Review of the use of oral hypoglycaemics in Children

Alfred Sackeyfio BPharm(Hons), PG Dip Health Economics
MRPharmS, M GhC.
Manchester
United Kingdom
alsacks07@gmail.com
BACKGROUND:

The frequency of diabetes is rising around the world, and studies are showing children are at increasing risk of developing the disease. More than 180 million people worldwide have the illness, a number likely to more than doubled by 2030 without intervention, according to estimates released in 2004. The reasons for the growing threat are not fully understood. Over time, diabetes can damage the heart, blood vessels, eyes, kidneys and nerves - causing chronic problems and early death. (WHO 2010)

In 2004 it was estimated that, worldwide, more than 22 million children under the age of five years were obese or overweight, and more than 17 million of them are in developing countries. Each of these children is at risk of developing type 2 diabetes (WHO 2004). Type 2 diabetes in children and adolescents is becoming an increasingly important public health issue throughout the world.(Miller and Silverstein 2006)

Changes in food consumption and exercise are fuelling a worldwide increase in obesity in children and adolescents.(Kiess et al. 2003). As a consequence of this dramatic development, an increasing rate of type 2 diabetes mellitus has been recorded in the USA and, more recently in many countries round the world(Kiess, Bottner, Raile, Kapellen, Muller, Galler, Paschke, & Wabitsch 2003).

Certain ethnic groups show particularly high prevalence of glycemic abnormality among young persons and diabetes prevalence appears to be increasing. In U.K. the risk of type 2 diabetes is 13.5 times greater among Asian than white children

Other reports indicate that increasing rates of type s diabetes with concurrent obesity are also being observed in children in Thailand, China, India, New Zealand, Australia and throughout Europe(Miller & Silverstein 2006)

This document is a review of the evidence of the effectiveness and safety of oral hypoglycaemic agents for the WHO essential medicines list. The usual
definition of age ranges would be 0 to 28 days for neonates, 1 to 12 months infants and 1 to 12 years child. In certain cases the BNF for children gives dosages for children up to the age of 18 years.

**MEDICINES AND INDICATIONS**

Hypoglycaemic agents are also known as anti diabetic medicines. The oral medicines include Alpha-glucosidase inhibitors, such as acarbose; Amylin analogues, such as pramlintide; Biguanides such as metformin Dipeptidylpeptidase-4 inhibitors such as sitagliptin; Meglitinides such as repaglinide and mitiglinide; Sulfonylureas such as glibenclamide, glimepiride, and gliclazide; and then the thiazolidinediones such as pioglitazone and rosiglitazone.

Oral antidiabetic drugs are used for the treatment of type 2 diabetes mellitus which is normally associated with insulin resistance and obesity. They should be prescribed only if the patient fails to respond adequately to at least 3 months’ restriction of energy and carbohydrate intake and an increase in physical activity. They should be used to augment the effect of diet and exercise, and not to replace them. (Martindale 2010).

There is also type 1 diabetes which is usually managed with insulin. However there have been some investigations in the management of children with type 1 diabetes and the addition of insulin sensitizers such as metformin and rosiglitazone to insulin to increase patient benefit (Jefferies et al. 2004;Stone et al. 2008).

Both the Martindale and the British National Formulary for children have lists of dosages and indications for the oral antidiabetic medicines as they are used in children.

The (BNFc 2010) states that the starting dose for metformin in 8 to 10 year olds should be 200mg daily increasing to a maximum of 2g daily. Children between the age of 10 and 18 years should be given an initial dose of 500mg daily to a maximum of 2g daily The BNFc goes on to state that these should
be given under specialist supervision only. It is also not licensed in children under the age of 10 years.

The (BNFc 2010) also gives doses for glibenclamide and gliclazide in children between the age of 12 and 18 years. Both medications should be given for type 2 diabetes mellitus, maturity onset diabetes of the young. They should be given under specialist management only.

Glibenclamide- 2.5mg daily increasing to a maximum daily dose of 15 mg daily

Gliclazide - 20mg daily increasing to a maximum daily dose of 160mg

It also says that both these medicines are not licensed for children. (Martindale 2010) also states that there is limited experience with the use of sulfonylureas in children. It makes reference to (Gottschalk et al. 2007) a study which is reviewed in this document. Both the Martindale and children's BNF do not recommend the thiazolidinediones for children.

