The influence of indomethacin on renal haemodynamics in sickle cell anaemia


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Summary

1. Glomerular filtration rate and effective renal blood-flow were normal in a series of patients with sickle cell anaemia. Fractional creatinine excretion and fractional urea excretion were increased.

2. During indomethacin administration there were significant falls in glomerular filtration rate, effective renal blood-flow, creatinine clearance and urea clearance in the patients with sickle cell anaemia; fractional urea excretion also fell markedly. In control subjects none of these variables changed after indomethacin.

3. Serum concentration of urea rose markedly during indomethacin administration in sickle cell anaemia, owing to both the decrease in glomerular filtration rate and the increase in fractional urea reabsorption.

4. We conclude that prostaglandins have an important role in maintaining a normal glomerular filtration rate and effective renal blood-flow in sickle cell anaemia. The abnormal urea handling in patients with this disease remains to be elucidated.

Key words: indomethacin, kidney function test, sickle cell anaemia, urea handling.

Abbreviations: ANG I, angiotensin I; GFR, glomerular filtration rate.

Introduction

Sickle cell nephropathy is characterized by gross pathology of the renal medulla with almost complete absence of the vasa recta (Statius van Eps, Pinedo-Veels, de Vries & de Koning, 1970a). This could explain the observed defects in renal concentrating-capacity (Keitel, Thompson & Itano, 1956; Levitt, Hauser, Levy & Polimeros, 1960; Statius van Eps, Schouten, ter Haar Romeny-Wachter & la Porte-Wijsman, 1970b) and in urinary acidification (Ho Ping Kong & Alleyne, 1971; Goossens, Statius van Eps, Schouten & Giterson, 1972). We have also demonstrated increased tubular reabsorption of phosphate in these patients, indicating increased proximal-tubular activity (de Jong, de Jong-van der Berg & Statius van Eps, 1978b).

An elevated glomerular filtration rate (GFR) has been found in children (Etteldorf, Tuttle & Clayton, 1952) and adolescents with sickle cell anaemia (Hatch, Azar, Ainsworth, Nardo & Culbertson, 1970). In adult patients with the disease normal values have been described (Etteldorf, Smith, Tuttle & Diggs, 1955; Oster, Lespier, Lee, Pellegrini & Vaamonde, 1976; de Frongo, Taufield, Black, Mc-Phedran & Cooke, 1979). Creatinine clearance was elevated in 27 patients whose mean age was 17-7 years (Statius van Eps et al., 1970b) and also in some older patients (Alleyne, Statius van Eps, Addae, Nicholson & Schouten, 1975). Effective renal plasma-flow was increased in children (Etteldorf et al., 1952) and young adults (Etteldorf et al., 1952, 1955; Statius van Eps, Schouten, la Porte-Wijsman & Struyker-Boudier. 1967; Oster et al., 1976), but was normal in older age groups (Etteldorf et al., 1955). Effective renal blood-flow was also elevated in young patients (Etteldorf et al., 1952; Hatch et al., 1970), but normal or only moderately elevated in adults (Etteldorf et al., 1955).
An explanation for the normal or raised GFR and effective renal blood-flow in patients with sickle cell anaemia, in whom infarctions in the microcirculation are frequent but in whom renal cortical infarctions are seldom found (Fern-Pearse & Odundo, 1968), has not yet been provided. These observations cannot be explained by the anaemia per se since multiple transfusions of normal blood to patients with sickle cell anaemia resulted in a transient increase in the concentration of haemoglobin, but not in decreases in GFR, effective renal plasma-flow and effective renal blood-flow (Statius van Eps et al., 1967). Previously we proposed that increased synthesis of prostaglandin in sickle cell nephropathy was a cause of these abnormalities in renal haemodynamics (de Jong, de Jong-van den Berg, Donker & Statius van Eps, 1978a). We studied, therefore, GFR and renal plasma-flow in patients with sickle cell anaemia both before and during inhibition of prostaglandin synthesis with indomethacin.

