Pharmacologic Update

The status of metformin in Canada

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During the 1970s two biguanide drugs, phenformin and metformin, were used to control hyperglycemia. Phenformin was phased out of the Canadian market because it carried an unacceptable risk of causing lactic acidosis, but metformin remains available. All documented cases of lactic acidosis associated with metformin administration, which are rare, have occurred abroad in patients who were taking the drug in spite of having contraindications to its use. The two drugs are metabolized differently, phenformin being deactivated and concentrated in the liver, and metformin being excreted rapidly, unchanged, by the kidneys. In properly selected diabetic patients therapeutic doses of metformin do not raise the blood levels of intermediary metabolites enough to induce ketoacidosis or lactic acidosis. The safety of the drug is supported by the clinical experience over about 56 000 patient-years in Canada.

Au cours des années 70, deux dérivés biguanides, la phenformine et la metformine, étaient utilisés pour maîtriser l'hyperglycémie. La phenformine fut retirée du marché canadien à cause du risque inacceptable d'acidose lactique qui lui était rattaché, mais la metformine est demeurée disponible. Tous les cas prouvés d'acidose lactique reliés à l'administration de metformine, une complication rare, sont survenus à l'étranger chez des patients qui prenaient ce médicament en dépit de contre-indications d'emploi. Les deux médicaments sont métabolisés différemment: la phenformine est désactivée et concentrée dans le foie, alors que la metformine est rapidement excrétée, inchangée, par le rein. Chez les diabétiques adéquatement choisis, les doses thérapeutiques de metformine n'augmentent pas suffisamment les taux sanguins des métabolites intermédiaires pour provoquer une acidocétose ou une acidose lactique. La sécurité de ce médicament repose sur une expérience clinique au Canada portant sur plus de 56 000 patients-années.

Metformin (1,1-dimethylbiguanide hydrochloride) was developed in the 1950s as an antihyperglycemic agent by Sterne and was first introduced for medical use in France in 1959.[1] Clinical trials were begun in Canada in the late 1960s,[2] and metformin was found to be useful and well tolerated in the control of hyperglycemia in obese individuals with non-insulin-dependent diabetes. It is to be used when the hyperglycemia cannot be controlled by dietary management, exercise and weight reduction or when insulin therapy is inappropriate. The hyperglycemia should be responsive, stable and mild, and not prone to lead to ketosis..

On the basis of experience with several hundred patients in Canada and abroad, metformin was cleared for marketing in Canada in 1972. It was already recognized as the least likely of the biguanides to induce the serious complication of lactic acidosis.[3] By the mid-1970s, however, there were numerous reports linking lactic acidosis with phenformin and buformin therapy.[4,5] This caused grave concern about the safety of all biguanides.

In the spring of 1977 the Canadian Diabetic Association advisory committee to the health protection branch of the Department of National Health and Welfare submitted to the branch a report on the benefits and risks of the two biguanides available in Canada: phenformin hydrochloride (DBI and DBI-TD) and metformin hydrochloride (Glucophage). The substance of the report was later published in *CMAJ*.[6] Of the approximately 130 000 diabetic patients who were then being treated with oral hypoglycemic drugs in Canada, some 15% were thought to be receiving a biguanide, especially phenformin. The diabetic population taking metformin in 1976 was estimated at 2000, and 75% of these patients were in the province of Quebec.

The advisory committee concluded that there was a limited justification but no absolute need for the use of biguanides in the treatment of diabetes mellitus. There was a risk, however, of lactic acidosis at even low therapeutic dosages of phenformin in the absence of demonstrable risk factors. Considering the relatively high risk of this serious complication and its mortality rate of 40% to 50%, the committee recommended withdrawal of phenformin products from the Canadian market.[6] The drug was phased out of the Canadian market over about 3 months without any notable complications or hardship. After August 1977 phenformin products were no longer distributed. The general marketing of phenformin in the United States ended in October of the same year.[7] While permitting metformin to remain on the Canadian market, the bureau of drugs concurred with the recommendations of the advisory committee regarding the introduction of specific guidelines for the use and monitoring of this drug.

From information provided by the drug manufacturer we can estimate the number of Canadian patients receiving metformin in 1977 at

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about 5300. The number gradually increased to reach about 11 600 in 1981. Metformin now appears to be used in some 9% of patients who are being given oral antidiabetic drugs. About 60% of patients taking metformin are in Quebec, 29% in Ontario and the Maritime provinces, and 11% in the western provinces.

