Effect of indomethacin on clinical progress and renal function in cystinosis

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SUMMARY Three children with nephropathic cystinosis were treated with indomethacin 3 mg/kg a day for periods ranging from 9 to 18 months. The drug produced worthwhile clinical improvement in all, with marked beneficial effects on polyuria, polydipsia, and general wellbeing. Clearance studies performed under conditions of maximal water diuresis showed that proximal tubular sodium reabsorption was increased in all children, with consequent reduction in sodium delivery to the distal nephron leading to reduced free water clearance and distal tubular cation exchange. Plasma sodium and potassium concentrations became normal in all patients, with improvement in phosphate and bicarbonate concentrations in one. Renal function continued to deteriorate, but without obvious acceleration of the process by the drug. We were unable to demonstrate a beneficial effect on growth; nevertheless, indomethacin is a useful adjunct to the symptomatic treatment of children with severe nephropathic cystinosis.

The specific metabolic defect underlying nephropathic cystinosis has not been identified, and no treatment has yet been shown convincingly to arrest, or even retard, the progression of the disease to end stage renal failure. Recent reports of a possible beneficial effect of cysteamine and phosphocysteamine must be regarded as preliminary and in need of confirmation by longer-term studies. Some palliation of the metabolic effects of the Fanconi syndrome is usually possible, and the judicious use of modern vitamin D metabolites is certainly of benefit in the treatment of hypophosphataemic rickets; nevertheless, affected children rarely thrive and the results of symptomatic therapy are less than satisfactory, particularly as regards growth. Reports of the sodium- and water-retaining properties of prostaglandin synthetase inhibitors in various conditions prompted us to investigate the effects of indomethacin on renal function and clinical progress in 3 cystinotic children.

Case reports

Case 1. A girl, was investigated at age 4 years for long-standing polyuria, polydipsia, and hypokalaemia. The diagnosis of cystinosis was established by the finding of typical ophthalmoscopic and bone marrow appearances. Her growth was the least severely affected of the 3 patients at the time of diagnosis; at 4 years and 2 months her height was 97.5 cm and her weight 13.25 kg. Her treatment before the study was 6 effervescent potassium tablets daily and dihydrotachysterol 0.25–0.5 mg daily. At the time of starting indomethacin she was found to be hypothyroid and L-thyroxine 0.1 mg daily was given.

Case 2. Also a girl, failed to thrive from age 2 years with polyuria, polydipsia, and photophobia. Corneal and bone marrow examination confirmed the diagnosis of cystinosis when she was 3½. For the next 2 years she was treated with vitamin D (calciferol) 6000–60 000 units daily, a mixture of sodium and potassium citrate in varying doses, and energy supplements. L-thyroxine 0.1 mg daily was added at 6 years 7 months. At entry into the study aged 5 years 11 months her height was 99 cm and her weight 13.5 kg.

Case 3. A boy, was the most severely affected child studied. Polyuria, polydipsia, and severe growth retardation began in the first year of life. During an episode of dehydration at age 14 months crystals were noted in the cornea, and characteristic bone marrow appearances were seen a little later. When first seen at Guy’s Hospital aged 8 years 5 months his height was 91.4 cm and his weight 13.2 kg. His
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Indomethacin was induced by the intravenous infusion of isotonic saline 20 ml/kg over 20-40 minutes, after which two further timed urine and blood samples were obtained.

Inulin in plasma and urine was estimated by the method of Heyrovsky, modified for 10 µl samples. Urine and plasma osmolality was measured by freezing point depression on an Advanced 3W osmometer. Plasma electrolytes were estimated by standard methodology using a Vickers multichannel automatic analyser.

