TITLE: Use of Metformin in Patients with Type 2 Diabetes who have Liver Dysfunction: A Review of Safety, Dosing Recommendations, and Guidelines for Use

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CONTEXT AND POLICY ISSUES:

Metformin is an oral hypoglycemic agent belonging to the biguanide drug class that is widely used as first-line therapy in the treatment of high blood sugar in type 2 diabetes.[1] Other oral hypoglycemic drugs approved in Canada for the treatment of type 2 diabetes mellitus include sulfonylureas (chlorpropamide, glimepiride, gliclazide, glyburide, tolbutamide); alpha-glucosidase inhibitors (acarbose); meglitinides (repaglinide and nateglinide); and thiazolidinediones (pioglitazone, rosiglitazone).[2] For overweight and obese individuals with diabetes, treatment with metformin has advantages over other oral hypoglycemics, including modest weight loss, lipid-lowering activity, and decreased rates of myocardial infarction and all-cause mortality.[3]

Metformin acts by directly lowering hepatic glucose production.[3] In addition, metformin improves the sensitivity of muscle and the liver to insulin, thereby enhancing the metabolism of glucose by these tissues.[4] Metformin also increases intestinal glucose utilization, producing lactate in the process, which is largely metabolized in the liver as a substrate for gluconeogenesis.[3] Metformin use may result in lactic acid accumulation due to increased cellular lactate production and decreased hepatic metabolism of lactate.[1] Lactate is normally cleared from the blood by the liver, kidney and skeletal muscle. Lactic acidosis, a rare but life- threatening form of metabolic acidosis, occurs when the body's buffering systems are overloaded and lactate builds up, causing decreased blood pH.[5]

While the development of lactic acidosis in those receiving treatment with metformin is rare, a fatality rate of up to 50% has been reported.[6] A 1999 population study of Saskatchewan residents taking metformin documented nine cases per 100,000 patient-years of metformin exposure.[7] Other sources cite a lower incidence of metformin-associated lactic acidosis at 3 cases per 100,000 patient-years.[8]

A high incidence of lactic acidosis (40 to 60 cases per 100,000 patient-years) led to the withdrawal in 1976 of phenformin, an earlier biguanide drug.[9] In contrast to metformin, phenformin was associated with lactic acidosis in the absence of other predisposing conditions such as renal insufficiency or liver disease.[9] Serious liver disease may increase the risk of lactic acidosis by blocking lactate metabolism.[10] While the term metformin-associated lactic acidosis is commonly used, true metformin-associated lactic acidosis has rarely been reported to cause mortality without other precipitating factors, including renal or liver dysfunction[4] or tissue hypoxia.[11]

In the product monograph, the manufacturer of metformin (Glucophage®, Sanofi-Avantis Canada Inc.) lists the following clinical conditions as contraindications to the use of metformin: unstable and/or insulin-dependent (type 1) diabetes; acute or chronic metabolic acidosis; patients with a history of lactic acidosis; renal impairment; congestive heart failure; severe hepatic dysfunction; excessive alcohol intake (acute or chronic); cardiorespiratory insufficiency; severe infection, trauma or surgery; known hypersensitivity or allergy to metformin; severe dehydration; pregnancy and breastfeeding.[5] These conditions may predispose individuals to hypoxia and therefore, the development of lactic acidosis.[12] In addition, the manufacturer recommends that metformin be temporarily discontinued in patients receiving iodinated contrast materials for radiologic studies since these materials can result in acute alteration of renal function.[5] Other clinical conditions cited as potentially dangerous for those receiving metformin include any condition leading to hypoxia, age greater than 80 years, peripheral vascular disease, and proteinuria.[6]

