Metformin hydrochloride: The most prescribed treatment for type II diabetes - gets banned

Joan Vijetha R*, Kaviyarasan K, Annie Bhuvana Mary A, Gopinath N, Sam Daniel J, Vasanth B

School of Pharmacy, Sathyabama Institute of Science and Technology (Deemed to be University), Chennai – 600119, Tamilnadu, India

Article History:
Received on: 06 Jan 2024
Revised on: 18 Feb 2024
Accepted on: 20 Feb 2024

Abstract
Metformin hydrochloride (MH) is synthesis of N, N-dimethylguanidine medicament which is used for the treat of type-II diabetes which was discovered by Emil Werner and James Bell, which belongs to BCS class III. MH is chosen first-line oral blood glucose-lowering medication for the treatment of type-II diabetes, almost around 120 million patients are using worldwide. It works by decreasing the hepatic glucose production through a mild inhibition of mitochondrial respiration chain complex. MH which has been further tested and also proven that it can be used for various treatments such as, weight loss, improving fertility, slow the growth of tumour, anti-malaria, and few others. MH is synthesis from Galega officinalis which is a perennial plant that blooms in the summer and is native to most temperate areas. In this study, complete information about the drug history, drug profile, pharmacokinetic, drug interaction, clinical symptoms, advantages & disadvantages of MH and reason why its getting banned has been explained in detail.

Keywords:
Metformin hydrochloride (MH), Drug profile, pharmacokinetics, Banned drug

INTRODUCTION
The term diabetes mellitus is derived from the Greek word ‘diabetes’, which means ‘to pass through’, and the Latin word ‘mellitus’, which means ‘sweetened with honey. Diabetes mellitus is a long-term and diverse metabolic disorder with a complicated cause. It is marked by high blood sugar levels or hypoglycaemia, which comes from problems in either insulin production or insulin action or both [1]. Furthermore, there were other kinds, or classes, of drugs that reduced blood glucose, or blood sugar, in various ways. Non-insulin treatments include metformin, alpha-glucosidase inhibitors, bile acid sequestrants (BASs), dopamine-2 agonists, and DPP-4 inhibitors (gliptins), which are taken orally and others are injected.

Diabetes mellitus (DM)

Diabetes mellitus (DM) is a metabolic disorder in which the body does not create enough insulin or does not respond adequately to insulin, resulting in abnormally high blood sugar (glucose) levels. Diabetes is a major source of mortality as well as morbidity, albeit these results are not directly related to the condition. On the contrary, they are
associated with conditions that arise from long-term diabetes mellitus. These include disorders of the nerves as well as disorders of the large and small blood vessels, such as microvascular illnesses, which include renal and retinal vascular diseases, coronary heart disease, and peripheral arterial disease [2].

**Causes**

The pancreatic islets of Langerhans are cell clusters that house beta cells, which secrete the hormone insulin. Its function in the body is to cause cells to absorb glucose so they may use this sugar, which provides energy. Diabetes patients may have malfunctioning beta cells, resulting in decreased insulin secretion, or their muscle and adipose cells may be insulin resistant, resulting in a reduced ability of these cells to take up and utilize glucose [3]. In both circumstances, blood glucose levels rise, resulting in hyperglycemia. Excess glucose is eliminated in the urine if it accumulates in the blood. Because more glucose is excreted in the urine, more water is expelled with it, resulting in an increase in urinary volume, frequency of urination, and thirst.

**The role of glucose**

Glucose, a type of sugar, is the primary source of energy for cells in muscles and other tissues.

- Food and the liver are the main sources of glucose.
- Insulin helps sugar to enter the cells through the bloodstream.
- The liver can store or produce glucose depending on the body’s needs [4].

