Nephrogenic Diabetes Insipidus
Effects of 3,5, Cyclic-adenosine Monophosphate

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Jones, N. F., Barraclough, M. A., Barnes, N., and Cottom, D. G. (1972). Archives of Disease in Childhood, 47, 794. Nephrogenic diabetes insipidus: effects of 3,5, cyclic-adenosine monophosphate. In view of the evidence that the actions of vasopressin are mediated by the release of adenosine 3,5, cyclic monophosphate (‘cyclic-AMP’), the effects of this nucleotide were studied in 3 children with nephrogenic diabetes insipidus (NDI) who were insensitive to vasopressin.

Intravenous injections of cyclic-AMP reduced urine flow in 2 of the 3 patients, but did not increase urinary osmolality nor the urinary concentrations of sodium, creatinine, and urea. In these respects the antiuresis differed from that normally produced by vasopressin.

The reduction in urine flow produced by cyclic-AMP was probably related to a fall in glomerular filtration rate associated with the prominent circulatory effects of the nucleotide. These effects appear to preclude the use of cyclic-AMP as an antidiuretic agent in the treatment of NDI.

Nephrogenic diabetes insipidus is an hereditary disorder of the kidney characterized by insensitivity to the antidiuretic action of vasopressin (Waring, Kajdi, and Tappan, 1945; Forssman, 1956). Evidence for the current belief that vasopressin is present in this disorder but that the nephron cannot respond to it has been summarized by Orloff and Burg (1966). The basis for the failure to respond to vasopressin is unknown.

There is evidence that vasopressin influences the metabolism of the renal medulla in vivo (Jones and Welt, 1967). Vasopressin is believed to act at cellular level by increasing the formation of adenosine 3,5, cyclic monophosphate (‘cyclic-AMP’), which then increases epithelial permeability. Both cyclic-AMP and vasopressin increase the epithelial permeability to water and stimulate active sodium transport in the isolated toad bladder (Orloff and Handler, 1962; Edelman, Petersen, and Gulyassy, 1964). Both substances increase the permeability to water of isolated rabbit collecting tubules (Granatham and Burg, 1966). The concentration of cyclic-AMP in toad bladder cells is increased by vasopressin, and this hormone also stimulates production of cyclic-AMP by homogenates of dog kidney (Handler et al., 1965; Brown et al., 1963).

Cyclic-AMP is present in human urine (Butcher and Sutherland, 1962) and its excretion may increase in response to vasopressin (Pawlson et al., 1970). Moreover, the administration of cyclic-AMP causes antidiuresis (Levine, 1968; Barraclough and Jones, 1970). There is thus considerable evidence that vasopressin’s actions on the kidneys are mediated by cyclic-AMP. It is possible that in NDI the defect at cellular level involves a failure to generate cyclic-AMP in response to vasopressin. If this were true, then the nucleotide might retain its antidiuretic action thereby offering an approach to therapy. The effects of cyclic-AMP were therefore tested in patients with NDI.

Patients and Methods

The relevant features of the 3 patients studied are shown in Table I. In each patient the diagnosis was established in infancy by the absence of a detectable response to vasopressin after correction of the initial fluid deficit and at a time when the blood urea level was normal. There was no evidence of other defects in tubular function. Case 2 was complicated by dilatation of the urinary tracts. This patient was studied after bilateral ureterostomies had been performed, when the

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blood urea was normal and the creatinine clearance was 82 ml/min per 1·73 m². The studies were performed only when the children were well hydrated and this was supported by a normal plasma osmolality in each case. Fluid was infused intravenously at a rate to match the urine output. 2·5% dextrose was used in Cases 1 and 2, but Case 3 received 4·8% dextrose in 0·18% saline as this solution had been used immediately before the study when the infant had been vomiting about once a day.

Urine was collected by spontaneous voiding in Case 1, via the ureterostomy tubes draining each kidney in Case 2, and by bladder catheter in Case 3. Venous blood was sampled only 3 times (Cases 1 and 2) or twice (Case 3), as it was expected that close matching of fluid input to urine output should lead to steady concentrations of plasma solutes. Changes in the concentrations of these solutes varied by under 4% in all studies.

Intravenous injections of vasopressin ('Pitressin', Parke Davis), cyclic-AMP, and normal saline were given into the tubing of the intravenous drip. The cyclic-AMP used in Cases 1 and 2 was supplied by Sigma Chemicals. That used in Case 3 was donated by Koch-Light Chemicals Ltd.

Osmolality was measured with an Advanced Osmometer, creatinine and urea by Autoanalyser (Technicon), and sodium by flame photometer.