In clinical practice, controversy exists about the link between metformin use and lactic acidosis.[13] Some clinicians have suggested that the association between metformin and lactic acidosis is coincidental, with the risk factors themselves predisposing individuals to lactic acidosis.[14] Several recent published editorials have argued for and against using metformin in patients with contraindications described in the product monograph. Sigal argued in a 2004 commentary that overly restrictive contraindications to metformin may result in many patients being denied access to an excellent, possibly life-saving drug, while preventing few if any cases of lactic acidosis.[15] Similarly, McCormack *et al*. in a 2005 commentary discussed that even in patients with contraindications, the benefits of metformin use clearly outweigh any potential risks.[16] On the other hand, Fantus argued that until a favourable risk-benefit ratio is documented from clinical trial data, the maintenance of currently accepted contraindications would appear to be prudent.[17]

This report reviews the guidelines for metformin use and evidence for the safety of the drug in individuals with type 2 diabetes who have contraindications to its use, including liver dysfunction.

RESEARCH QUESTION(S):

1. Is there evidence to support decisions on when therapy with metformin should be withheld based on liver function in patients with type 2 diabetes?

2. What are the guidelines for the use of metformin in individuals with type 2 diabetes and liver dysfunction?

3. How safe is metformin compared with other oral hypoglycemic drugs when used in individuals with type 2 diabetes and liver dysfunction?

4.   Is there clinical evidence to support dosing recommendations for metformin when used in individuals with type 2 diabetes and liver dysfunction?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including OVID Pre-Medline, MedLine and Embase, Pubmed, The Cochrane Library (Issue 3, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 1993 and July 2008, and are limited to English language publications only. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analysis, clinical guidelines, randomized clinical trial (RCT) studies, and observational studies with a safety filter. Internet links are provided where available.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews and meta-analyses are presented first. These are followed by economic evaluations, randomized controlled trials, observational studies and evidence-based guidelines.

SUMMARY OF FINDINGS:

The search identified two systematic reviews,[18,19] and four observational studies[6,14,20,21] that addressed the overall safety of metformin and its use in patients with formal contraindications to the drug. In addition, five clinical practice guidelines were identified.[22-26]

Systematic reviews

1.   A Cochrane systematic review and meta-analysis (Salpeter *et al.*; originally published in 2002 and updated in 2006)[19,27] evaluated the incidence of fatal and nonfatal lactic acidosis with metformin compared with placebo or other non-metformin anti-hyperglycemic treatments. Levels of blood lactate were measured at baseline and during treatment. For the updated report, a comprehensive search was performed through September 2007. Prospective clinical trials of at least one month duration were included if they evaluated metformin use compared with placebo or any other glucose-lowering therapy. Observational cohort studies were also included if they evaluated at least one month of metformin use. Excluded trials lasting less than one month were evaluated separately for any cases of lactic acidosis. Two independent reviewers appraised the studies for inclusion and consensus was reached in cases of disagreement. The methodological quality of each study was evaluated based on criteria modified from Schulz,[28] Jadad,[29] and Stroup.[30] A subgroup analysis was planned to examine the association of lactic acidosis with hypoxemic co-conditions, including liver disease.

Of the 274 studies included in the analysis, 176 were prospective comparative trials, 85 were prospective cohort studies and 13 were retrospective cohort studies. Of the studies analyzed, 77 were double-blind, randomized controlled trials (RCTs). Another 99 were single-blind or open-label comparative trials (71 randomized and 28 non-randomized.) The 98 cohort studies were all open-label and observational. Of the 261 prospective studies, 135 studies (52%) listed liver disease as an exclusion criteria. A total of 76,253 participants were followed for 110,948 patient-years, with 54,192 participants (59,321 patient-years) in the metformin group and 22,061 participants (51,627 patient-years) in the non-metformin group. The mean age of participants was 57.1 years and 61% were

men. The mean trial duration was 1.5 years (range 0.1 to 10.7 years). The drop-out rate was estimated to be 9.2%. Metformin was given in daily doses of 1 g to 3 g, with dosage titrated based on glucose control. Comparison treatments included placebo, diet, insulin, glyburide (glibenclamide), gliclazide, glipizide, glimepiride, chlorpropamide, tolbutamide, acarbose, nateglinide, repaglinide, miglitol, troglitazone, rosiglitazone maleate and guar gum. Only 19 trials were specifically designed to assess the incidence of lactic acidosis, but side effects or adverse events were described in almost all the trials.