**Botanical background**

*Galega officinalis*, commonly known as galega or goat's-rue, as it boosts breast milk production, which is why it's known as 'Goat's Rue,' because young goat moms eat it and flourish. Is an herbaceous plant in the subfamily Faboideae of the legume family Fabaceae. It is native to parts of northern Africa, western Asia and Europe, but is widely cultivated and naturalised elsewhere [5]. The plant has been extensively cultivated as a forage crop, an ornamental, a bee plant, and as green manure. Herbaceous perennial growing to 1.2 m by 0.8 m at a fast rate. It is in flower from June to July, and the seeds ripen in August. The flowers are hermaphrodite (have both male and female organs) and are pollinated by insects. It can fix Nitrogen. Suitable for: light (sandy), medium (loamy) and heavy (clay) soils and can grow in nutritionally poor soil. Suitable pH: acid, neutral and basic (alkaline) soils. It can grow in semi-shade (light woodland) or no shade. It prefers moist soil. The flowering aerial parts of galega (Galegae herba) were used in the past to alleviate the polyuria associated with long-term hyperglycemia, but also to treat many other conditions from tuberculosis, bubonic plague, and malignant fevers to epilepsy, helminthiasis, and various infectious diseases [6].

![Figure 1: Galega officinalis](image)

**Characteristic [7]**

- Ground-based environment.
- The flower petals range in color from blue and purple to shades of pink, red, and white.
- The leaves exhibit a compound structure, composed of two or more distinct leaflets.
- The leaves are arranged alternately, with a single leaf per node along the stem.
- The leaf blade has an entire edge, devoid of teeth or lobes.
- The flower displays bilateral symmetry, with only one way to evenly divide it.
- The flower possesses a total of five petals, sepals, or tepals, or alternatively, it has a count of four.
- Either the petals or sepals are fused, forming a cup or tube structure.
- There are a total of 10 stamens.
- The fruit is of a dry nature and undergoes splitting upon reaching maturity.
- The length of the fruit ranges from 30 to 50 mm.
Taxonomical classification

Around 13th compound were isolated from *Galega officinalis* Linn. Among which the most common identified compounds are flavonoids (0.0972%) and their broad classification are listed in Table 1.

**Table 1 Taxonomical classification [8]**

<table>
<thead>
<tr>
<th>Biological name</th>
<th><em>Galega officinalis</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>kingdom</td>
<td>plantae</td>
</tr>
<tr>
<td>class</td>
<td>Dicotyledons</td>
</tr>
<tr>
<td>family</td>
<td>fabaceae</td>
</tr>
<tr>
<td>subfamily</td>
<td>faboideae</td>
</tr>
<tr>
<td>order</td>
<td>fabales</td>
</tr>
<tr>
<td>genus</td>
<td>Galega</td>
</tr>
<tr>
<td>Common name</td>
<td>Galega, goat’s-rue,</td>
</tr>
<tr>
<td></td>
<td>Milkpea, French Lilac</td>
</tr>
<tr>
<td>Distribution</td>
<td>North Africa, Pakistan, South America, Turkey and New Zealand</td>
</tr>
</tbody>
</table>

Pharmacokinetics

Absorption

- MH is given orally at a dosage of 500 mg, either twice daily or three times daily, with a total daily dose not exceeding 2,550 mg or around 35 mg per kilogram of body weight.
- The onset of action is approximately 1.5 hours, and the half-life in circulation ranges from 1.5 to 4.9 hours.
- Primarily absorbed in the upper segment of the small intestine, specifically in the jejunum [11].

Bioavailability

Approximately 50-60% of the substance is bioavailable.

Research involving varying MH tablet doses (ranging from 500 mg to 1500 mg and 850 mg to 2550 mg) indicates that as the dose increases, the drug’s absorption efficiency diminishes. This phenomenon has a more pronounced impact on the drug’s effects compared to its elimination from the body.

There are also various factors that affect absorption and bioavailability of MH such as Dose, Formulation, Age, Bodyweight, Kidney function and Food intake.
Table 3 Drug Profile [10]

<table>
<thead>
<tr>
<th>GENERIC NAME</th>
<th>Metformin hydrochloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAND NAME</td>
<td>Actoplus Met,</td>
</tr>
<tr>
<td></td>
<td>Avandamet, Portamet</td>
</tr>
<tr>
<td>USES</td>
<td>Antihyperglycemic drug</td>
</tr>
<tr>
<td>CHEMICAL FORMULA</td>
<td>C$<em>4$H$</em>{11}$N$_5$</td>
</tr>
<tr>
<td>STRUCTURE</td>
<td></td>
</tr>
</tbody>
</table>