Calculations:

\[ C_{in} = \frac{U_{in} \times V}{P_{in}} \]
\[ C_{osm} = \frac{U_{osm} \times V}{P_{osm}} \]
\[ C_{Na} = \frac{U_{Na} \times V}{P_{Na}} \]
\[ cH_2O = \frac{V - C_{osm}}{C_{Na}} \]
\[ F_{Na} = C_{in} \times C_{Na} \]
\[ F_{Na} = \frac{U_{Na} \times V}{P_{Na}} \]
\[ DD_{Na} = \frac{F_{Na} \times (C_{Na} + cH_2O)}{C_{in}} \]
\[ DR_{Na} = \frac{DP_{Na} - F_{Na}}{F_{Na}} \]
\[ PR_{Na} = \frac{F_{Na} - DD_{Na}}{F_{Na}} \]
\[ FPP_{Na} \% = \frac{PR_{Na} \times F_{Na} \times 100}{100} \]
\[ FDR_{Na} \% = \frac{DR_{Na} - F_{Na} \times 100}{F_{Na}} \]
\[ FE_{Na} \% = \frac{F_{Na} - F_{Na}/F_{Na}}{100} \]

U = urinary concentration, P = plasma concentration, C = clearance concentration, in = inulin, Na = sodium, osm = osmolality, V = urine flow rate, F_{Na} = sodium filtration rate, E_{Na} = sodium excretion rate, DD_{Na} = rate of delivery of sodium to the distal nephron, DR_{Na} = distal tubular sodium reabsorption rate, PR_{Na} = proximal tubular sodium reabsorption rate. The F– prefix indicates 'fractional' – that is the proportion of the filtered load reabsorbed or excreted.

Results

Indomethacin reduced glomerular filtration rate (GFR) (C_{in}) from a mean of 28.9 to 19.5 ml/min

### Table Renal tubular sodium handling before and during treatment with indomethacin

<table>
<thead>
<tr>
<th>Case</th>
<th>GFR (ml/min per 1.73ms)</th>
<th>FNa (mEq/min per 1.73ms)</th>
<th>PRNa</th>
<th>DRNa</th>
<th>ENa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before volume expansion</td>
<td>1</td>
<td>28</td>
<td>3.67</td>
<td>1.767 (48)</td>
<td>1.134 (30)</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>3.36</td>
<td>2.627 (78)</td>
<td>0.375 (11)</td>
<td>0.356 (11)</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>3.84</td>
<td>2.451 (64)</td>
<td>0.621 (16)</td>
<td>0.764 (20)</td>
</tr>
<tr>
<td>29</td>
<td></td>
<td>3.62</td>
<td>2.282 (63)</td>
<td>0.710 (20)</td>
<td>0.631 (17)</td>
</tr>
<tr>
<td>After volume expansion</td>
<td>1</td>
<td>22</td>
<td>2.99</td>
<td>1.914 (64)</td>
<td>0.587 (20)</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>3.30</td>
<td>2.349 (67)</td>
<td>0.699 (20)</td>
<td>0.447 (13)</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>1.94</td>
<td>0.624 (32)</td>
<td>0.25 (24)</td>
<td>0.687 (36)</td>
</tr>
<tr>
<td>22</td>
<td>2.81</td>
<td>1.629 (58)</td>
<td>0.637 (23)</td>
<td>0.541 (19)</td>
<td></td>
</tr>
<tr>
<td>During treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before volume expansion</td>
<td>1</td>
<td>15</td>
<td>2.00</td>
<td>1.613 (81)</td>
<td>0.243 (12)</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>2.33</td>
<td>1.663 (71)</td>
<td>0.416 (18)</td>
<td>0.252 (11)</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>3.26</td>
<td>2.164 (67)</td>
<td>0.661 (19)</td>
<td>0.490 (15)</td>
</tr>
<tr>
<td>20</td>
<td></td>
<td>2.53</td>
<td>1.813 (72)</td>
<td>0.420 (17)</td>
<td>0.297 (12)</td>
</tr>
<tr>
<td>After volume expansion</td>
<td>1</td>
<td>23</td>
<td>3.09</td>
<td>2.189 (71)</td>
<td>0.576 (19)</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
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<td>3.236 (76)</td>
<td>0.634 (15)</td>
<td>0.392 (9)</td>
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<tr>
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<td>2.223 (79)</td>
<td>0.359 (13)</td>
<td>0.243 (9)</td>
</tr>
<tr>
<td>26</td>
<td>3.39</td>
<td>2.549 (75)</td>
<td>0.523 (15)</td>
<td>0.320 (9)</td>
<td></td>
</tr>
</tbody>
</table>

Figures in parentheses express the same quantities as percentage of filtered load.