**PHARMACOKINETICS**

Metformin hydrochloride is slowly and incompletely absorbed from the gastrointestinal tract; the absolute bioavailability of a single 500-mg dose is reported to be about 50 to 60%, although this is reduced somewhat if taken with food. Protein binding in plasma is negligible. Metformin is excreted unchanged in the urine. The plasma elimination half-life is reported to range from about 2 to 6 hours. Metformin crosses the placenta and is distributed into breast milk in small amounts. (Martindale 2010)

Glibenclamide is readily absorbed from the gastrointestinal tract and peak plasma concentrations usually occur within 2 to 4 hours. It is extensively bound to plasma proteins. Absorption may be slower in hyperglycaemic patients and may differ according to the particle size of the preparation used. It is metabolised, almost completely, in the liver, the principal metabolite being only very weakly active. About 50% of a dose is excreted in the urine and 50% via the bile into the faeces. (Martindale 2010)
Gliclazide is readily absorbed from the gastrointestinal tract. It is extensively bound to plasma proteins. The half-life is about 10 to 12 hours. Gliclazide is extensively metabolised in the liver to metabolites that have no significant hypoglycaemic activity. Metabolites and a small amount of unchanged drug are excreted in the urine. (Martindale 2010)

**CLINICAL EFFECTIVENESS REVIEW**

**Literature Searches and Methodology**

Medline (1950-October 2010), the Cochrane database of systematic reviews and the guideline clearing house were searched to identify all published papers and that described the use of the oral antidiabetics in children from birth to the age of 19 years. Alpha-glucosidase inhibitors, acarbose; Amylin analogues, pramlintide, biguanides, metformin dipeptidylpeptidase-4 inhibitors, sitagliptin, meglitinides, repaglinide and mitiglinide, sulfonylureas, glibenclamide, gllimepiride, gliclazide, thiazolidinediones, pioglitazone, rosiglitazone, child, children, p(a)ediatric, young, adolescent, diabetes mellitus, insulin resistance, type 1 and type 2 and pharmacokinetics were included as search terms. References of the retrieved articles were reviewed to identify any papers and studies which were not identified through the database search but which were relevant. Summaries of the evidence were assessed by outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria when appropriate. The criteria are limitations, indirectness, imprecision, inconsistency and other considerations. Evidence is graded high quality, moderate quality, low quality and very low quality. There is some more information on the GRADE criteria on the GRADE working group website http://www.gradeworkinggroup.org/

**EFFICACY**

The following covariates which represent the critical clinical outcomes have been evaluated HbA$_{1c}$ level reduction, insulin resistance(plasma fasting insulin), obesity as measured by the body mass index (BMI)
**HbA$_{1c}$ Levels**

One systematic review (Kane et al. 2005) reviewed the utility of metformin, glyburide, glipizide, acarbose and rosiglitazone in reducing HbA$_{1c}$ levels in children age between 4 months and 19 years. These patients had been diagnosed as type 2 diabetes patients.

For metformin, (Kane et al 2005) reported a reduction of HbA$_{1c}$ levels ranging between 0.8% and 4.4%. They had been followed up from 16 weeks to 6 months and their ages were between 8 and 18 years. The dose was 1g twice daily for most participants. Although the authors concluded that metformin is effective they also commented that monotherapy in this population would unlikely to be enough for sustained effects.

**Summary of Metformin effects on HbA$_{1c}$ levels.**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Age Range yrs</th>
<th>Number of patients</th>
<th>Dose Range</th>
<th>HbA$_{1c}$ reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>8-18</td>
<td>142</td>
<td>1g bd</td>
<td>0.8%-4.4%</td>
</tr>
</tbody>
</table>

(Kane et al 2005) also reviewed the use of acarbose at a daily dose of between 50mg and 300mg for the reduction of HbA$_{1c}$ levels. The range of the patients ages were 5 to 19 years. The reduction of HbA$_{1c}$ was from 1.1% to 2.3%. This study was conducted in 85 participants. The follow up for these set of patients ranged from 1 day to 135 days.

**Quality of Evidence**

As far as this outcome was concerned, quality of evidence was graded low. This was due to the fact that there was a lot of heterogeneity in follow up, Follow up was not long enough and the sample size(85) for this outcome using acarbose was too small to determine efficient and precise results.
Summary of Acarbose effects on HbA1c levels

<table>
<thead>
<tr>
<th>Medication</th>
<th>Age Range</th>
<th>Number of patients</th>
<th>Dose Range</th>
<th>HbA1c reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acarbose</td>
<td>5-19 years</td>
<td>85</td>
<td>50mg -300mg</td>
<td>1.1%-2.3%</td>
</tr>
</tbody>
</table>

No results were presented for rosiglitazone and pioglitazone for reduction of HbA1c levels in the Kane et al review.