In January 1978 the manufacturer of metformin launched an intensified program to monitor the clinical safety of the drug.[8] During 1978 and 1979 no cases of lactic acidosis were found.[9,10] Indeed, since the introduction of metformin in Canada in 1972, clinical experience with this drug has covered some 56 000 patient-years without a single documented case of lactic acidosis. In Sweden the estimate of the risk of lactic acidosis is 1 per 12 000 patient-years. The worldwide diabetic population receiving metformin therapy is approximately 6,50 000, yet only 28 cases of lactic acidosis have been associated with metformin therapy. All of these, however, were in patients who had contraindications to the drug. The Canadian safety record with metformin is probably due to the limitation of the maximum daily dose to 2.5 g and strict observance of the prescribing recommendations.

Mode of action

The antihyperglycemic effect of metformin is demonstrable only in diabetic subjects, and only in the presence of insulin.[1,11] Therapeutic doses of the drug do not cause hypoglycemia, and metformin has no effect on pancreatic β-cells. These observations suggest some form of action at the cellular level.[1,11,12]

Metformin shifts the blood glucose level towards normal, reduces the blood level of immunoreactive insulin and improves the response to glucose tolerance tests in obese persons with responsive non-insulin-dependent diabetes.[1,2,12-15] In certain persons with insulin-resistant diabetes who require very high doses of exogenous insulin, metformin seems to improve the clinical response and reduce the daily insulin requirements.[1]

The mode of metformin's antihyperglycemic action and improvement of insulin utilization has been in dispute for many years. Holle and colleagues[16] have recently shown that the number of insulin receptors on the surface of membranes of human erythrocytes increases following metformin treatment. Using other cell lines derived from human lymphocytes and breast carcinomas Vigneri and coworkers[17] have shown that both metformin and phenformin enhance the binding of insulin to the receptors. They attribute this to changes in the affinity of the receptors rather than to an increase in the number of insulin-binding sites or in receptor synthesis. Comparable changes in cellular binding of insulin apparently do not occur with sulfonylureas. The interaction of metformin with cell membranes may well be partly responsible for the decrease in the organism's resistance to insulin and also for the improved utilization of insulin, whether endogenous or exogenous.

The effects of metformin therapy on lipid metabolism remain controversial. In some studies a reduction in plasma triglyceride levels and to a lesser extent plasma cholesterol levels has been noted. It has also been suggested that the drug has an effect on the metabolism of very-low-density lipoprotein,[18] although no consistent changes in blood lipid levels could be found in other investigations.[19]

Pharmacokinetics and metabolism

In humans metformin does not appear to be metabolized. Its bioavailability at therapeutic doses reaches 50% to 60%[20] but may drop as the dose is increased.[21] Intestinal absorption of the drug may extend over some 6 hours. The maximum blood concentration at a steady state after an oral dose of 0.5 g ranges between 2 and 4 μg/ml. The peak level is reached between 1 and 3 hours after the oral dose.

In the blood metformin is usually found in a free form with a low or negligible association with proteins. It is excreted mainly by the kidneys. The clearance of the drug in healthy subjects and in diabetic patients with normal renal function is about four times the creatinine clearance, which suggests that active tubular secretion is a significant mechanism of elimination.[22,23] In diabetics, as in healthy subjects, metformin is at first rapidly cleared from the blood during a phase in which the drug's half-life ranges between 1.7 and 3 hours. A rather slow terminal phase becomes manifest about 12 hours after the oral dose; it has been estimated to contribute to the clearance of only 4% to 5% of the drug, which then has a half-life of between 9 and 17 hours. Data obtained through intravenous administration of metformin labelled with carbon 14 suggest a mean volume of distribution of approximately 9.9 l. The cellular uptake of the drug appears to depend more on time than on concentration.

The drug is also excreted by the salivary glands.[20] Its concentration is markedly lower in saliva than in plasma, and it is cleared slowly, with a half-life of about 9 hours.[20] The unpleasant taste that patients experience is attributed to the presence of metformin in their saliva. Intravenous metabolic studies have shown that metformin is not eliminated by the gastrointestinal tract to any significant extent.

According to Noel[21] the transfer of metformin into the deep (tissue) compartment is some 10 times slower than its elimination by the kidneys. In patients with adequate renal function, then, the recommended dose, given orally two or three times daily, should not lead to a significant accumulation of the drug. Functional impairment of the kidneys, however, retards elimination and can thus produce an excessive accumulation of metformin in the tissues, which may have toxic manifestations if the dosage is not reduced.