F_{Na} = filtered sodium, PR_{Na} = proximally reabsorbed sodium, DR_{Na} = distally reabsorbed sodium, ENa = excreted sodium.
per 1.73 m²; however, volume expansion largely reversed the fall to a mean value of 25.4. Mean absolute sodium excretion rate was reduced from 0.631 to 0.297 mEq/min per 1.73 m² in the non-expanded, and from 0.541 to 0.320 in the expanded, state. The changes in FENa were similar. FPRNa was greatly increased in both the expanded and the non-expanded state, while FDRNa showed a small decrease. The full results are shown in the Table.

The effect of indomethacin on the reabsorption of water and sodium in the proximal tubular is illustrated in Fig. 1; at all levels of GFR the drug increased the proportion of the filtered load re-absorbed in this segment (2P<0.01 for water; 2P<0.005 for sodium). Fig. 2 shows the effect of indomethacin on distal tubular sodium reabsorption; a significantly greater proportion of the sodium delivered to the distal nephron was reabsorbed in the presence of the drug than in its absence (2P<0.02).

Plasma sodium and potassium concentrations were increased in all 3 children, as were those of phosphate and bicarbonate in the one child who had low values before the study (Fig. 3). All children showed an acute weight gain which averaged 7% of pretreatment weight.

All the children experienced clinical improvement. Polyuria, polydipsia, and salt craving were greatly reduced. Appetite increased in 2 patients but remained poor in the third. Increased wellbeing and energy were reported by all 3 families.

The effect of long-term treatment on renal function is shown in Fig. 4. Linear growth before and after the introduction of indomethacin is shown in Fig. 5.
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Discussion

Children with nephopathic cystinosis suffer growth failure, polyuria and polydipsia, hypophosphataemic rickets, and chronic electrolytic imbalance; these features are due, at least in part, to the presence of the renal Fanconi syndrome. Partial correction of the metabolic abnormalities may be achieved with supplements of salt, alkali, potassium, and phosphate; however, in at least some patients such attempts at replacement therapy may be self-defeating, since the volume expansion induced by the extra salt reduces tubular reabsorption, not only of sodium, but also of glucose, bicarbonate, and phosphate, thus actually worsening the situation.

The physiological role of prostaglandins in the control of nephronal function is not yet clear, and contradictory reports have appeared with regard to their effects. However, inhibition of prostaglandin synthetase with indomethacin consistently reduces renal blood flow and GFR and enhances tubular sodium reabsorption. This effect has been demonstrated in Bartter's syndrome, diuretic abuse, renal tubular acidosis, and in newborn infants with patent ductus arteriosus. The first reported use of indomethacin in cystinosis was by Bétend et al. who demonstrated a reduction in polyuria, improvement in plasma electrolyte values, and growth enhancement; the beneficial effect on polyuria was confirmed in 2 further patients by Lemire and Kaplan. Proesmans et al. obtained similar results and showed the reduced urine volume to be associated with reduced free water clearance. The present study was undertaken to investigate in more detail the effect of indomethacin on renal function, particularly renal sodium and water handling, and on the clinical progress of the disease.

The acute effect on GFR was clear and similar to that described in other conditions. The fact that saline volume expansion reversed the fall supports the view that the effect on GFR is secondary to a haemodynamic change; this would be entirely consistent with the assumption that renal prostaglandins are glomerular vasodilators. As regards the long-term effect on glomerular function, our data do not permit a firm conclusion to be drawn. In one of the 2 children in whom indomethacin was stopped there was a substantial subsequent fall in plasma

Fig. 5 Linear growth of the 3 patients in relation to indomethacin therapy.

