Dose related growth response to indometacin* in Gitelman syndrome

Lynster C T Liaw, Kaushik Banerjee, Malcolm G Coulthard

Abstract
Growth failure is a recognised feature of Gitelman syndrome, although it is not as frequent as in Bartter syndrome. Indometacin is reported to improve growth in Bartter syndrome, but not in Gitelman syndrome, where magnesium supplements are recommended. This paper presents 3 sisters with Gitelman syndrome who could not tolerate magnesium supplements, and whose hypotension and polyuria were eliminated by taking 2 mg/kg/day indometacin, but who grew poorly. However, increasing the indometacin dose to 4 mg/kg/day improved their growth significantly, without changing their symptoms or biochemistry. Gastrointestinal haemorrhage necessitated the use of misoprostol.

(Arch Dis Child 1999;81:508–510)

Keywords: Gitelman syndrome; Bartter syndrome; indometacin; height; growth

Barter and Gitelman syndromes are uncommon recessively inherited abnormalities of ion channels in the thick ascending limb of the loop of Henle (Bartter), and the distal convoluted renal tubule (Gitelman), and they can present with a wide clinical spectrum. They share some features, including normotension in the presence of raised plasma renin activity and aldosterone concentrations, increased urinary potassium excretion causing a hypokalaemic metabolic alkalosis, and polyuria. Bartter syndrome is characterised by hypercalciuria and nephrocalcinosis, and may be associated with maternal polyhydramnios, premature birth and low birth weight, and early onset of symptoms, including vomiting, polydipsia, dehydration with hypotension, muscle weakness, paraesthesia, and developmental delay.

In Gitelman syndrome there is hypomagnesaemia, hypocalciuria, and no nephrocalcinosis, and many patients are asymptomatic, but may present with weakness and tetany, sometimes with abdominal pain, vomiting, and fever.

Poor growth and short stature are seen in most children with Bartter syndrome, and a minority with Gitelman syndrome. Prostaglandin synthetase inhibitors, particularly indometacin, are used widely in children with Bartter syndrome, but not in Gitelman syndrome. Indometacin has also been reported to improve linear growth in Bartter syndrome, and appears to have prevented growth failure in one child treated from 1 day of age. Improved linear growth has been reported in one child with Bartter syndrome treated with growth hormone, and in one child with Gitelman syndrome treated with magnesium supplements. We report three sisters with Gitelman syndrome who were intolerant of magnesium supplements, and lost their hypotensive and polyuric symptoms when treated with indometacin 2 mg/kg/day, but who were growing poorly. All three grew substantially better when the indometacin was increased to approximately 4 mg/kg/day.

Case reports
CASE 1
This girl was born at term to unrelated parents, after an uncomplicated pregnancy, and presented at 0.4 years with failure to thrive. Investigations were characteristic of Gitelman syndrome, including very low plasma concentrations of potassium (2.3 mmol/litre) and magnesium (0.5 mmol/litre) in the face of a high fractional excretion into the urine (potassium, 49%; magnesium, 9.5%) and a high plasma bicarbonate concentration (27 mmol/litre). Her systolic blood pressure has been consistently normal in the presence of a raised aldosterone concentration (3720 pmol/litre at 0.42 years (upper limit of normal up to 1 year, 2929 pmol/litre)) and persistently raised plasma renin activity (8015 ng angiotensin I/litre/hour at 0.42 years (upper limit of normal up to 1 year, 3130); 4200 at 3.3 years (upper limit aged 1–4 years, 2610); 1850 at 18.2 years (adult upper limit, 311)). Her serum ionised calcium was normal (1.18 mmol/litre) but the urine calcium excretion (calcium to creatinine ratio, 0.1 mmol/mmol) was relatively low (mean (SD) in normal children aged 1–15 years, 0.40 (0.34)), and a renal ultrasound excluded nephrocalcinosis.

Indometacin was started at 1 mg/kg/day in three divided doses together with potassium supplements (which have been needed ever since) until she was referred to our unit at age 4.8 years, when the indometacin dose was increased to 2 mg/kg/day because she remained hypokalaemic. She then remained clinically well, with normal plasma bicarbonate concentrations, and potassium concentrations at the low end of the normal range. However, she grew poorly over the next four years, with a mean height velocity of 6.5 cm/year (fig 1). Because of this, the indometacin dose was increased to 4 mg/kg/day at age 8.9 years, which resulted in a sharp increase in her height.

*ADC has adopted the Royal Pharmaceutical Society recommendation that journals use the recommended international non-proprietary name (dNIN) for medicinal substances, following the recent European directive (92/27/EEC).