Insulin resistance

Two systematic reviews analysed insulin resistance as measured by homeostasis model assessment of insulin resistance (HOMA-IR) and plasma fasting insulin. (Park et al. 2009; Quinn et al. 2010)

Quinn et al presented a pooled mean difference of -2.65(-3.59,-1.71) while Park et al determined the pooled mean difference to be -2.01(-3.26,-0.75). Both results were statistically significant. For plasma fasting insulin, the pooled mean differences were -9.63(-13.01, -6.25) and -5.3(-11.96, 1.36) respectively. Only the Quinn result was significant. The metformin doses were between 1g and 2g daily. The age group for this population was 6 to 19 years.

Quality of Evidence

In evaluating the evidence using GRADE, the quality of evidence was adjudged to be low this was due to the fact that there was some imprecision due to the fact that the sample size did not have enough power to detect a precise mean difference (wide confidence intervals). One limitation which was identified was also due to generalisability. The trial populations were not entirely representative of those in whom the essential list would apply. They did not included patients from South America, Africa, and Asia. There was also heterogeneity in the metformin doses ranging from 1g daily to 2g daily.
### Summary of systematic reviews of metformin effects on HOMA-IR

<table>
<thead>
<tr>
<th>Review</th>
<th>Age Range</th>
<th>Number of patients</th>
<th>Dose</th>
<th>HOMA-IR pooled difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park et al 2009</td>
<td>6-18 years</td>
<td>234</td>
<td>1g-2g daily</td>
<td>-2.01(-3.26,-0.75)</td>
</tr>
<tr>
<td>Quinn et al 2010</td>
<td>9-19 years</td>
<td>173</td>
<td>1g-2g daily</td>
<td>-2.65(-3.59,-1.71)</td>
</tr>
</tbody>
</table>

### Summary of metformin effects on Plasma fasting insulin

<table>
<thead>
<tr>
<th>Review</th>
<th>Age Range</th>
<th>Number of patients</th>
<th>Dose</th>
<th>Plasma fasting insulin pooled difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park et al 2009</td>
<td>6-18 years</td>
<td>257</td>
<td>1g-2g daily</td>
<td>-5.3(-11.96,1.36)</td>
</tr>
<tr>
<td>Quinn et al 2010</td>
<td>9-19 years</td>
<td>173</td>
<td>1g-2g daily</td>
<td>-9.63(-13.01, -6.25)</td>
</tr>
</tbody>
</table>

### Obesity

Two systematic reviews were identified (Park, Kinra, Ward, White, & Viner 2009; Quinn, Baur, Garnett, & Cowell 2010). They reviewed the utility of metformin in managing obesity as measured by reduction in BMI in children compared with a placebo in participants from the ages of 6 to 19 years. Both reviews compared metformin to placebo in children populations from USA, Australia, Turkey from the same studies (Park et al 2009 included one more
study than Quinn et al 2010). The pooled mean differences were -1.68(-2.25,-1.10) and -1.42(-2.02,-0.83) for Quinn et al and Park et al respectively.

Quality of Evidence:

In evaluating the evidence using GRADE, the quality of evidence was adjudged to be low this was due to the fact that there was some imprecision due to the fact that the sample size did not have enough power to detect a precise mean difference (wide confidence intervals). One limitation which was identified was also due to generalisability. The trial populations were not entirely representative of those in whom the essential list would apply. They did not included patients from South America, Africa, and Asia. There was also heterogeneity regarding the dose of metformin administered. Some were on 1g daily while others were on the maximum of 2g.

Summary of metformin effects on BMI

<table>
<thead>
<tr>
<th>Review</th>
<th>Age range</th>
<th>Number of patients</th>
<th>Dose</th>
<th>BMI reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park et al 2009</td>
<td>6-19</td>
<td>342</td>
<td>1g-2g daily</td>
<td>1.42kg/m² (-2.02,-0.83)</td>
</tr>
<tr>
<td>Quinn et al 2010</td>
<td>9-19</td>
<td>207</td>
<td>1g-2g daily</td>
<td>-1.68kg/m² (-2.25,-1.10)</td>
</tr>
</tbody>
</table>

The review also identified four randomized controlled trials which had not been used in the systematic reviews.(Bhat et al. 2007; Gottschalk, Danne, Vlajnic, & Cara 2007; Hamilton et al. 2003; Stone, Walker, Chisholm, Craig, Donaghue, Crock, Anderson, & Verge 2008).