Materials and methods

We studied 12 patients with homozygous sickle cell anaemia, none of whom showed any overt signs of crisis. As controls eight healthy negroid subjects without any history of renal disease were studied. No medication was used except for folic acid in the patients with sickle cell anaemia. During the investigation none of the patients had haematuria, proteinuria, urinary casts or signs of urinary tract infection and all were hospitalized during the studies. Informed consent was obtained from all subjects. Both patients and controls received a diet containing sodium (100 mmol), potassium (100 mmol) and 3000 ml of water/day. After adhering to this diet for a few days, 'fasting' serum samples and 24 h urine collections were obtained for 3 days. On day 2 blood was drawn with the subjects supine for the determination of plasma renin activity and plasma aldosterone concentration. Mean arterial pressure was measured by radioimmunoassay. Mean arterial pressure was calculated as the sum of diastolic blood pressure plus one-third of pulse pressure.

Wilcoxon's two-sample test and the bilateral Wilcoxon test for paired data were used in the statistical analysis; a probability value of 5% was chosen as the level of significance.

Results

Glomerular filtration rate (inulin clearance) was not significantly higher in the patients with sickle cell anaemia (mean 121 vs 113 ml/min in the control subjects) (Table 1). Effective renal plasma-flow was significantly higher in the patients (mean 924 vs 597 ml/min; \( P < 0.02 \)) and filtration fraction lower (mean 0.14 vs 0.19; \( P < 0.01 \)). Effective renal blood-flow, however, was not significantly increased (mean 1187 vs 1006 ml/min).

Creatinine clearance was elevated in the patients with sickle cell anaemia (mean 159 vs 121 ml/min; \( P < 0.05 \)), as was also mean fractional creatinine excretion (creatinine clearance/inulin clearance × 100% (134 vs 108%; \( P < 0.02 \)).
TABLE 1. Results of renal function tests, plasma renin activity and plasma aldosterone concentration before and during indomethacin administration in patients with sickle cell anaemia and control subjects

<table>
<thead>
<tr>
<th>Age/sex (years)</th>
<th>Packed cell volume (%)</th>
<th>Inulin clearance (ml/min)</th>
<th>Effective renal plasma-flow (ml/min)</th>
<th>Creatinine clearance (ml/min)</th>
<th>Urea clearance (ml/min)</th>
<th>Plasma renin activity (pmol of ANG I h⁻¹ ml⁻¹)</th>
<th>Plasma aldosterone concn. (nmol/l)</th>
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Urea clearance was not significantly increased in the patients with sickle cell anaemia (mean 82 vs 66 ml/min); fractional urea excretion (urea clearance/inulin clearance x 100%), however, was significantly higher (mean 68 vs 59%; P < 0.05). Therefore, fractional urea reabsorption (100 fractional urea excretion) was decreased in the patients with sickle cell anaemia. Diuresis during the clearance studies did not differ between the two groups, either before (mean 3.3 vs 4.6 ml/min) or during indomethacin administration (mean 3.2 vs 4.6 ml/min).

After 3 days of indomethacin the patients with sickle cell anaemia showed marked decreases in GFR (mean 121 to 105 ml/min, difference 13%; P < 0.01), effective renal plasma-flow (mean 924 to 839 ml/min, difference 9%; P < 0.05) and effective renal blood-flow (mean 1187 to 1084 ml/min, difference 9%; P < 0.05). Filtration fraction did not change significantly (0.14 to 0.13). Creatinine clearance decreased by 16% (mean 159 to 133 ml/min; P < 0.01). Urea clearance fell by 24% (mean 82 to 62 ml/min; P < 0.01) and mean fractional urea excretion fell from 68 to 62% (P < 0.05). Mean fractional urea reabsorption therefore increased from 32 to 38%. There were no significant correlations between the packed cell volume and the absolute or percentage changes in the different variables after indomethacin administration in the patients with sickle cell anaemia. The correlation coefficients between packed cell volume and the absolute and percentage changes in GFR were 0.37 and 0.32, in effective renal plasma-flow 0.57 and 0.51, in creatinine clearance 0.40 and 0.48 and in urea clearance 0.22 and 0.27 respectively.

