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Use of Metformin in Pediatric Patients

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Metformin was approved by the Food and Drug Administration (FDA) for use in adults with type 2 diabetes in 1994. It has since become one of the most widely prescribed agents for this disease. In December 2000, the FDA approved the use of metformin for pediatric patients 10 years of age or older with type 2 diabetes. Pediatric dosing information was added to the labeling of the combination of metformin and glyburide in March 2004.[1] Metformin, a biguanide oral hypoglycemic agent, acts by decreasing hepatic glucose production, decreasing intestinal absorption of glucose, and increasing insulin sensitivity. This issue of *Pediatric Pharmacotherapy* will review the studies of metformin in pediatric patients and provide a brief overview of its pharmacology and dosing in this population.

Clinical Use in Children

The benefit of metformin was first demonstrated in children identified as at risk for the development of type 2 diabetes, those with both fasting hyperinsulinemia and a positive family history. In 2001, Freemark and Bursey conducted a randomized, placebo-controlled, double-blind trial in 29 obese adolescents (ages 12-19 years) with known risk factors for diabetes.[2] All subjects had a body mass index (BMI) greater than 30 kg/m^2, a fasting insulin concentration greater than 15 microunits/ml, and a first or second degree relative with type 2 diabetes. All had fasting glucose concentrations less than 110 mg% and a hemoglobin A_{1c} less than 6%. Patients received either metformin 500 mg twice daily or placebo for 6 months.

Metformin administration resulted in a 1.3% decline in BMI compared to baseline. The average BMI value rose by 2.3% in the placebo group. Treatment resulted in a decline in fasting blood glucose (84.9 to 75.1 mg%) and fasting insulin levels (31.3 to 19.3 microunit/ml), while blood glucose rose slightly in the placebo group and insulin levels remained unchanged. There were no significant changes in hemoglobin A_{1c}, serum lipids, or lactate in either group. Based on their results, the authors concluded that metformin may be considered as an adjunct to diet and exercise in adolescents at risk for type 2 diabetes.

In 2002, Jones and colleagues conducted a multicenter, randomized, placebo-controlled, double-blind study of metformin in 82 children, ages 8 to 16 years, with type 2 diabetes.[3] Patients received either metformin, initiated at 500 mg twice daily and titrated up to a maximum of 2000 mg/day based on response, or placebo for up to 16 weeks. The study was unblinded after interim analysis upon recommendation of an independent review board and continued as an open-label trial. At the final blinded visit, the adjusted mean change from baseline in fasting plasma glucose was -2.4 mmol/L (-42.9 mg/dl) for the metformin group, compared to +1.2 mmol/L (+21.4 mg/dl) in the placebo group. Mean hemoglobin A_{1c} values were also lower in the metformin group (7.5% versus 8.6% with placebo). Both results were statistically significant. Rescue medication was required to control hyperglycemia in 26 (65%) of the placebo patients, versus 4 (9.5%) of the metformin subjects. The authors concluded that metformin was an effective therapy for adolescents with type 2 diabetes.

The combination of metformin and glyburide has also been studied in the pediatric population. A total of 167 children (9-16 years of age) were enrolled in a 26-week study comparing the combination to either agent given alone. The

combination produced an average change in hemoglobin A_{1c} of –0.86%, not significantly different than either single agent used alone.[1]

In addition to its use in type 2 diabetes, metformin has also been studied as an adjunctive therapy in adolescents with type 1 diabetes.[4-6] In 2002, Gomez and colleagues conducted a six month open-label trial of metformin in 10 adolescents and young adults with type 1 diabetes.[4] Metformin was initiated at a low dose (250 mg twice daily) and increased to a maximum of 2500 mg/day. Insulin dosages were reduced as needed to prevent hypoglycemia. Seven patients exhibited a significant decrease in hemoglobin A_{1c}. There was no change in insulin dose, BMI, or lipid levels in the study subjects.

Two randomized, placebo-controlled trials of metformin in type 1 diabetic patients were published last year. Hamilton and coworkers studied 27 adolescents (12-17 years of age) over a three month period.[5] At the end of the study period, the average hemoglobin A_{1c} was 0.6% lower in the metformin group than in the placebo group. Insulin dosages were also significantly lower in the metformin group. There was no significant difference in BMI or in insulin sensitivity. Mild hypoglycemia was more frequent in the metformin group (1.75 ± 0.8 versus 0.9 ± 0.4 events/patient/week in the placebo group). The incidence of severe hypoglycemic episodes and gastrointestinal adverse effects was similar in both groups.