Gottschalk et al was a multicentre randomized study with children with a mean age of 13.8 years with type 2 diabetes. 143 children were randomized to receive glimepiride at dose range between 1mg and 8mg daily and 142 to receive metformin at a dose of between 500mg to 2000mg daily. This trial investigated changes in HbA₁c levels from base line to 12 weeks and 24
weeks of treatment. Gottschalk et al also investigated changes in fasting plasma glucose, lipid profile and BMI levels.

The authors concluded that glimepiride reduced a1c level similarly to metformin p=0.749. Significant reductions were seen in both groups at week 24. Glimepiride (-0.54%, p=0.001) and metformin (-0.71%, p=0.0002).

Gottschalk et al also noted that when adjusted mean changes from baseline BMI were compared between the groups, significant differences were seen at week 12 (0.55 vs 0.07 kg/m$^2$ for glimepiride and metformin respectively; p=0.001) and at week 24 (0.26 and -0.33 kg/m$^2$ respectively; p=0.03). No differences either between the two groups or at follow up were seen in fasting plasma glucose and lipid profile.

There was a Cochrane review investigating the addition of metformin to insulin therapy in adolescents.(Abdelghaffar and Attia 2009)

The 60 participants in the two trials that they identified were adolescents between 12 and 20 years (14 to 20 in one and 12 to 17 years in the other). Patients were also on metformin.

The authors concluded that there is some evidence suggesting improvement of metabolic control in poorly controlled adolescent with type 1 diabetes, on addition of metformin to insulin therapy. Stronger evidence is required from larger studies, carried out over longer time periods to document long term effects of metabolic control, health related quality of life as well as morbidity and mortality in those patients (Abdelghaffer et al 2009)

Bhat et al 2007 and Stone M.L. et al were trials which looked at the efficacy of the thiazolidinediones in patients with type 1 diabetes. Bhat et al was a randomized double blind placebo controlled study conducted in India in 60 children aged at least 14 years selected to receive either 30mg daily of pioglitazone or placebo. Each group (30 in each) was maintained on subcutaneous insulin. Patients were followed up for six months. Analysis of Plasma post prandial glucose(PPPG) levels and HbA$_{1c}$ were done. In the pioglitazone group significant reductions were observed after six months from
baseline, \( p=0.002 \) and \( 0.001 \) for PPPG and HbA\(_{1c} \) respectively. In the placebo group no such differences were observed. In this study other covariates were also investigated. They included weight, BMI, waist to hip ratio (WHR), fasting plasma glucose insulin requirement, blood pressure and lipid profiles. All these did not show any statistically significant results. The authors concluded that pioglitazone is modestly effective in lean type1 diabetic subjects. They commented that post prandial glucose levels and HbA\(_{1c} \) levels are improved without much alterations in body weight, blood pressure and lipid profiles. Since this was the only study identified looking at this particular intervention it was not combined with other studies looking at the outcomes which they addressed. Using the GRADE system to assess this evidence showed that the quality of evidence with respect to the statistically significant outcomes was low. It was downgraded due to the fact that the population was from India and it would be impossible to generalize the findings to the children population in whom the essential list would apply. It had a small sample size (60). Stone et al also investigated type1 diabetes patients. They conducted a multicentre randomized controlled crossover trial. The population they analysed were 36 adolescents between 10 and 18 years of age. The participants were randomized to receive either rosiglitazone or placebo. Each patient remained on the same insulin regime. The dose of rosiglitazone was 2mg twice daily for the first two weeks then increased to 4mg twice daily. They were followed up for a total of 24 weeks. They then had a washout period for 4weeks, after which the groups were crossed over. The procedure was then repeated. Upon combining the distinct results of the findings before and after the cross over, no significant results were observed for reduction in HbA\(_{1c} \) levels comparing rosiglitazone and placebo groups (\( p=0.57 \)). Reduction in Fasting Glucose levels also did not show any significant differences between the two groups (\( p=0.78 \)). Applying the GRADE criteria to this study gave a result of low quality evidence. It was just one study which had examined this intervention; the patients were just from Australia. It would not be appropriate to generalize the findings to populations of other geographical origins. The sample size was also small..
No evidence was identified for the use of dipeptidylpeptidase-4 inhibitors and the mitiglinides in children.

