient with non-insulin-dependent diabetes mellitus, type 2 DM (NIDDM). In Europe it is prescribed as a sole oral hypoglycemic in 40% of patients with NIDDM, and used adjunctively with a sulfonylurea in 60% of this patient population. Metformin’s popularity as a first-line hypoglycemic agent can be attributed to its equally efficacious glycemic control as the sulfonylureas and its relatively high margin of safety. Metformin’s advantages over the sulfonylureas, with its target being insulin resistance, include less chance of induced hypoglycemia,1 decreased fasting levels of insulin (which may decrease the risk of macrovascular disease), and no net increase in body weight.

Metformin as a biguanide differs from other classes of hypoglycemics in its pharmacologic mechanisms. Metformin decreases hepatic glucose production in conjunction with decreasing the intestinal absorption of glucose. By increasing peripheral glucose uptake and utilization, metformin improves insulin sensitivity, the main dysfunction of the obese NIDDM patient. Glucophage has a relatively brief half-life (approximately 6 hours). Hence, after 6 hours, 50% of metformin is eliminated, 75% in 12 hours, and 90% is eliminated after a 24-hour period. The usual dosing regimen is 500 mg 3 or 4 times a day, or 850 mg 2 or 3 times a day. The maximal dose should not exceed 2.55 g a day.

According to recommendations from Bristol Squibb, the exclusion criteria for prescribing metformin to a patient with NIDDM are:

- Renal impairment: plasma creatine values ≥1.5 mg per deciliter for men, and ≥1.4 mg per deciliter for women.
- Cardiac or respiratory insufficiency that is likely to cause reduced peripheral perfusion or central hypoxia.
- History of lactic acidosis.
- Patients older than 80 years, unless renal function is uncompromised.
- Severe infection that can lead to decreased tissue perfusion.
- Liver disease, including alcoholic liver disease.

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Alcohol abuse with binge drinking sufficient to cause acute hepatic toxicity.
Use of intravenous radiographic contrast agents.

What Is Lactic Acidosis?

Lactate is produced from pyruvate in a reaction catalyzed by lactate dehydrogenase:

\[
\text{Pyruvate} + \text{NAD}^+ + H^+ \rightleftharpoons \text{Lactate} + \text{NADH}
\]

At rest, the distribution of tissues that normally produce excess lactate are skin (25%), red blood cells (20%), brain tissue (20%), muscle tissue (25%), and the gastrointestinal tract (10%). During intense periods of exercise, the skeletal muscles are responsible for an increase in circulating lactate, and in pregnancy, the placenta is an important producer. The metabolism of lactate is predominantly in the liver (60%) and kidney (30%). Half of that produced undergoes gluconeogenesis forming glucose, while the remainder is further metabolized to CO₂ and H₂O in the citric acid cycle. The result is no net production of H⁺ (or of the lactate anion) for excretion from the body. Other tissues can use lactate as a substrate, but it is only the liver and kidney that have the enzymes that can convert lactate to glucose.

The balance between release into the bloodstream and hepatorenal uptake maintains plasma lactate at about 1 mmol/L. The renal threshold for lactate is about 5 to 6 mmol/L so at normal plasma levels, no lactate is excreted into the urine. The small amount of lactate that is filtered (180 mmol/day) is fully reabsorbed.

Lactic acidosis is commonly classified into either type A or type B,² with the main differentiating point being the adequacy of tissue oxygen delivery. In both types, the fundamental problem is the inability of the mitochondria to cope with the amount of pyruvate with which they are presented. Type A lactic acidosis refers to circumstances where the clinical assessment is that tissue oxygen delivery is inadequate. The inadequate oxygen supply slows mitochondrial metabolism, favoring a right-sided shift in the above reaction-

pyruvate to be converted to lactate and NAD⁺. The mitochondrial reactions are presumed to be intact but unable to function because of inadequate oxygen. If hypoxemia is the only factor present, it needs to be severe (eg, paO₂ < 35 mm Hg) to precipitate lactic acidosis because of the protection afforded by the body’s compensatory mechanisms, which increase tissue blood flow. Similarly, anemia needs to be severe (eg, [Hb] < 5) if present alone because tissue blood flow is increased in compensation.