A second trial, conducted in five cities in Sweden, showed similar results.[6] Twenty-six adolescents (mean age 16.9 ± 1.6 years) with type 1 diabetes were evaluated over a three month period. Metformin was initiated at 500 mg once daily and titrated up to 1000 mg twice daily. Hemoglobin A_{1c} decreased significantly in the metformin group (from 9.6% to 8.7%), while remaining unchanged in the placebo group. Peripheral glucose uptake divided by mean plasma insulin concentration was also increased in the metformin group, but not with placebo. Patients with decreased initial insulin sensitivity showed the greatest benefit from metformin. There were no significant differences in insulin dosage or BMI. The authors of both papers concluded that metformin may be useful in type 1 diabetic patients as an adjunct to insulin.

In addition to its use in diabetic patients, metformin has also been studied in normoglycemic adolescents and adults to produce weight loss or aid in weight control.[7] Kay and colleagues from the University of Tennessee found enhanced insulin sensitivity, as well as significant reductions in body fat, plasma leptin, cholesterol, triglycerides, and free fatty acid levels in 12 hyperinsulinemic nondiabetic obese adolescents given metformin 850 mg twice daily, compared to 12 controls given placebo for 8 weeks. Both groups had been placed on a low-calorie diet.

In addition, metformin has been studied as an adjunct in patients receiving psychotropic drugs known to cause significant weight gain, including atypical antipsychotics. Morrison and colleagues studied the effects of metformin in 19 adolescents between 10 and 18 years of age receiving olanzapine, risperidone, quetiapine, or valproate.[8] In this 12-week open-label trial, patients were given metformin at a dose of 500 mg three times daily. At the end of the observation period, 15 patients had lost weight, three had gained weight, and one patient's weight was unchanged. The mean weight change for the group was -2.93 kg, and the mean reduction in BMI was -2.22 kg/m^2.

Metformin has also been useful in the treatment of adolescent females with polycystic ovary syndrome, although its role in this condition remains controversial. To date, three small studies have been published.[9-11] In 2001, Ibanez and colleagues conducted an open-label 6-month trial of metformin in 18 nonobese anovulatory female adolescents.[9] Doses were titrated to a maximum of 1275 mg/day. By the end of the study, all patients were having regular menses. Ovulation occurred in 78%. Similar results were observed in two subsequent open-label trials, suggesting a potential role for metformin.[10,11] At this time, however, no placebo-controlled trials have been conducted in this population.

Pharmacokinetics

The absolute bioavailability of oral metformin is 50 to 60%. In adults, the volume of distribution is approximately 650 L. Metformin undergoes little protein binding and is excreted unchanged in the urine. It does not undergo hepatic metabolism. The elimination half-life in adults is approximately 6 hours. Preliminary pediatric pharmacokinetic studies have shown results similar to those in adults.[12-14]

Drug Interactions

Cationic drugs that are eliminated by renal tubular secretion may compete with metformin for elimination. Examples of these agents include amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin. Patients receiving metformin with these agents should be monitored for potential toxicity.[12-14]

Metformin plasma concentrations may also be increased by concurrent administration of cimetidine, furosemide, or nifedipine. The administration of iodinated contrast media may produce acute renal failure, placing patients receiving metformin at risk for drug accumulation and lactic acidosis. It is recommended that metformin be discontinued at least 48 hours prior to the procedure and restarted only after renal function has been shown to be normal.[12-14]

Adverse Effects

The most commonly reported adverse effects following metformin use are nausea (occurring in 53% of adult study patients), vomiting (6-25%), abdominal pain and gas (6-12%), asthenia (9%), diarrhea (6-9%), and headache (6%). These effects are generally transient. Adverse effects reported in 1-5% of study subjects include hypoglycemia, myalgia, lightheadedness, dyspnea, rash, nail changes, diaphoresis, altered taste, chest discomfort, chills, flu-like symptoms, and palpitations.[12-14] Studies in adolescents have shown comparable results. In the paper by Freemark and Bursey, 40% of the patients reported abdominal discomfort or diarrhea.[2] Jones and colleagues reported the same adverse effects in 25% in their patients.[3]

In patients with underlying renal, hepatic, respiratory, or cardiac dysfunction, the administration of metformin may produce lactic acidosis. Although the estimated incidence of lactic acidosis in patients receiving metformin is very low, 0.03 cases/1000 patient-years, the risk of mortality in those patients is approximately 50%. As a result, metformin is considered contraindicated in these populations. All patients receiving metformin should be aware of the potential for lactic acidosis. Symptoms of malaise, myalgias, difficulty breathing, lethargy, and abdominal pain should immediately be reported to a health care provider.[12-14]

Dosing and Availability

Metformin is available as Glucophage® or a generic product in 500, 850, and 1000 mg tablet strengths. It is also marketed as 500 and 750 mg extended release tablets (Glucophage XR® or generic). The combination of glyburide and metformin (Glucovance® or generic) is available in three strengths: 1.25 mg glyburide/250 mg metformin, 2.5 mg glyburide/500 mg metformin, and 5 mg glyburide/500 mg metformin.[12-14]