**SAFETY**

Park et al 2009 and Quinn et al 2010 reported that there were adverse effects with metformin. These were mainly gastrointestinal side effects such as diarrhoea, nausea, and abdominal discomfort. Both reviews commented that one participant left because of gastrointestinal problems and migraine respectively.

In the Gottschalk et al 2007 study the authors reported that the incidence of hypoglycaemia was similar in both groups. They also noted that the most common adverse events observed in the glimepiride and metformin groups respectively were upper abdominal pain (1.4 vs 0.7%), abdominal pain (1.4 vs 1.4%), diarrhoea (0.7 vs 4.2%), nausea (0.7 vs 2.8%) and headache (0 vs 2.1%)

Stone et al 2008 concluded that there were no adverse events attributable to rosiglitazone, while Bhat et al 2007 noted that there were minor hypoglycaemic episodes which were comparable in both pioglitazone and placebo groups. No major hypoglycaemic events were observed.

**SUMMARY**

Typically children would be the ages between 1 and 12 years of age. In certain cases those between the age of 13 and 18 years would be classified as children. The quality of evidence identified through the review has been low.

There have been several limitations with the evidence which has been reviewed.

**Population**

- There has been heterogeneity in the age ranges. The minimum age for which there were any analyses was 6 years. There was no evidence identified for children below the age of 5. The findings would therefore
not apply to children under the age of 5. For an essential drug list for oral hypoglycaemics for children, there is not enough evidence

- The countries from which the participants in the studies were Australia, Indian, United States, Turkey, Canada, Russia, Belarus, Poland and Ukraine. The review did not identify studies with participants from South America and Africa. The findings of these studies cannot be generalized to all populations of the world health organization

- There was heterogeneity in the clinical conditions the studies reviewed. Some of the reviews investigate type 2 diabetes, or type 1 diabetes, while others looked at more secondary outcomes such as obesity. Doses did not seem to be have a systematic protocol

- The systematic reviews did not have sample sizes big enough to improve precision and efficiency in the results.

- The length of follow up of these patients was short. In most cases up to six months

Interventions

- Most of the studies identified reviewed metformin. The only other antidiabetic(s) which were investigated were rosiglitazone, pioglitazone and glimepiride. One study each was identified which reviewed these medicines.

- The length of follow up was six month in most cases.

Outcomes

- The main outcome which was investigated was reduction in HbA₁c levels. Secondary outcomes such as obesity and insulin resistance were determined.

CONCLUSION

There is not much evidence on the efficacy and safety of oral hypoglycaemics in children. The evidence identified does not adequately address the question
of which oral antidiabetics should be used in children. Studies need to be conducted which stratify the age of children. Comprehensive trials are needed to investigate the use of oral hypoglycaemics in children of the age 12 years and below.

For the low quality of evidence identified it does appear that metformin shows some efficacy especially in participants aged above 8 years of age. One study identified was a head to head trial between metformin and glimepiride which showed the similar efficacy. The Martindale and children’s BNF have recommended metformin, glibenclamide and gliclazide under medical supervision.

Treating children with type 2 diabetes cannot be undertaken as a simple extrapolation of our knowledge from type 2 diabetes in adults. (Matthews and w 2002). We can be confident about the need for optimizing metabolic control and can be realistically optimistic that such intervention will reduce accrual rate of complications. (Matthews et al 2002)

There is an ongoing study which is investigating treatment options for type 2 diabetes in adolescents and youth (Zeitler et al. 2007). The study authors have stated that when completed this study will provide critical new information regarding the natural history of type 2 diabetes in youth, the benefits of initiating early aggressive treatment in these patients, and the efficacy of delivering an intensive and sustained lifestyle intervention to children with type 2 diabetes. (Zeitler et al. 2007). The only drawback with ongoing study is that the population group for investigation have an age range of 10 to 17 years.

Studies are definitely needed for the very young with long term follow up with large and multicultural settings.
References


Ref Type: Electronic Citation


Ref Type: Electronic Citation


Ref Type: Generic


Ref Type: Electronic Citation


Ref Type: Electronic Citation