In type B lactic acidosis there is no clinical evidence of inadequate tissue oxygen delivery. Furthermore, the subsets of type B lactic acidosis encompass B1 (associated with underlying diseases, acquired immune deficiency syndrome [AIDS], lymphoma, etc), B2 (associated with drugs and toxins phenformin, cyanide, beta-agonists, methanol, etc), and B3 (associated with inborn errors of metabolism) (Table 1).

The clinical presentation of lactic acidosis is essentially consistent with that of tissue hypoperfusion: hypotension, oliguria or anuria, deteriorating mental status, and tachypnea. Vague symptoms of malaise, myalgia, nonspecific abdominal discomfort, hypothermia, and resistant bradycardia can be additionally found. If the degree of acidosis stimulates respiratory compensation, Kussmaul hyperventilation may be observed.

Metformin and Lactic Acidosis

It is normal for a nominal increase (within normal range) in basal and postprandial blood lactate concentrations with metformin therapy. This increase is likely attributed to the anaerobic metabolism of glucose to pyruvate reducing to lactate by the intestinal mucosa.¹ When levels become excessively high, it is lactic acidosis that is the metabolic malady of most concern when taking metformin. Its estimated incidence is 0.03 cases per 1,000 patient-years. Although it is an uncommon complication, its mortality is 50% and therefore warrants our attention. Although renal insufficiency causing high levels of metformin is among the more common causes of lactic acidosis, as

<table>
<thead>
<tr>
<th>Table 1. CLASSIFICATION OF LACTIC ACIDOSIS</th>
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<tr>
<td>Tissue Hypoxia</td>
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<td><strong>Type A</strong></td>
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<tr>
<td>Tissue hypoperfusion: Hypovolemia, sepsis, cardiogenic failure, etc</td>
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<tr>
<td>States of low oxygen content: severe anemia, CO poisoning, etc</td>
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described in the aforementioned section, lactic acidosis does not necessarily have to reflect elevated levels of metformin. Again, any insult causing decreased tissue perfusion or hypoxemia can lead to an elevated lactate level.

After over 2 decades of use, it was this complication that caused the banishing of the biguanide class of drugs in the United States in 1976. This report was of 330 patients with lactic acidosis taking biguanides, 12 of whom were actually on metformin, all of whom had significant renal dysfunction (creatinine >3 mg/dL). It was then that sulfonylureas gained in popularity. It was not until 1995 that the biguanide metformin was reintroduced to the United States. When compared with its cohort drug phenformin, still used in Europe, metformin proves to be 20 times less likely to induce lactic acidosis.

To date, there have been 2 case reports published relating perioperative mortality to metformin. Lactic acidosis after recommencement of metformin 24 hours postoperatively was a consistency between the 2 patients. In the case described by Gowardman, a 56-year-old woman with a well-controlled history of NIDDM was admitted for anterior resection with a loop ileostomy for a rectal carcinoma. On postoperative day 1, she was restarted on her oral hypoglycemics (metformin 850 mg and glibenclamide [second generation sulfonylurea] 5 mg once daily). Forty-eight hours after surgery her course deteriorated, presenting with hypotension, tachycardia, and dyspnea. With ensuing renal failure and an elevated WBC count (26,000) with a concomitant left shift, she became unable to clear her lactate of 24.8 mmol/L. Pressors were started to maintain her mean arterial blood pressure, and her arterial blood gas showed a severe metabolic acidosis (pH 6.87; base excess 27.9). The patient was intubated due to hypoxia and respiratory distress. According to the author, there was no evidence of ischemia in the immediate postoperative period, despite which her lactate continued to climb to 35.6 mmol/L before her death. Postmortem examination showed a large left-sided cerebral infarct, hepatic congestion with areas of hepatic necrosis, and lung findings consistent with adult respiratory distress syndrome. No metformin levels were noted.

