Tooth discoloration and glibenclamide therapy

Tooth discoloration in patients with neonatal diabetes after transfer onto glibenclamide: a previously unreported side effect

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Objectives: To assess if tooth discoloration is a novel side effect of sulfonylurea therapy in patients with permanent neonatal diabetes due to mutations in KCNJ11.

Methods: Sixty-seven patients with a known KCNJ11 mutation who had been successfully transferred from insulin injections onto oral sulfonylureas were contacted and asked about the development of tooth discoloration following transfer.

Results: Altered tooth appearance was identified in 5 of the 67 patients. This was variable in severity, ranging from mild discoloration/staining (n=4) to loss of enamel (n=1), and was only seen in patients taking glibenclamide (glyburide).

Conclusion: These previously unreported side effects may relate to the developing tooth and/or to the high local concentrations in the children who frequently chewed glibenclamide tablets or took it as a concentrated solution. Given the multiple benefits of sulfonylurea treatment for patients with activating KCNJ11 mutations, this association warrants further investigation but should not preclude such treatment.
Activating mutations in KCNJ11, which encodes the Kir6.2 subunit of the ATP-sensitive potassium (K\textsubscript{ATP}) channel, are the most common known cause of permanent neonatal diabetes (1, 2). High-dose glibenclamide (glyburide) allows discontinuation of insulin and improves metabolic control in about 90% of cases (2, 3). Apart from transient diarrhea (4), no significant side effects have been reported. We report the development of tooth discoloration in five patients with a KCNJ11 mutation after successful transfer onto glibenclamide.

RESEARCH DESIGN AND METHODS
This study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients or their legal guardians. Genetic testing was performed at the Peninsula Medical School, Exeter, UK, or the University of Chicago, IL, USA, as previously described (1, 2). Following an observation by the authors of patient 1 (see below), the association between sulfonylurea treatment and tooth discoloration was further investigated by contacting the referring clinicians of another 66 patients with neonatal diabetes resulting from a KCNJ11 mutation who had successfully transferred onto sulfonylureas.

RESULTS
Tooth discoloration was identified in five patients, representing approximately 7.5% of the 67 subjects with a KCNJ11 mutation treated with sulfonylureas in the two centers. These subjects and their genotypes have previously been reported (1-3). A summary of their clinical characteristics is provided in Table 1.

Discoloration of the permanent teeth (markedly the incisors) was noted in patient 1 six months after transfer, whilst on high-dose glibenclamide. She used to chew the tablets. Although glibenclamide dose was decreased to 0.6 mg/kg/day without deterioration in metabolic control and the patient stopped chewing the pills, there has been no improvement in her teeth color. Patient 2 developed loss of enamel in the upper molars and discoloration of deciduous incisors over 4 years after transfer onto a glibenclamide syrup (2.5 mg/mL). Interestingly, no discoloration of the recently erupted permanent teeth has been noted. In patient 3, a yellowish discoloration of the deciduous teeth was noted approximately one month following transfer, during which time the tablets were being crushed and placed in liquid or food. A couple of months later, she began partially chewing or swallowing the tablets whole. The discoloration resolved since and has not recurred. Patient 4, who was swallowing her pills, was noted about 3 months after transfer to have a plaque-like yellowish discoloration affecting primarily the front teeth that is easily removed by routine cleaning every 3-4 months. Patient 5 was initially dissolving the pills in liquid but around the time he began chewing the pills, he was noted to have inconsistent grayish discoloring of his deciduous teeth that is much improved after thorough brushing of the teeth. None of the patients reported recent changes in food intake, drug use other than glibenclamide, family history or any other known risk factors for tooth discoloration that could explain the association.

CONCLUSIONS
We describe five patients with a KCNJ11 mutation developing tooth
discoloration 1-55 months after transfer from insulin onto glibenclamide. The severity of this novel side effect varied from easily removable tooth staining to non-reversible discoloration and loss of enamel.