Pooled data from the 274 studies showed no cases of fatal or nonfatal lactic acidosis in either the metformin or non-metformin groups. Mean lactate levels in patients taking metformin were not significantly different from those taking placebo or other diabetes therapy. Using Poisson statistics, the upper limit for the true incidence of clinical lactic acidosis per 100,000 patient-years was 5.1 cases in the metformin group and 5.8 cases in the non-metformin group. A review of 69 additional trials that were excluded from analysis because the duration was unclear or less than one month also showed no cases of lactic acidosis.

There was insufficient information to estimate the number of participants studied with contraindications to metformin use, including hypoxemic co-conditions such as renal insufficiency, cardiovascular disease, liver disease, or pulmonary disease. Of the 261 prospective studies, 254 (97%) allowed the inclusion of participants with at least one of these contraindications. However, it was unclear how many participants with each of these conditions were included in the trials.

The reviewers concluded that there was no evidence to suggest that metformin is associated with an increased risk of lactic acidosis compared with other anti-hyperglycemic treatments. They were unable to quantitatively assess the safety of metformin in the presence of conditions that increase the risk for development of lactic acidosis, such as liver disease.

The limitations of this systematic review include the sample size and insufficient information available to perform subgroup analyses for participants with risk factors for the development of lactic acidosis. In order to assess the risk of a rare occurrence such as lactic acidosis, it may be necessary to evaluate more than 55,000 patient-years of metformin use. There may also have been potential bias since many of the comparative trials were sponsored by pharmaceutical manufacturers producing anti-hyperglycemic medications other than metformin. The authors suggested that large, prospective, comparative trials are necessary in patients with type 2 diabetes mellitus who have conditions that are presently contraindicated for its use.

2. A systematic review (Bolen *et al.*; 2007)[18] evaluated the comparative effectiveness and safety of oral diabetes medications for adults with type 2 diabetes. Six key questions were addressed and of these, the following three key questions were pertinent to this CADTH review: I) Do oral diabetic medications differ in terms of risk of life-threatening adverse events, including severe lactic acidosis. 2) Do safety and effectiveness of oral diabetes medications differ across particular adult populations, including those with co-morbid conditions, such as liver disease. 3) Do the safety and effectiveness of oral diabetes medications for the treatment of adults with type 2 diabetes differ across particular adult populations, such as those based on demographic factors (e.g., race/ethnicity, age greater than 65 years, or gender) or co-morbid conditions (e.g., renal insufficiency, congestive heart failure, liver disease, obesity, depression, or

schizophrenia). A comprehensive literature search was performed through January 2006. The levels of evidence sought to answer these three key questions included systematic reviews, randomized and non-randomized trials, retrospective or prospective cohort studies with or without a comparison group, and case-control studies. Case reports and case series were excluded. Two independent reviewers first appraised study abstracts for eligibility and then the full-text articles. Disagreements were resolved through consensus adjudication. Data were extracted and then confirmed by a second reviewer.

A total of 216 articles met the inclusion criteria, including the initial 2002 Salpeter Cochrane review.[19] Supplementing the studies identified in the 2002 Cochrane review, an additional three RCTs and five cohort studies were identified that evaluated cases of clinical lactic acidosis in patients taking oral diabetes medications. Of these, all three RCTs and two of the five cohort studies were consistent with the Cochrane review, showing no cases of lactic acidosis. Three other cohort studies reported a small number of clinical lactic acidosis cases, giving estimates in two studies ranging from 2.2 cases per 10,000 person-years to 4.5 cases per 100,000 person-years. One of the cohort studies evaluated readmissions for metabolic acidosis in Medicare patients within one year of hospital admission for congestive heart failure. Patients discharged with a prescription for metformin had similar readmissions for metabolic acidosis (2.3%) compared with patients discharged with thiazolidinediones (2.2%) and those discharged on other diabetes medications (2.6%), which were mainly insulin or second-generation sulfonylureas. These rates were consistent with the Cochrane review.