In the case report by Mercker et al, a 66-year-old man with a history of hypertension, NIDDM, peripheral vascular disease, obesity, and a prior pulmonary embolism, was admitted for the repair of an abdominal wall hernia. The patient’s daily medications, including nifedipine, isosorbimodinitrate, metformin (500 mg once daily) and coumadin, were not taken the morning of surgery. The patient was heparinized preoperatively and the surgery was performed without complications. On postoperative day 1, the patient’s BUN and creatinine were 13 mg/dL and 1 mg/dL, respectively. The patient’s home medications were again resumed and his blood glucose levels were between 200 and 280 mg/dL. On postoperative day 2, the patient complained of transient dyspnea, and on postoperative day 4 the patient was admitted to the Surgical Intensive Care Unit for hypotension and respiratory distress. Upon admission to the unit, the patient was described as somnolent with a fever of 39.7°C. Shortly thereafter, the patient’s condition acutely worsened, necessitating intubation and pressors. A metabolic acidosis (pH 7.32; base excess 12.5) and a serum lactate level of 95 mg/dL preceded the patient’s new onset of acute renal failure. The patient was subsequently ruled out for any intra-abdominal infection, central line sepsis, urosepsis, endocarditis, mesenteric infarction, and pulmonary embolism. The metformin was discontinued at this time and the patient was transferred for a rectal carcinoma. On postoperative day 1, she was restarted on her oral hypoglycemics (metformin 850 mg and glibenclamide [second generation sulfonylurea] 5 mg once daily). Forty-eight hours after surgery her course deteriorated, presenting with hypotension, tachycardia, and dyspnea. With ensuing renal failure and an elevated WBC count (26,000) with a concomitant left shift, she became unable to clear her lactate of 24.8 mmol/L. Pressors were started to maintain her mean arterial blood pressure, and her arterial blood gas showed a severe metabolic acidosis (pH 6.87; base excess 27.9). The patient was intubated due to hypoxia and respiratory distress. According to the author, there was no evidence of ischemia in the immediate postoperative period, despite which her lactate continued to climb to 35.6 mmol/L before her death. Postmortem examination showed a large left-sided cerebral infarct, hepatic congestion with areas of hepatic necrosis, and lung findings consistent with adult respiratory distress syndrome. No metformin levels were noted.

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Why Should This Interest the Oral and Maxillofacial Surgeon?

The patient population for the typical oral and maxillofacial surgeon is vastly heterogeneous in age. Years ago we could state that the bulk of our patients were essentially healthy and in the young teenage years. Now, with the longevity of the baby boomers and the popularity of dental implantology, the appeal of the oral and maxillofacial surgeon continues to grow. Although a great majority of our patients may be on oral hypoglycemics such as metformin, the majority of outpatient procedures, even with sedation deeming the patient nothing by mouth, put the patient at slight risk for hypoperfusion.

Orthognathic surgery is an aspect of oral surgery that typically addresses the surgical needs of the patient with a dentofacial deformity in their late teens or early twenties. The medical history more times than not presented a healthy patient, with few if any health concerns, excluding many syndromic patients with associated comorbidities. Over the past decade this patient population has changed, as has our surgical know-how. Concomitantly, a change in the population of the diabetic patient can be noted as well. While type 2 DM had been traditionally thought to affect individuals older than 40 years, it is being recognized increasingly in younger persons, particularly in highly susceptible racial and ethnic groups, falling
disproportionately on African and Hispanic Americans. In some areas, more type 2 than type 1 DM is being diagnosed in teenagers and young adults. In fact, 25% to 50% of new-onset childhood diabetics are type 2. The growing issue of pediatric obesity accounts for much of the new incidence of type 2 diabetes, and is increasing at a rate of 20% to 30% per decade. One cannot ignore the genetic predispositions towards DM 2. The concordance rate for type 2 DM in monozygotic twins is >90%. Some cases of type 2 DM occur in young, nonobese adolescents (maturity-onset diabetics of the young [MODY]) with an autosomal dominant inheritance. Many families with MODY have a mutation in the glucokinase gene. Impairments in insulin secretion and in hepatic glucose regulation have been demonstrated in these patients. As the age range of NIDDM patients widens, so does the range of those interested in surgeries of this nature whether it be from a paramount interest in cosmetics fueled by the media or the increasing vanity of older generations. Regardless, a great many of the older patient pool have compromised glycemic control managed with metformin.

