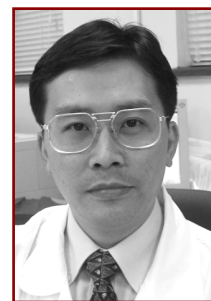




Metformin and Contrast Media

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METFORMIN is an oral antihyperglycaemic agent commonly used in non-insulin dependent (type 2) diabetes mellitus. It was first introduced in the 1950s along with phenformin. Phenformin was available in the United States until 1977 when the FDA withdrew it due to the frequency of lactic acidosis. Metformin then became the biguanide of choice in various countries.¹

Metformin lowers both basal and postprandial glucose levels in type 2 diabetes patients through several mechanisms: decreases hepatic glucose production, decreases intestinal absorption and increases peripheral glucose uptake and utilisation by improving insulin sensitivity.^{2,3} Approximately 50 to 60% of metformin is absorbed from the small intestine. It is eliminated entirely by the kidney unmetabolised and has a plasma half-life of 6.2 hours. It is not bound to plasma proteins. (Table 1)^{2,4}

Gastro-intestinal side effects such as nausea, vomiting, diarrhea (usually transient) and abdominal pain are initially common with metformin. In addition, metformin may provoke lactic acidosis which is most likely to occur in patients with renal impairment.⁵

Lactic Acidosis

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with metformin hydrochloride; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis is characterised by elevated blood lactate levels (greater than 5mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels greater than 5mcg/ml are generally found.^{4,6}

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years)^{4,7} In the reported cases there are usually existing contraindications to the prescribing of metformin. The contraindications to metformin are listed in Table 2.^{8,9,13}

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin hydrochloride, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170ml/min under good haemodynamic conditions), prompt haemodialysis is recommended to correct the acidosis and remove the accumulated metformin.^{4,8}

Metformin and Contrast Media

Administration of intravenous iodinated contrast media during radiologic procedures has been associated with an acute decline in renal function and may place a patient receiving metformin therapy who previously was at low risk at a higher risk of lactic acidosis. The frequency of contrast material-associated nephropathy is estimated to range from 0.1-13%; preexisting renal insufficiency is recognised as an important factor.^{10,11} No known interaction exists between metformin and iodinated contrast media. However, acute renal failure is associated with metformin accumulation and subsequent lactic acidosis.¹²

Recommendations

According to the manufacturer's recommendation:¹³ "As the intravascular administration of iodinated contrast materials in radiologic studies can lead to renal failure, metformin should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal."

The use of contrast media in patients receiving metformin should be carried out with care. There is no conclusive evidence indicating that the intravascular use of contrast media precipitated the development of metformin induced lactic acidosis in patients with normal serum creatinine (<130 µmol/l). The complication has almost always been observed in non-insulin dependent diabetic patients with abnormal renal function before injection of contrast media.¹⁴

The Contrast Media Safety Committee (CMSC) of the European Society of Urogenital Radiology (ESUR) has produced guidelines for the administration of contrast media to diabetics taking metformin. (Table 3)¹⁵ In Hong Kong, guidelines for the use of intravascular contrast medium in persons under treatment with metformin has been jointly composed by COC (Radiology) and COC (Internal Medicine) of Hospital Authority. (Table 4).¹⁶

Conclusion

When a contrast-enhanced examination is considered necessary in the work-up of patients treated with metformin who have increased risk of developing contrast-induced nephropathy and subsequent lactic acidosis, the risk may be reduced by preparing them for examination through adequate hydration, withholding the intake of metformin and close monitoring of the renal function of these patients.



Table 1. Pharmacokinetics of Metformin

- **Absorption**
 - Bioavailability : 50% to 60%
- **Distribution**
 - Vd: 654L +/- 358L
 - Protein binding: negligible
- **Metabolism**
 - Not metabolised
- **Excretion**
 - Renal: approximately 90%
 - Dialyzable: yes (haemodialysis)
- **Elimination half life**
 - 6.2h
 - Renal insufficiency: prolonged

Table 2. Contraindications of Metformin

- Hypersensitivity to metformin hydrochloride or to any of the excipients.
- Diabetic ketoacidosis, diabetic pre-coma.
- Renal failure or renal dysfunction (creatinine clearance < 60 mL/min).
- Acute conditions with the potential to alter renal function such as:
 - dehydration
 - severe infection
 - shock
- Intravascular administration of iodinated contrast agents (Withhold therapy when iodinated contrast media is used)
- Acute or chronic disease which may cause tissue hypoxia such as:
 - cardiac or respiratory failure
 - recent myocardial infarction
 - shock
- Hepatic insufficiency, acute alcohol intoxication, alcoholism
- Lactation

Table 3. European Society of Urogenital Radiology (ESUR) guidelines for the administration of contrast media to diabetics taking metformin (Summary)

1. Serum creatinine level should be measured in every diabetic patient treated with biguanides prior to intravascular administration of contrast media. Low-osmolar contrast media should always be used in these patients.
2. Elective studies
 - a) If the serum creatinine is normal, the radiological examination should be performed and intake of metformin stopped from the time of the study. The use of metformin should not be resumed for 48 h and should only be restarted if renal function/serum creatinine remains within the normal range.
 - b) If renal function is abnormal, the metformin should be stopped and the contrast study should be delayed for 48h. Metformin should not be restarted 48 h later, if renal function/serum creatinine is unchanged.
3. Emergency cases
 - a) If the serum creatinine is normal, the study may proceed as suggested for elective patients.
 - b) If the renal function is abnormal (or unknown), the physician should weigh the risks and benefits of contrast administration. Alternative imaging techniques should be considered. If contrast media administration is deemed necessary and the following precautions should be implemented:
 - Metformin therapy should be stopped
 - The patient should be hydrated, e.g. at least 100ml/h of soft drinks or intravenous saline up to 24 h after contrast medium administration - In warm areas more fluid should be given
 - Monitor renal function (serum creatinine), serum lactic acid and pH of blood
 - Look for symptoms of lactic acidosis (vomiting, somnolence, nausea, epigastric pain, anorexia, hyperpnoea, lethargy, diarrhoea and thirst). Blood test results indicative of lactic acidosis: pH<7.25 and lactic acid >5 mmol

Table 4. Use of intravascular contrast media in persons under treatment with metformin (Summary)

1. For patients at high risk of contrast nephropathy, such as patients with impaired renal function and diabetic patients, examinations not requiring iodinated contrast media, the use of a minimum volume of non-ionic low-osmolality contrast and discontinuation of drugs such as NSAIDs should be considered.
2. Intravascular contrast media is not contra-indicated in persons with normal renal function and receiving metformin.
3. Patient's renal function should be assessed before the investigation.
4. For patients with normal renal function, metformin should be discontinued at the time of the investigation and withheld for the subsequent 48 h.
5. For patients with abnormal renal function:
 - a) Alternative non-contrast examinations should be considered.
 - b) Patients who require administration of intravascular contrast media, their renal function should be re-evaluated in 24-48 h.
 - c) Clinicians may consider replacing metformin with other hypoglycaemic agents if patient's diabetic control is not satisfactory upon the withhold of metformin.
 - d) If metformin has not been discontinued before investigation, it must be taken off at the time of investigation, and reinstated only if the cause of renal impairment is reversible and renal function becomes normal on follow-up evaluation..

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