Clinical observations and experimental evidence indicate that metformin, like other biguanides, tends to inhibit gluconeogenesis, mitochondrial oxidative phosphorylation and respiration. This inhibition appears to be primarily in energy-consuming reactions, with reduction of adenosine triphosphate formation and a negative shift of the nicotinamide adenine dinucleotide redox potential ($NADH/NAD^+$).[1,11,12,24] Inhibition of hepatic gluconeogenesis is associated with increased blood lactate levels. In this regard metformin appears to act synergistically with ethanol.[25] Metabolic studies in some patients receiving metformin

have shown an increase in the blood lactate and pyruvate levels, as well as in the ratio of these two metabolites.[12,13,24,26] An increase in the ratio of β-hydroxybutyrate to acetoacetate has also been noted. These observations can be attributed to the binding of biguanide to the mitochondrial membrane. Disturbed mitochondrial oxidation of the reduced form of nicotinamide adenine dinucleotide may account for the increase in the β-hydroxybutyrate/acetoacetate ratio.

Although the effects of all biguanides upon cellular or subcellular membranes are probably similar in their nature, the magnitude of the effects appears to be related to the length of the molecule's side chain.[12,27] Phenformin, for instance, has a long side chain. It is inactivated by hepatic microsomal hydroxylation, and high concentrations of this drug are found in the liver.[27] Metformin, on the other hand, possesses short methyl side chains, and the molecule is not concentrated in the liver but is excreted via the kidneys, without metabolic transformation. These differences in metabolism and distribution apparently account for metformin's relatively high degree of clinical safety.

Effects on lactate metabolism

The main sources of the lactic acid in the systemic circulation are skeletal muscle, erythrocytes and brain tissue. The influx of hydrogen ions lowers plasma bicarbonate levels, which would normally be restored as the lactate is removed by the liver and kidneys for conversion to glucose or for complete oxidation. Lactic acidosis can result from overproduction of lactic acid, failure of the liver or kidneys to remove lactate or a combination of these events. In diabetic subjects an acute illness or some other event may impair tissue perfusion or accentuate arterial desaturation and lead to relative hypoxia of the tissues.

Metformin's effect on lactate metabolism has been extensively investigated.[1,4,11,13,28-31] The principal risk factor in the precipitation of lactic acidosis is impaired renal function. If the kidneys are not removing metformin, the drug accumulates in the body and there is impairment of cellular functions. Other risk factors include advanced age and acute tissue hypoxia, whether provoked by trauma, anesthesia, surgery, cardiopulmonary insufficiency, angiography, pyelography, severe infection or dehydration. Alcohol consumption and hepatic insufficiency are contributory factors. It is possible that tetracycline therapy can play a part in the precipitation of biguanide-induced lactic acidosis.[31]

Lactic acidosis is a potentially lethal metabolic condition. It is characterized by an arterial pH of less than 7.2, lactic acid blood levels above 7 mmol/l, an anion gap ($[(Na^+) + (K^+)] - [(Cl^-) + (HCO_3^-)]$) of more than 12 mmol/l, a serum bicarbonate level under 15 mmol/l and a markedly increased lactate/pyruvate ratio, but an absence of significant ketoacidosis. The blood glucose level is frequently low and only occasionally high.[12,22,28]

In a group of individuals with non-insulin-dependent diabetes and normal renal function who were being treated with metformin the mean blood lactate level was reported as 1.6 mmol/l and the range as 0.6 to 4.2 mmol/l.[24] Stowers[13] studied 13 patients with moderate functional impairment of the kidneys (urea nitrogen levels 9.5 to 27 [mean 14.4] mmol/l) who were also receiving metformin. Their blood lactate values 2 hours after breakfast ranged between 0.77 and 4.08 (mean 1.94) mmol/l. Stowers noted that in spite of the moderate impairment of renal function in these patients, and despite some increase in blood lactate and pyruvate levels, symptomatic lactic acidosis did not occur. This was attributed to the biphasic pattern of metformin excretion. The rapid initial phase seemed to provide a good margin of safety and did not induce a metabolic burden with toxic consequences. However, these observations do not diminish the need for appropriate patient selection and follow-up. Physicians are advised to refer to the product monograph for metformin for detailed recommendations on contraindications, precautions and dosages.

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