Tooth discoloration has not previously been described despite widespread use of glibenclamide in adults. There are many possible explanations for this. Firstly, our patients are much younger than patients with type 2 diabetes and tooth discoloration is more noticeable in white deciduous than in the permanent teeth, which tend to be darker. Secondly, the doses used in children are usually higher than the maximum doses used in adults (3). However there seems to be no clear relationship between glibenclamide dose and the development of tooth discoloration within our cohort as patient 2 was on a low dose (0.1 mg/kg/day) and no tooth discoloration was noted in a further 62 patients with KCNJ11 diabetes who were successfully managed on similar doses of sulfonylureas. Thirdly, and most likely, the teeth may have been exposed to high local concentrations of glibenclamide because of tablets being chewed or taken in solution. In keeping with this, most evidence indicates that the cause of tooth staining is the precipitation of ingested chromogens onto dental surface (5). The possible pathogenic mechanism for the more severe effect on enamel seen in patient 2 however remains unclear. Many other pediatric liquid medicaments have an erosive effect on the primary enamel surface (6). In addition to this local effect, it may relate to a decrease in blood flow to the teeth as glibenclamide, a non-selective sulfonylurea, reduces blood flow to the dental pulp by 70% (7) by acting on vascular $K_{\text{ATP}}$ channels (composed of Kir6.1 and SUR2B) (8). It might also be possible that loss of enamel is unrelated to sulfonylurea therapy as it was present in deciduous teeth but not in permanent teeth.

Clinicians should be aware of this novel side effect of glibenclamide therapy in patients with neonatal diabetes resulting from a KCNJ11 mutation. While the cause is uncertain patients should probably be advised not to chew tablets. Although the effect seems to have mainly a cosmetic consequence and should thus not preclude such treatment, this previously unreported association warrants further investigation.

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Table 1. Clinical details of the four patients with tooth discoloration who have KCNJ11-permanent neonatal diabetes and are on sulfonylurea therapy.

| Case | 1   | 2   | 3   | 4   | 5   |
|------|-----|-----|-----|-----|-----|
| Mutation | V59M | V59M | R201H | R201C | V59M |
| Ethnicity | Caucasian | Black | Caucasian | Caucasian | Caucasian |
| Birth weight (g) | 3172 | 2700 | 2926 | 2812 | 2385 |
| Gestational age (wk) | 41 | 41 | 38 | 39 | 35 |
| Age at diagnosis of diabetes | 15 wks | 5 wks | 26 wks | 4 wks | 25 wks |
| Non-diabetic clinical features | Developmental delay | Developmental delay, epilepsy | None | ADHD | Developmental delay |
| Glycemic control before transfer | HbA1c : 9.2% | HbA1c : 7% | Fructosamine: 319 µmol/L* | HbA1c : 9.3% | HbA1c : 9.4% |
| Pre transfer insulin dose (U/kg/day) | 1.3 | 0.6 | 0.5 | 0.9 | 0.5 |
| Transfer to glibenclamide (glyburide): | | | | | |
| Age at transfer (yr) | 18 | 2 | 3.0 | 6.6 | 2.5 |
| Maximum glibenclamide dose (mg/Kg/day) | 0.9 | 0.4 | 0.95 | 1.1 | 1.0 |
| Duration on glibenclamide when tooth discoloration first noticed | 6 mths | 4.6 yr | 1 mth | 3 mths | 14 mths |
| Glibenclamide dose when tooth discoloration noticed (mg/Kg/day) | 0.9 | 0.1 | 0.7 | 0.8 | 0.8 |
| Current age (yr) | 20.3 | 6.8 | 6.0 | 8.9 | 4.5 |
| Current glibenclamide dose (mg/Kg/day) | 0.6 | 0.1 | 0.7 | 0.7 | 0.8 |
| Current glycemic control (after transfer) | HbA1c : 6.1% | HbA1c : 6.3% | Fructosamine: 228 µmol/L* | HbA1c : 5.6% | HbA1c : 5.8% |

*Because of thalassemia, fructosamine is used for monitoring glycemic control instead of HbA1c (Fructosamine normal range: 0 - 285 µmol/L)
ADHD: Attention deficit and hyperactivity disorder