Bolen *et al.* concluded that the rate of lactic acidosis was similar between metformin and other oral diabetes medications or placebo (8.4% versus 9 cases per 100,000 patient years) There was insufficient information about the use of metformin in patients with chronic conditions such as chronic liver disease, chronic renal insufficiency, congestive heart failure or severe pulmonary disease. Therefore no conclusions could be drawn about the safety of metformin use in the presence of co-morbid conditions that predispose individuals to lactic acidosis.

Limitations of the systematic review included inconsistent reporting of adverse events among the included studies. Few RCTs evaluated specific outcomes such as elevated liver transaminases; therefore a small number of cohort studies were relied upon for these outcomes. Many studies excluded individuals with co-morbidities such as renal or hepatic insufficiency, therefore the findings cannot be generalized to those with specific co-morbidities. The review also excluded studies comparing oral diabetes medications with insulin, therefore relevant information regarding metformin used may have been missed. The authors suggested that additional observational studies are needed to determine the safety of metformin compared with other oral diabetes medications in patients with liver disease and other co-morbid conditions predisposing them to lactic acidosis.

Observational studies

1. A 2004 cross-sectional survey assessed if risk factors for lactic acidosis influenced prescribers' dosing of metformin, which would indirectly reflect Australian guideline interpretation. At the time of the survey, two commonly used Australian guidelines provided different recommendations for metformin dosing; one provided a detailed list of contraindications and cautions, while the other summarized contraindications as any

condition, excluding renal impairment, that decreases tissue oxygenation. Millican *et al.*[14] retrieved data from all patients taking metformin at the time of admission to two Australian hospitals during an eight-week period. Structured patient interviews were conducted and patient charts and hospital electronic laboratory databases were reviewed for patient demographics, metformin dose upon admission, current metformin dose, and presence of risk factors for lactic acidosis. Risk factors included renal impairment; congestive heart failure; respiratory insufficiency; concomitant illness likely to affect acid-base balance; age greater than 80 years; surgery; use of radiological contrast media; and hepatic disease (defined as values of liver function tests two times greater than normal). Patients were revisited every two to three days and upon discharge to review their risk factors and any changes in metformin therapy. Eighty-three patients were included in the review, 60 of whom had at least one risk factor for lactic acidosis. Median age was 67 years, with 50.6% being female. When risk factors for lactic acidosis were present, significantly more patients had dose adjustments compared with those who had no risk factors ($P < 0.01$). Dose adjustments and withdrawal of metformin were most common in patients with renal or hepatic impairment or if they underwent surgery or received radiological contrast media. The authors commented that since there is no strong evidence that metformin dose is correlated to plasma lactate concentrations, drug withdrawal would likely be more appropriate than dose reduction if concerns about lactic acidosis exist. The authors concluded that metformin prescribing deviates from guidelines in the presence of risk factors, which reflects uncertainty in the evidence on the relationship between lactic acidosis and metformin. Metformin dose was influenced by the number and particular risk factor(s) present. The limitations of this study include the small sample size and the retrospective design, which made it difficult to "truly" discern from the chart review the clinicians' prescribing intent and interpretation of risk factors.

2. A cross-sectional observational survey was published by Khandwala *et al.*[6] in 2004. The objective of the study was to review hospital charts of all patients admitted to the Royal University Hospital in Saskatoon during a six-month period to determine the prevalence of any of three identified risk factors for the development of lactic acidosis in patients who received metformin during their admission. The risk factors included congestive heart failure, renal insufficiency, and hepatic dysfunction, such as known history of chronic liver disease or cirrhosis, and/or elevations in liver enzymes three times the upper limit of normal. During the study period, 204 patients (116 male and 88 female) were dispensed metformin at least once. Mean patient age was 66.75 ± 12.67 years. Of 204 patients, 58 had contraindications to metformin use; 52 of 204 (25.5%) had one contraindication and six of 204 (2.9%) had more than one contraindication. Seven patients (12%) had hepatic dysfunction; five had a known history of cirrhosis and two had elevated liver enzymes secondary to hepatic metastasis. Once contraindication to metformin use was identified, the drug was discontinued in 8 of 58 patients (13.0%). The authors concluded that metformin is prescribed frequently to patients who have a contraindication to its use, potentially increasing the risk of developing lactic acidosis. Despite this, the frequency of lactic acidosis is quite low, suggesting a coincidental rather than causal association between metformin and the development of lactic acidosis. The authors noted that if all precautions to the use of metformin were rigorously applied, at least 50% of patients would not be considered appropriate candidates. Given the rarity of lactic acidosis despite widespread use in the presence of contraindications, the authors stated that the benefit of metformin therapy could be argued to outweigh the risks, even in patients with underlying contraindications to its use. They also suggested that the list of contraindications could perhaps be revisited