In orthognathic surgery, specifically during Le Fort I osteotomies, controlled hypotensive anesthesia has become popular in many institutions. The technique entails the controlled lowering of blood pressure, and is defined as a reduction of the systolic blood pressure to between 80 and 90 mm Hg. More commonly followed is the mean arterial pressure (MAP) to 50 to 70 mm Hg in a normotensive patient. Among its theoretical benefits include a reduced intraoperative hemorrhage, decreasing the need for transfusion, and decreasing operative time owing to better surgical field visibility. In the orthopedic literature, this appears to be true. Sum et al noted a decrease in the average blood loss by nearly 55%, a reduced need for transfusion by 53%, and a shorter than average operating time by over 1 hour. In the oral and maxillofacial surgery literature, while the estimated blood loss was significantly less, and an improved surgical field was noted, there was no significant difference in duration of the procedure with induced hypotensive anesthesia. Is this level of sustained hypotension enough to threaten lactic acidosis to the metformin patient?

**Flaws in the Studies, Controversies**

Referring back to the 2 case reports that were cited above, in both cases it is unclear whether metformin was contributory to the lactic acidosis. In neither the case report by Gowardman nor by Mercker was the metformin level commented upon. In the case report by Gowardman it was unclear when and if metformin therapy was discontinued once the patient’s condition worsened. In the case report by Mercker it appears that metformin was continued for 1 or 2 days after renal function worsened. In both cases it appears as though the patients became hypoxic in the delayed postoperative period. The lactic acidosis in the 2 cases is compatible with type A lactic acidosis. The metformin was very likely a contributory factor due to accumulation after deterioration of renal function, but unlikely the primary culprit.

Lalau et al measured plasma concentrations in 14 patients who experienced lactic acidosis (pH < 7.35 and lactate concentration > mmol/L) while receiving chronic metformin treatment. Ten patients had significantly high levels of metformin (4.1-8.9 mg/L, normal value 0.6 ± 0.5 mg/L), while 4 of the patients did not accumulate metformin due to less severe renal failure. Mortality in the 2 groups was 30% and 75%, respectively. Correlation studies showed a positive correlation between serum creatinine and plasma metformin. Additionally, a correlation was observed between plasma metformin and arterial lactate but only in patients with metformin accumulation. The conclusion from this is that the metformin level, therefore, is not predictive of patient mortality in lactic acidosis.

As pointed out in a correspondence by Lustik, with regard to the Mercker publication, it is difficult to believe that 500 mg of metformin for postoperative days 1 to 4 could have produced an elevated metformin level in lieu of a normal renal function as this patient had, and the relatively wide therapeutic margin and relatively short half-life of the drug. The dangers of lactic acidosis, theoretically, should be a nonissue with its half-life of 6 hours in someone with normal renal function.

Literature supporting the safety of metformin, such as that of Lucis, looked at 56,000 patient-years of metformin use while following the guidelines set forth by the manufacturer. No cases of lactic acidosis were reported.