In the control subjects indomethacin induced no significant decreases in GFR (mean 113 to 109 ml/min; difference 4%), effective renal plasma-flow (mean 597 to 572 ml/min; difference 4%) or effective renal blood-flow (mean
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Mean serum concentration of urea ± SEM, 3 days before and 3 days during indomethacin administration in patients with sickle cell anaemia (●●; n = 12) and control subjects (O—O; n = 8). Significance of difference vs last value (—) indomethacin: **P < 0.01, *P < 0.05; † Difference not significant.

![Graph](image)

FIG. 1. Mean serum concentration of urea (mmol/l) before and during indomethacin administration in patients with sickle cell anaemia.

Mean plasma aldosterone concentration was 0.02 nmol/l before and 0.02 nmol/l after indomethacin administration (n = 10). Mean plasma aldosterone concentration fell from 0.94 to 0.47 nmol/l (n = 7; P < 0.05).

Mean arterial pressure was not influenced by indomethacin in the patients with sickle cell anaemia: the average mean arterial pressure during the 3 days before indomethacin was 85 mmHg and in the 3 days during indomethacin administration was 84 mmHg. In the control subjects mean arterial pressure rose from 91 mmHg before to 99 mmHg during indomethacin administration (P < 0.05).

Urinary concentrating-capacity was lower in the patients with sickle cell anaemia compared with the control subjects (mean 445 vs 935 mmol/kg of water; P < 0.01).

Discussion

The results of the clearance studies performed in patients with sickle cell anaemia in the absence of indomethacin are in agreement with the findings of other authors (Etteldorf et al., 1952, 1955; Hatch et al., 1970; Statius van Eps et al., 1970b; Alleyne et al., 1975; Oster et al., 1976; de Fronzo et al., 1979). Effective renal plasma-flow was significantly increased. In the group as a whole, GFR (inulin clearance) and effective renal blood-flow were not significantly higher than in the control subjects, although in the younger patients increased values were frequently found.

After giving indomethacin we found a significant decrease in GFR, effective renal plasma-flow, effective renal blood-flow, creatinine clearance and urea clearance in the patients with sickle cell anaemia, while none of these functions changed significantly in the control subjects. These observations are consistent with an important role for renal prostaglandins in maintaining a normal GFR and effective renal blood-flow in sickle cell anaemia.

Prostaglandin synthesis has been demonstrated in the renal medulla, particularly in the collecting duct cells and the renal medullary interstitial cells (Nissen & Anderson, 1968). Renal prostaglandin production occurs in response to anoxia, often due to various vasoconstricting stimuli (Iskovitz & McGiff, 1974a; Zins, 1975). Renal prostaglandins seem to counterbalance the vasoconstricting stimuli, probably by dilating the efferent arterioles, particularly those of the inner cortical nephrons (McGiff, Crowshaw, Terragno & Lonigro, 1970; McGiff, Crowshaw & Iskovitz, 1974; Chang, Splewnisky, Oates & Nies, 1975). The pathology of the renal medullary vasculature in patients with sickle cell anaemia (Statius van Eps et al., 1970a), which is probably caused by sickling and infarction in an environment of high osmotic...
pressure (Perillie & Epstein, 1963), may result in enhanced medullary prostaglandin synthesis. Such an increase in synthesis of prostaglandin might lead to a higher renal blood-flow and GFR (Chang et al., 1975; Tannenbaum, Splawinsky, Oates & Nies, 1975), while a reduced renal blood-flow (Itskovitz, Terragno & McGiff, 1974b; Solez, Fox, Miller & Heptinstall, 1974) and GFR (Donker, Arisz, Brentjens, van der Hem & Hollemans, 1976) might occur after inhibition of prostaglandin synthesis. Therefore, the decrease in GFR and renal haemodynamics, which we observed in sickle cell anaemia, may have been due to the fact that renal prostaglandins are of particular importance in controlling haemodynamics in sickle cell anaemia.