and revised to prevent unnecessary discontinuation of metformin therapy in patients who might benefit from the drug without realistically increasing any risk to their safety. Limitations of the study include retrospective trial design and the small sample size that limit the generazability of these results. In addition, only three of the several contraindications to the use of metformin were examined, which likely underestimates the prevalence of metformin prescribing in the presence of contraindications.

3.   A cross-sectional survey was published by Holstein et al.[21] in 1999. The aim was to examine the use of metformin and to determine if contraindications predisposing to lactic acidosis were always taken into account. Patients with type 2 diabetes on metformin therapy and admitted to hospital from 1 January 1995 to 31 May 1998 (n=308) were investigated for contraindications to metformin. Other inclusion criteria in terms of co-morbidities were not reported. The following conditions were identified by specialist committees, experts, and manufacturers to be contraindications to metformin use: renal impairment; hepatic impairment (defined as a reduction in coagulation parameters, serum albumin and cholinesterase); chronic respiratory insufficiency; heart failure; advanced coronary heart disease; peripheral vascular disease; chronic alcohol abuse; severe infection; pregnancy and breastfeeding; use of contrast agents; and surgery under general anaesthesia.

On admission to a hospital in Germany, 224 patients (73%) had contraindications to metformin use; 106 (34.4%) had one contraindication and 115 (37.3) had two or more contraindications.
The mean age of the 308 patients (150 women and 158 men) was 66 ± 11.3 years, the mean duration of metformin therapy was 1 ± 0.9 years and the metformin daily dose was 1200 ± 530 mg. Hepatic insufficiency was found in four patients (1.3%) and chronic alcohol abuse was found in 10 patients (3.3%). No cases of lactic acidosis were observed. Metformin therapy was stopped immediately when contraindications were identified. The authors concluded that failure to consider contraindications or precautions to metformin therapy is common and that therapy is often inadequately monitored. Limitations of the study include retrospective design, small sample size, and incomplete reporting of inclusion criteria or how data were collected. In addition, the authors point out that the nonrandom patient sample is not representative of metformin prescribing in Germany.

4.   A 1997 cross-sectional survey published by Sulkin et al.[20] examined the prevalence of conditions regarded as contraindications or cautions among metformin-treated patients attending a university hospital diabetes clinic in the UK during a three-month period. Contraindications were derived from a literature review and included: renal impairment; chronic hepatic dysfunction or abnormal hepatic function tests (plasma transaminases, alkaline phosphatase); alcohol abuse; cardiac failure; coronary heart disease; peripheral vascular disease; significant pulmonary disease; severe infection; major surgical procedures; metastatic malignancy; proteinuria; or acute trauma. The hospital's database was searched to identify metformin-treated patients who attended the diabetes clinic during the study period. The case notes for 89 consecutive patients were reviewed. The mean age was 62 ± 12 years, with 42 being female. Of 89 patients, 59 (66%) had at least one condition regarded as a contraindication or caution to metformin. Two patients had chronic liver disease. Eight patients had two contraindications or cautions; five patients had three conditions and one patient had four conditions. The authors concluded that despite the low incidence of reported cases of lactic acidosis in the UK during the previous 10 years (approximately two cases per year), many patients with

potential cautions and contraindications receive metformin. Only one case of lactic acidosis was reported in the authors' clinic during the previous decade. This occurred in a patient receiving metformin who had no contraindications to the drug. Limitations of the study include small sample size, and the retrospective cross-sectional study design, which makes it difficult to determine if a clear association exists between the development of lactic acidosis and treatment with metformin.