The following formulae were used in the calculations:

\[
\text{Osmol clearance: } C_{\text{Osm}} = \frac{U_{\text{Osm}} V}{P_{\text{Osm}}}
\]

where \( U_{\text{Osm}} \) = Urinary osmolality, mOsm/kg

\( P_{\text{Osm}} \) = plasma osmolality, mOsm/kg

\( V \) = urine flow, ml/min.

**Results**

Urine flow fell briefly after each dose of cyclic-AMP in Cases 1 and 3 but did not change appreciably in Case 2 (Fig. 1 to 3). Urinary osmolality and urinary sodium concentration were not altered detectably by cyclic-AMP (Table II). Whenever cyclic-AMP reduced urinary flow there were associated falls in osmolal clearance, free water clearance, and in creatinine and urea clearances. All these concentrations returned to control levels concurrently with the return of urine flow to control. When cyclic-AMP did not reduce urine flow (Case 2) no significant change occurred in these renal clearances.

Injections of vasopressin (Cases 1 and 3), or of saline (Case 2), were without apparent effect. In the doses used cyclic-AMP always caused a brief tachycardia lasting 2 to 10 minutes. In Case 1, the first dose of cyclic-AMP (40 mg) caused a

**TABLE I**

Clinical Features of the Patients Studied

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Family History</th>
<th>Creatinine Clearance ml/min per 1·73 m²</th>
<th>Blood Urea mg/100 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>15</td>
<td>—</td>
<td>115</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>6</td>
<td>+</td>
<td>62</td>
<td>32</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>6/12</td>
<td>—</td>
<td>105</td>
<td>30</td>
</tr>
</tbody>
</table>

*The 'control' period values are the means of 3 consecutive 5 to 12 minute collection periods immediately before cyclic-AMP was given. The values shown in each 'C-AMP' period refer to the period in which urine flow was lowest after cyclic-AMP. In every case this was the period immediately after injection of cyclic-AMP.

**TABLE II**

Details of Urine Flow and Urinary Solute Concentrations Before and After Injections of Cyclic-AMP

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Period*</th>
<th>Urinary Concentration</th>
<th>Urine Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Concentration</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flow</td>
<td>Osmolality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ml/min</td>
<td>mOsm/kg</td>
</tr>
<tr>
<td>1</td>
<td>Control</td>
<td>12·25</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>C-AMP</td>
<td>3·30</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>(1 mg/kg)</td>
<td>10·67</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>C-AMP</td>
<td>2·27</td>
<td>39</td>
</tr>
<tr>
<td>2</td>
<td>Left kidney</td>
<td>3·80</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>3·56</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>C-AMP</td>
<td>3·83</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>(3 mg/kg)</td>
<td>3·90</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>Right kidney</td>
<td>1·52</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>1·56</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>C-AMP</td>
<td>1·50</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>(1 mg/kg)</td>
<td>1·40</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>C-AMP</td>
<td>3·89</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>(3 mg/kg)</td>
<td>2·50</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>4·03</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>C-AMP</td>
<td>2·32</td>
<td>100</td>
</tr>
</tbody>
</table>
transient fall in blood pressure from 104/72 to 98/50 mmHg, but no change in blood pressure was detected after the second dose. In Case 2, cyclic-AMP 25 mg produced no detectable change in blood pressure, but this changed from 105/65 to 105/45 mmHg after 62.5 mg. Blood pressure was not measured in Case 3.

Case 1 felt 'light-headed' and faint for about 5 minutes after each dose of cyclic-AMP. Facial flushing was observed in Cases 2 and 3 after each dose.

**Discussion**

Though cyclic-AMP transiently reduced urine flow in Cases 1 and 3, it did not increase urinary osmolality nor the urinary concentrations of sodium, creatinine, or urea. In these respects its actions differ completely from those of vasopressin. In view of the observed circulatory changes and because of the known cardiovascular actions of cyclic-AMP it is likely that a fall in glomerular filtration rate caused antidiuresis.

It is possible that continued exposure to cyclic AMP might allow the development of a tubular
response to this nucleotide, or that use of the more
permeant dibutyryl cyclic-AMP, might produce
an antidiuresis resembling that normally caused
by vasopressin. The present results do not there-
fore establish firmly that the tubular defect in
NDI is after the stage at which cyclic-AMP is
formed. Any attempt at circumventing this
problem was prevented by the unacceptable
circulatory effects already caused by the dosage
used and it is concluded that cyclic-AMP has no
therapeutic value in NDI.

We thank Koch-Light Chemicals Limited for
supplying some of the cyclic-AMP used.

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