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Accepted 17 August 1999
velocity (fig 1), with the height velocity standard deviation score reaching a peak of +3.4 (fig 2).

She was started on misoprostol after one of her younger sisters developed upper gastrointestinal bleeding while also on high dose indometacin. At 12.4 years, while taking indometacin at 5 mg/kg/day, she suffered a large gastrointestinal bleed herself, despite remaining on misoprostol, and her indometacin was then discontinued. Without indometacin, she developed polyuria and polydipsia to the point of social embarrassment, and postural hypotension so severe that she was unable to stand up. However, these symptoms resolved immediately on re-introducing indometacin at 1 mg/kg/day. Because her growth was almost complete by then, she has remained on this low dose ever since.

At 15.1 years, she was treated with oral magnesium supplements, increasing from 0.3 to 0.6 mmol/kg/day. Even at the lowest dose she developed diarrhoea, and at the highest dose, her plasma magnesium failed to increase noticeably, she remained dependent on indometacin to prevent hypotension and polyuria, and her diarrhoea became intolerable, so treatment was stopped.

**CASES 2 AND 3**

These two girls were identified as having Gitelman syndrome on screening in the 1st week of life, with almost identical biochemistry to the first sister. Simultaneously with their older sister, they were initially treated with 1–2 mg/kg/day of indometacin and potassium supplements, with similar biochemical benefit. They had their indometacin dosages increased to approximately 4 mg/kg/day at the same time as the first sister, also for poor growth, when they were aged 6.5 and 4.6 years (fig 1), and subsequently showed dramatic increases in their height velocity standard deviation scores (fig 2).

When the oldest sister had her indometacin temporarily stopped because of gastrointestinal haemorrhage, and restarted at a lower dose, the other two also had their dosage reduced to 1–2.2 mg/kg/day. They also tried oral magnesium supplements at the same time as their older sister, but they too developed intolerable diarrhoea without receiving any clinical or biochemical benefit. After 1.6 years on low dose indometacin, they had again achieved poor height velocities (fig 1), so their doses were increased back up to 4 mg/kg/day. As before, this resulted in increased height velocities (fig 1) and standard deviation scores (fig 2). As with their older sister, the dose of indometacin was reduced to 1 mg/kg/day once growth was complete. They remained clinically and biochemically well on this.

**Discussion**

Magnesium supplements have been described as being useful in Gitelman syndrome, but did not give any clinical or biochemical benefits in these three girls, in whom they had to be stopped because of intolerable diarrhoea. Mag-
nesium supplements have been shown to have no impact on intracellular or extracellular potassium concentrations in Gitelman syndrome.14

The exact mechanism whereby indometacin improves linear growth in Bartter syndrome is uncertain, and there have been no reports correlating the increased height velocity with indometacin dosage. In these three sisters, low dose indometacin of 1 to 2 mg/kg/day controlled the clinical symptoms and improved the biochemical abnormalities caused by their Gitelman syndrome, but did not affect growth. However, they all showed a pronounced increase in linear growth velocity when the dose was increased to 4 mg/kg/day. This effect was similar at all the ages that they received it, ranging from 4.6 to 15 years.

Gastrointestinal haemorrhage is a well known side effect of prostaglandin synthetase inhibitors. The two sisters who suffered this did so only while on high dose indometacin. Misoprostol, an orally active analogue of the naturally occurring prostaglandin E₁, inhibits gastric acid secretion and has cytoprotective properties in the gastric mucosa, and has been used successfully for preventing gastric ulcers being induced by non-steroidal anti-inflammatory drugs.17 Although it was probably partially protective in these girls, one still had a brisk bleed while being treated with this drug.

It could be postulated that misoprostol might negate the positive effect of indometacin, either on the renal tubule or on growth, because it is an analogue of prostaglandin E₁, which might have had separate direct extragastric effects. However, this was not the case; it remained effective in all three patients.

We recommend that children with Gitelman syndrome who are intolerant of magnesium supplements, or in whom these fail to control the clinical or biochemical abnormalities, are treated with indometacin at a dose of 1–2 mg/kg/day. We suggest that if they grow poorly, the dose is increased to 4 mg/kg/day until they have completed their linear growth, and also take misoprostol while they remain on this higher dose. It might be that there is also a dose dependent effect of indometacin on growth in Bartter syndrome, although this remains to be tested.

We are grateful for advice and help from Dr T Cheetham and E Avis.

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Arch Dis Child 1999 81: 508-510
doi: 10.1136/adc.81.6.508

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