Fig. 4 Plasma creatinine concentrations before, during, and after indomethacin treatment.
creatinine, suggesting that reversible glomerular vasoconstriction persisted throughout treatment. The general trend shown by all 3 patients is similar to that seen in untreated children, and there is no evidence that the drug accelerates their inevitable decline into end stage renal failure.

The method used to investigate tubular sodium handling relies for its validity on the assumption that 'solute-free water' is generated in the distal tubule by reabsorption of sodium (with an attendant anion) without water; hence the need for water diuresis to suppress antidiuretic hormone. The distinction between proximal and distal tubule made in this way is functional rather than anatomical, the two segments meeting at the point in the ascending limb of the loop of Henle at which the tubular fluid is isotonic with respect to plasma, presumably near the corticomedullary boundary. Thus the proximal tubule, as defined in this way, includes the loop.

Analysis of tubular reabsorption of salt and water (Figs 1 and 2) shows that both proximal and distal nephron segments reabsorb a larger fraction of the sodium presented to them under the influence of indomethacin than under control conditions. The reduction in sodium delivery to the distal tubule leads to diminished tubular sodium-potassium exchange, which is probably the major cause of the hypokalaemia characteristic of the disease, and to relief of polyuria and salt wasting. These effects could be mediated in at least three ways: (1) by enhancing sodium transport in proximal convoluted tubule, (2) by increasing active chloride reabsorption in the ascending limb of the loop, or (3) by a haemodynamic change alone, modifying the Starling forces in the peritubular capillaries, which are known to affect the rate of fluid reabsorption in the proximal convoluted tubule.24 Glomerular vasoconstriction would reduce peritubular capillary hydrostatic pressure, altering the balance of forces in the required direction. Thus it is possible to explain the observed effect of indomethacin on both GFR and sodium reabsorption without necessarily having to postulate an action of the drug (or of prostaglandins) on sodium transport per se.

Formal tests of tubular reabsorption of glucose, bicarbonate, and other substances wasted in the Fanconi syndrome were not done, partly because both glucose and bicarbonate titration studies are dangerous in hypokalaemic subjects and partly because of the ordeal for the children. Nevertheless, the rise in plasma bicarbonate and phosphate concentrations in Case 3 suggest that reabsorption was enhanced. There are grounds for expecting this to happen, in that factors such as extracellular fluid volume which affect proximal tubular sodium reabsorption also affect the renal threshold for these other substances.

The lack of obvious growth enhancement is disappointing. Given that the children were already in quite severe renal failure, it may be that their growth was better that it would have been without treatment. More extended studies on children at an earlier stage of the disease will be needed to settle this point. The general clinical benefits of treatment, however, were striking. Relief of polyuria and polydipsia led to one child (Case 1) sleeping through the night, having previously risen up to 6 times nightly to pass urine. Despite the experimental nature of the treatment and its risks (see below), all parents wished to continue treatment when the studies were completed. Since the investigation was performed, several more children with cystinosis have been treated with indomethacin, with marked clinical benefit in all cases. Improvement in appetite, energy, and general wellbeing, in addition to reduction in urine volume, were the effects most commonly commented upon by the families of these children.

A fourth child, treated but not included in the clearance studies, suffered a duodenal perforation which was successfully treated in another hospital. However, he had complained of dyspeptic symptoms for some time before the emergency, and this was not brought to medical attention. Since this event we have taken pains to stress to parents the importance of such symptoms, and the advisability of giving the drug on a full stomach: no further side effects have been encountered.

We conclude that, in children with nephropathic cystinosis who are not well controlled on conventional treatment, indomethacin produces significant clinical and biochemical improvement and is a beneficial adjunct to therapy. A useful effect on growth however, has not yet been demonstrated.

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References

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