Since we did not compare patients with sickle cell anaemia with those suffering from anaemia due to other causes, we cannot completely exclude the possibility that the effect of indomethacin in sickle cell anaemia was due to the anaemia per se. Such an effect, however, seems highly unlikely since the increased GFR and effective renal blood-flow observed in sickle cell anaemia are not corrected by multiple blood transfusions (Statius van Eps et al., 1967) and since we did not find a relation between the severity of the anaemia and the decreases in GFR, effective renal plasma-flow, creatinine clearance and urea clearance in our patients.

One could argue that indomethacin does not exert its effect on renal haemodynamics by a particular influence on renal prostaglandins but by an effect on peripheral vascular resistance since prostaglandins do have a vasodilating effect (Vane & McGiff, 1975). This suggestion can be discarded, however, because indomethacin induced no rise in blood pressure in the patients with sickle cell anaemia.

Since we did not measure renal venous concentration of p-aminohippurate we could not calculate extraction of p-aminohippurate, which has been found to be decreased in sickle cell anaemia (Hatch et al., 1970), despite an increased tubular maximum for p-aminohippurate (Etteldorf et al., 1952). Therefore, the increased clearance of p-aminohippurate truly indicates an increased renal plasma-flow. In this respect it is noteworthy that prostaglandins increase cortical-plasma transit time and decrease extraction of p-aminohippurate (Velasquez, Notargiacomo & Cohn, 1972). Indomethacin might therefore increase extraction of p-aminohippurate. The decrease in p-aminohippurate clearance, which we observed in sickle cell anaemia, thus cannot be due to an inhibitory effect of indomethacin on tubular secretion of p-aminohippurate but has to be due to a real decrease in renal plasma-flow.

A decrease in GFR after indomethacin administration has also been described in patients with the nephrotic syndrome (Arisz, Donker, Brentjens & van der Hem, 1976), in patients without proteinuria (Donker et al., 1976) and in normal subjects, particularly after sodium depletion (Donker et al., 1976). In our patients there was no evidence of sodium depletion. (Sodium excretion and plasma renin activity before indomethacin administration were similar in both groups.)

Fractional creatinine excretion before indomethacin administration was higher in the patients with sickle cell anaemia compared with the control subjects. This implies an increased secretion of creatinine which is consistent with an elevated tubular maximum for p-aminohippurate (Etteldorf et al., 1952), and is further evidence of increased proximal-tubular activity in sickle cell anaemia.

Fractional urea excretion before indomethacin administration was also higher in the patients with sickle cell anaemia. Although there is evidence of active secretion of urea in the straight segments of both superficial and juxtamedullary proximal tubules in the rabbit (Kawamura & Kokko, 1976), urea reabsorption is of more importance and has been shown to occur in the proximal tubule and inner medullary collecting duct. The higher fractional urea excretion in sickle cell anaemia could be explained by increased secretion or decreased reabsorption in the proximal tubule or decreased reabsorption in the inner medullary collecting duct. After indomethacin administration fractional urea excretion decreased markedly in the patients with sickle cell anaemia, whereas it did not change in the control subjects. Because of the abnormalities in renal medullary function in sickle cell anaemia (Keitel et al., 1956; Levitt et al., 1960; Statius van Eps et al., 1970b; Ho Ping Kong & Alleyne, 1971; Goossens et al., 1972), it is likely that the increased fractional urea-excretion before indomethacin administration was due to defective medullary transport of urea. During indomethacin administration this abnormal urea handling can be corrected.

Further studies of renal medullary function after inhibition of prostaglandin synthesis, especially during maximum diuresis and antidiuresis, will be necessary to elucidate this abnormal pattern in urea handling. Also measurement of prostaglandin concentrations in urine and renal venous samples are needed in sickle cell anaemia.
Acknowledgments

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References