| TYPE                | Small molecule          |
| MOLECULAR WEIGHT    | 129.16 g/mol            |
| SYNONYMS           | N,N-dimethylimidodicarbonimidic diamide |
|                     | 1,1-Dimethylbiguanide   |
|                     | Metiguanide             |
| CLASS              | Guanides (Biguanides)   |
| IUPAC NAME         | 3-(diaminomethylidene)- |
|                    | 1,1dimethylguanidine    |
| BOILING POINT      | 224.1ºC at 760 mmHg     |
| MELTING POINT      | 223-226 ºC             |
| SOLUBILITY         | Freely soluble          |
| SIDE EFFECTS       | Physical weakness, myalgia, nausea, vomiting, diarrhoea, flatulence, hypoglycemia, upper respiratory tract infection, abdominal pain, lactic acidosis, chest discomfort, chills and dizziness, constipation, heartburn, bloating. |
| CLEARANCE          | The renal clearance exceeds creatinine clearance by approximately 3.5 times, signifying that the primary pathway for MH elimination is through tubular secretion. |
| FOOD INTERACTIONS | Avoid alcohol. Take with food. Food reduces irritation. |

Distribution

Organic cation transporters facilitate the widespread distribution of the drug into various body tissues, including the intestine, liver, and kidney. MH doesn’t attach much to blood proteins like sulfonylureas do. It tends to gather in red blood cells over time. When people take regular MH doses, the amount of MH in their blood becomes steady within a day or two and is usually quite low, around less than 1 microgram per millilitres. Even with higher doses, like in clinical trials, the most MH in the blood doesn’t go above 5 micrograms per millilitres. Following a single oral dose of 850 mg MH, the apparent volume of distribution (V/F) averaged 654 ± 358 L [11].

- It doesn’t stick much to blood proteins, so it moves around freely.
- It gathers in organs like the liver and kidneys, where it works.
- MH doesn’t gets distributed to the brain very much because of its properties.
- MH can cross the placenta during pregnancy, but it does not accumulate significantly in the fetal tissues. But still a little amount is distributed into breast milk, but not too much.
- The places it goes affect how it leaves the body, mainly through the kidneys.

Metabolism

MH undergoes minimal metabolism in the body, which means it is not extensively broken down into different substances. Instead, the main route of excretion is through the kidneys.

Elimination

The primary way MH is eliminated from the body is through active tubular secretion in the kidneys. MH is removed from the body mainly through the kidneys, and certain proteins called transporters help move it around. These transporters, like OCT1 and OCT3, are found in liver cells and are crucial for MH uptake into the liver. Another transporter, MATE1, is important for moving MH out of the liver and kidneys. In the kidneys, transporters like OCT2, MATE1, and MATE2-K help get MH from the blood into the kidney cells and then into the urine. While MH isn’t changed in the liver, its movement can be affected by other drugs that interfere with these transporters. A recent study indicates a potential drug interaction between MH and certain tyrosine kinase inhibitors (e.g., imatinib, nilotinib, gefitinib, erlotinib). This could impact MH’s effectiveness, toxicity, and overall clinical outcomes [12].
Mechanism of action [14]

The organic cation transporter-1 (OCT1) took up MH and transported it into the hepatocyte. MH’s ionization and positive charge in the cells is due to the difference in hepatocyte pH and pKa, which causes it to accumulate in the cells. Furthermore, there are concentrations up to 1000 times higher in the mitochondria than in the extracellular medium. The membrane potential difference between the plasma membrane and the inner mitochondrial membrane, which has a positive charge on the outside, affects metformin’s capacity to enter the mitochondria. Once inside, metformin interferes with complex 1, causing ATP synthesis to decrease and AMP and ADP levels to rise. Inhibiting the respiratory chain has the consequence of increasing the ratio of ADP to ATP, which as seen in experimental cells involved in this process, slightly impairs the process of gluconeogenesis. Due to its high energy requirement, it also prevents hepatocytes from effectively synthesizing gluconeogenesis. Changes in the ratios of NAD+ to NADH are another effect that have a detrimental impact on gluconeogenesis.

Figure 2: MH mechanism of action

Clinical symptoms of MH

Gastrointestinal distress can lead to significant discomfort. This discomfort is most frequently experienced during the initial administration of MH or when the dosage is raised.

Starting at a lower dosage (1.0 to 1.7 g/day) and gradually increasing it can often prevent discomfort, although approximately 5% of individuals may still find metformin intolerable even at lower doses.