For children 10 to 16 years of age, the recommended starting dose of metformin is 500 mg given once daily. If this dose fails to produce adequate results, the dose may be increased to 500 mg twice daily. Further increases may be made in 500 mg increments to a maximum daily dose of 2000 mg. Metformin may be administered with food to decrease nausea.[12-14]

In adults, metformin is typically started at 500 mg given twice daily or 850 mg given once daily. The extended release product should be initiated at a dose of 500 mg once daily, given with the evening meal. The maximum recommended dose of metformin in adults is 2550 mg/day, or 2000 mg/day of the extended release product.[12-14]

Summary

Metformin provides a new option for the management of adolescents with type 2 diabetes. It may also be useful as an adjunctive therapy in children with type 1 diabetes or obesity. In addition, metformin has been used in a variety of other conditions, including polycystic ovary syndrome and to control weight gain in pediatric patients receiving atypical antipsychotics. While initial studies with metformin in children and adolescents have been favorable, more research is needed to establish the efficacy and safety of long-term use in the pediatric population.

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Pharmacology Literature Review

Oxycodone Pharmacokinetics

The pharmacokinetic profile of oxycodone was studied in 40 children (ages 6-93 months) undergoing surgery. While under anesthesia, patients received a single 0.1 mg/kg dose of oxycodone either intravenously (IV), intramuscularly (IM), buccally, or through a nasogastric tube into the stomach. Blood samples were collected over the next 12 hours. Peak drug concentrations were approximately twice as high after IV administration than after IM dosing (mean 82 versus 34 mcg/L) and were considerably higher than buccal or gastric administration (9.8 and 0.2 mcg/L, respectively). Terminal elimination half-life was approximately 150 minutes in all groups. The authors concluded that the pharmacokinetic parameters of oxycodone in children were similar to those observed in adults. While IM administration provided a relatively constant rate of drug absorption, concentrations after buccal or gastric administration were highly variable. Kokki H, Rasanen I, Reinikainen M, et al. Pharmacokinetics of oxycodone after intravenous, buccal, intramuscular and gastric administration in children. **Clin Pharmacokinet 2004;43:613-22.**

Weight Gain with Atypical Antipsychotics

A retrospective study of 103 children and adolescents receiving either olanzapine or quetiapine was conducted to evaluate the effects of these agents on weight gain and body mass index (BMI). Baseline measurements were compared with results after a minimum of two weeks of treatment. Patients receiving olanzapine gained an average of 3.8 kg, with an average increase in BMI of 1.3 kg/m^2. Quetiapine, as expected, produced less weight gain, an average of 0.03 kg. The patients receiving quetiapine had a mean decrease in BMI of 0.2 mg/m^2. The authors suggest that the likelihood for weight gain be carefully considered when selecting an atypical antipsychotic for pediatric patients. Patel NC, Kistler JS, James EB, et al. A retrospective analysis of the short-term effects of olanzapine and quetiapine on weight and body mass index in children and adolescents. **Pharmacotherapy 2004;24:824-30.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee during their meeting on 6/25/04:

1. Memantine (Namenda®) was added to both the Inpatient and Outpatient Formularies for use in patients with moderate to severe Alzheimer's disease.
2. Ribavirin (Rebetol®) was added to the Inpatient Formulary for use with an interferon in the treatment of chronic hepatitis C.
3. Sildenafil (Viagra®) was added to the Inpatient Formulary for use in patients with pulmonary hypertension. It was added to the Outpatient Formulary for use in erectile dysfunction or pulmonary hypertension.
4. The restriction on the use of high dose aldesleukin was amended to include select patients with metastatic renal cell carcinoma or melanoma.
5. As a result of the annual Formulary review, chlorzoxazone, metoproterenol, metaraminol, and pirbuterol inhaler were deleted from the Inpatient Formulary because of lack of use. Muromonab-CD3 (Orthoclone OKT3®) was removed from the Formulary due to limited use. It may be ordered for individual patients. Nefazodone (Serzone® or generic) was removed from the Formulary due to reports of hepatoxicity and lack of use.
6. The restrictions on oxcarbazepine, tiagabine, topiramate, and zonisamide were amended to include prescribing by the Pain Service.
7. Propoxyphene/acetaminophen (Darvocet-N 100® or generic) was added to the Outpatient Formulary. Propoxyphene was deleted.
8. Tositumomab and Iodine ^{131}I-tositumomab (Bexxar™) was added to the Outpatient Formulary, with restriction to patients with CD20-positive, follicular non-Hodgkin's lymphoma refractory to other therapies.

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