**Treatment of Lactic Acidosis**

Aside from hemodialysis, the mainstay in treating lactic acidosis is treating the symptoms. In the setting of lactic acidosis, hemodialysis allows for clearance of metformin as well as the administration of bicarbonate without fluid overload. Both hemodialysis and peritoneal dialysis appears to be beneficial, although continuous hemodialysis may be better tolerated in the unstable patient. Although its true efficacy is controversial, bicarbonate is oftentimes used in treating lactic acidosis. To date, no controlled study has shown improved hemodynamics attributable to sodium bicarbonate infusion, regardless of any normalizing effect on pH, and many show worsening of some hemodynamic variables.
Dichloroacetate, shown to increase the activity of pyruvate dehydrogenase, has been successful in lowering the levels of circulating lactate, although clinically insignificant. A new neutralizing agent, Carbicarb, is currently being tested, and has been effective in animal models. It is an equimolecular mixture of sodium bicarbonate and sodium carbonate, and compared with sodium bicarbonate does not produce carbon dioxide. Controlled studies with Carbicarb in patients with metabolic studies are lacking at present.

**Guidelines and Our Recommendations**

Although there is no evidence-based standard of care in the perioperative management of metformin, much of the followed practice is based on anecdotal experience of various practitioners. No general consensus currently exists. O’Connor et al showed this as they reviewed the records of 474 patients who were taking metformin and came for preoperative evaluation prior to surgery (December 1995-March 2000). Of the 474 patients, 406 were instructed by the anesthesiologist to withhold taking metformin on the morning of surgery, 8 were told to take it the evening before, 38 were told to ingest it the morning of surgery, 2 were told to bring the medication with them, 19 were given no instruction, and one was told to stop taking metformin 7 days prior to the procedure.

Mercker et al, based on their experience, recommend stopping metformin “for several days before and after surgery.” Furthermore, if the metformin cannot be stopped due to the emergent nature of a case, they recommend serum lactate concentration, arterial blood gas analysis, and that renal performance be monitored perioperatively. Alberti recommends holding metformin 2 days prior to surgery.

Recommendations published by Lustik et al states, “patients with major surgery (with chance of hypoperfusion), we recommend eliminating only the day of surgery dose. For ambulatory surgery, we recommend taking metformin the day of surgery. For ambulatory surgery, we recommend eliminating the day of surgery dose. For ambulatory surgery, we recommend eliminating only the day of surgery dose.” Peters, in a review of the perioperative management, states that metformin must be stopped and replaced with insulin. The recommendations put forth by the manufacturer are listed as “...temporarily suspended in patients undergoing any surgical procedures (except minor procedures not associated with restricted intake of food and fluids) and not restarted until the patient’s oral intake has resumed and renal function had been evaluated as normal.” They further explained that their reason for concern stems from an inherent risk of hypoxia or reduced renal perfusion associated with many surgical procedures. As a result, patients remaining on Glucophage are at higher risk for developing lactic acidosis than those patients in whom Glucophage had been temporarily suspended around surgery.

Although the signs and symptoms of lactic acidosis are subtle and can easily be missed, its severity cannot be understated. And it is the responsibility not only of the anesthesiologist, but also the surgeons, to be aware of the potential dangers of this drug in the postoperative period. As our patient population continues to evolve and the number of patients on oral biguanides grows, the likelihood of these 2 fronts meeting cannot be denied. It is the opinion of the authors that the management of metformin in the perioperative period be case dependent. Assuming there is no contraindication of the patient to be taking metformin, we believe that stopping metformin the day before minor surgery, regardless of nothing by mouth status, is appropriate. Checking preoperative renal function and creatinine clearance would additionally be of good measure. In cases such as orthognathic surgery where hypotensive anesthesia is desirable, or cases in which hypotension due to excessive blood loss occurred, the resumption of metformin should be delayed. In these situations, particularly when postoperative nutritional intake may be low (intermaxillary fixation, postoperative ileus, etc), this patient should be placed on an insulin sliding scale. Additionally, a lactate level and perhaps an arterial blood gas should be checked before resuming metformin. If the patient has marked deterioration or signs and symptoms consistent with lactic acidosis, metformin should be stopped and this patient should be treated aggressively in the intensive care setting.

**References**