Clinical practice guidelines

Five clinical practice guidelines for the management of type 2 diabetes were identified, including information pertaining to metformin use in patients with hepatic dysfunction or alcoholism.

1. In 2008, the UK-based National Collaborating Centre for Chronic Conditions updated national clinical guidelines for type 2 diabetes previously published by the National Institute for Health and Clinical Excellence (NICE) in 2002.[26] The guidelines, *Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (Update)* were based on a systematic literature review and critical appraisal of the evidence. This evidence was synthesized into evidence statements, which were then reviewed by a multidisciplinary team of experts to formulate recommendations. One such statement was: "A Cochrane review[19] looked at the risk of lactic acidosis in patients treated with metformin. There were no cases of fatal or non-fatal lactic acidosis reported." This statement was assigned a Level 1+ evidence grade since it was based on a systematic review with a low risk for bias. The guideline's final recommendations stated that the cardioprotective benefits of metformin demonstrated in the 1998 UK Prospective Diabetes Study[31] and in a large observational Scottish study conducted by Evans *et al.* in 2006[32] "far out weighed the concerns over lactic acidosis (provided renal function was adequate) in people with mild to moderate hepatic and cardiac disease." The guideline authors pointed out that nearly all the data related to overweight people and could not necessarily be extrapolated to individuals who were not overweight; however the overwhelming majority of people with type 2 diabetes are overweight. They also pointed out that attention should be paid to differences between ethnic groups. In their final recommendations, the authors recommend that the benefits and risks of metformin should be discussed with individuals with mild to moderate liver dysfunction so that an informed decision can be made on whether to continue or stop metformin.

2. The guidelines titled *Management of type 2 diabetes mellitus* were updated by the Institute for Clinical Systems Improvement (ICSI) in 2006.[25] Evidence was identified through searches of electronic databases and the quality of the evidence was graded according to study methodology and design. The methods used to analyze the evidence were not provided, nor were the methods used to formulate the recommendations. The ICSI guidelines list severe hepatic disease or alcoholism as a contraindication to metformin use; however no reference citation was provided. The following consensus statement was made regarding metformin use in hepatic disease: "Hepatic disease or insufficiency increases the risks of lactic acidosis and hypoglycemia and influences the metabolism of many oral agent medications. Metformin should not be used if alanine aminotransferase (ALT) is 2.5 to 3 times the upper limits of normal." No evidence citation was provided for this statement.

3. *Diabetes* Care is a 2005 guideline produced by the Guidelines & Protocols Advisory Committee in British Columbia.[24] No description was provided regarding the methodology used to identify, analyze or grade evidence to support the

recommendations included in the guideline. The guideline contains an unreferenced statement that metformin is contraindicated in patients with hepatic dysfunction.

4. The 2003 *Pharmacologic Management of Type 2 Diabetes* was prepared by the Canadian Diabetes Association Clinical Practice Guidelines Expert Committee.[22] The guideline recommends that metformin, unless contraindicated, should be used as the primary drug for overweight patients with type 2 diabetes. This statement is based on evidence from the 1998 report from the UK Prospective Diabetes Study Group. Contraindications for metformin are listed as renal dysfunction, hepatic dysfunction or cardiac failure; readers are directed to the most current edition of *Compendium of Pharmaceuticals and Specialties* and product monographs for detailed prescribing information.