Utilizing slow or extended-release formulations may enhance tolerability.

Prolonged use of MH has been linked to elevated homocysteine levels and vitamin B12 malabsorption.

Increased doses and prolonged usage are correlated with a higher likelihood of vitamin B12 deficiency [1].

Over Dose leads to

An overdose of MH typically manifests with symptoms such as vomiting, diarrhea, abdominal pain, tachycardia, drowsiness, and, in rare cases, hypoglycemia or hyperglycemia.

Managing metformin overdose is primarily supportive, as there is no specific antidote identified. Severe overdoses may require extracorporeal treatments.

Extracorporeal treatments are recommended in severe cases due to metformin’s low molecular weight and absence of plasma protein binding. These methods effectively eliminate metformin from the blood plasma, preventing excessive lactate production.

Monitoring metformin levels in blood, plasma, or serum is useful for therapy management, confirming poisoning diagnoses, or aiding forensic death investigations.

Normal blood or plasma metformin concentrations range from 1 to 4 mg/L in individuals receiving therapeutic doses, 40 to 120 mg/L in cases of acute overdose, and 80 to 200 mg/L in fatalities.

Although a massive metformin overdose heightens the risk of metformin-associated lactic acidosis, even substantial doses often do not result in fatality [16].

Drug interaction

The H2-receptor antagonist cimetidine elevates MH plasma concentration by diminishing MH clearance through renal processes. Additionally, MH interacts with anticholinergic medications, influencing gastric motility.

Anticholinergic drugs, by decreasing gastric motility, extend the duration that drugs remain in the gastrointestinal tract.
This delay may result in a greater absorption of MH when an anticholinergic drug is present, consequently raising the plasma concentration of MH and amplifying the potential for adverse effects [17].

**Medicinal uses of MH**

MH was the first-choice oral treatment for type 2 diabetes and its various medicinal uses are shown in figure 3.

![Figure 3: Medicinal uses of MH](image)

**Advantages of MH [18]**

- MH can do much more than treat diabetes.
- MH can help with weight loss and reduce the size of your waist.
- MH can also improve fertility.
- It even helps people with certain medical conditions live longer.
- There's evidence that MH can help treat obesity and obesity-related conditions, like metabolic syndrome.
- MH can slow some tumor growth and stop certain tumors from forming.

**Disadvantage of MH [19]**

- Feeling queasy
- Sickness (vomiting)
- Take small, frequent sips of water or squash to avoid dehydration.
- Diarrhea.
- Stomach discomfort

- Appetite loss.
- A sensation of metallic taste in the tongue.

It's important to note that some side effects of MH may arise, typically not requiring immediate medical attention. These effects often diminish as the body adjusts to the medication. Healthcare professionals can offer guidance on preventive measures or ways to alleviate these side effects, such as addressing gastrointestinal irritation, impaired renal function, impaired hepatic function, pharmacologically treated congestive heart failure (CHF) and alcoholism.

**Why MH is being recalled**

According to the average rating out of 100%, 55% have given positive feedback and 45% have given negative feedback. And few documents shows that MH contains N-nitrosodimethylamine which may promotes cancer. Hence FDA has announced that to recall MH from market (July 2020). The maximum limit of N-nitrosodimethylamine can be consumed is 96 ng/day. But study shows that MH has excess amount, so it was banned [20].

**CONCLUSION**

Sixty years after its introduction in diabetes treatment, MH has become the most prescribed glucose-lowering medicine worldwide with the potential for further therapeutic applications. MH as the first-choice treatment for obese patients with type 2 diabetes. The drug’s anti-atherosclerotic and cardioprotective effects have been confirmed in prospective and retrospective studies, but it took another decade for these findings to be translated into official recommendations. In 2012 diabetes experts in the USA and Europe declared that MH is the drug of the first choice for all patients with type 2 diabetes. Furthermore, MH was banned by FDA, but still it is being continued to use for antidiabetic medication which is recommended by American Diabetes Association.

**ACKNOWLEDGEMENT:** I would like to thank to the Dean and management of the Sathyabama Institute of Science and Technology, School of Pharmacy, Semmancheri for their constant support and guidance for completing this review.

**Funding Support:** The Author declares that there is no funding.
Conflict of Interest: The Author declares that there is no conflict of interest.

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