5. The 2003 New Zealand *Management of Type 2 Diabetes* evidence-based best practice guideline updated guidelines originally published in 2001.[23] Key issues and questions were developed, followed by an extensive literature search and a critical appraisal of the methodology of existing diabetes guidelines. Recommendations and summary statements about metformin use, with their corresponding level of evidence or bibliographic citations are as follows:

   - "Metformin should not be used in situations where lactic acidosis is likely." (Recommended best practice based on the clinical experience of the Guideline Development Team)
   - A list of suggested contraindications and guidelines for withdrawing metformin therapy did **not** include hepatic insufficiency or heavy alcohol use. (Recommended best practice based on a 2003 article by Jones *et al.*[11])
   - "Lactic acidosis associated with metformin therapy is very rare and when seen is usually in the setting of acute or chronic renal impairment." (Royal College of General Practitioners Level lll evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies.)
   - "The overall prevalence of metformin-associated lactic acidosis is reported to be three cases per 100,000 patient years. Safety concerns about the use of metformin may have been overestimated." (Statement references a 2003 article by Jones *et al.*[11])

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

Metformin is widely used as a first-line therapy in overweight and obese patients with type 2 diabetes because it has been shown to reduce mortality and complications in this patient population.[33]

The product monograph for metformin includes an extensive list of risk factors that are considered to be contraindications to the drug, including severe hepatic dysfunction and excessive alcohol intake (acute or chronic).

Controversy exists over the link between metformin use and lactic acidosis. [13] Although circumstantial evidence indicates that metformin may be linked with lactic acidosis, no causal relation has been proven.[11] Some clinicians have suggested that the link is coincidental, with the risk factors themselves predisposing individuals to lactic acidosis.[10,14] Of interest, the Sanofi-

Aventis product monograph states that when used as indicated, there has not been a single case of lactic acidosis reported in Canada.[5]

A Cochrane systematic review found no evidence that metformin was associated with an increased risk of lactic acidosis. Of the 261 prospective studies included in the review, 97% of them allowed inclusion of patients with at least one contraindication to metformin. However, it was unclear how many participants with specific conditions, including hepatic dysfunction, were included in the trials. Therefore the safety of metformin in the presence of individual risk factors could not be quantitatively assessed.[14]

If the contraindications to metformin use were strictly adhered to, metformin would seldom be prescribed.[11] In fact, evidence from the systematic reviews and observational studies included in this report indicates that contraindications to metformin use are widely disregarded.

One US guideline[25] and two Canadian guidelines[22,24] adhere to the manufacturer's standard contraindication to metformin use in patients with severe hepatic dysfunction. However, this term is vague and the parameters for severely abnormal liver function are not defined. Among the five guidelines reviewed in this report, only the ICSI guideline defined abnormal liver function as being an alanine aminotransferase (ALT) level 2.5 to 3 times the upper limits of normal.[25] Thus there is no clear evidence to support decisions on when to withhold therapy with metformin based on liver function.

A UK guideline[26] used the evidence provided in the Cochrane review to recommend that the risk-benefit ratio of metformin use be weighed in patients who have or who develop mild to moderate hepatic disease. A New Zealand guideline[23] stated that lactic acidosis is very rare and is generally associated with renal impairment. The guideline's list of suggested contraindications and guidelines for metformin withdrawal did not include hepatic insufficiency or heavy alcohol use.

Thus, there is considerable variation in published guidelines for metformin use in patients with type 2 diabetes and liver dysfunction. Furthermore, there are no clear recommendations that metformin dose should be adjusted in patients with type 2 diabetes with liver dysfunction.   This may limit the use of metformin in some patients and confuse physicians.[17]

It is difficult to conclude, based on a review of the available literature, if metformin use in individuals with type 2 diabetes and liver dysfunction is safe relative to other oral hypoglycemic drugs. There is limited research exploring rates of lactic acidosis among metformin users with rates among users of other oral hypoglycemic agents.

A double-blind prospective randomized clinical trial assessing clinically significant outcomes including hospitalization and mortality associated with lactic acidosis in patients receiving therapy with metformin compared with other oral hypoglycemics would be helpful. However, such a trial would be difficult to perform due of the large sample size that would be needed to detect this rare complication.[34] Until further evidence is available, an individualized benefit-risk assessment should be conducted to help determine whether metformin should be initiated in patients with type 2 diabetes and liver dysfunction and whether metformin should be continued if liver dysfunction develops during treatment.

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