Prostaglandin synthesis inhibition by indomethacin in normal and in some pathological conditions
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This thesis deals with the effects of indomethacin on renal function and PRA in normal man and in some pathological conditions. In order to measure some parameters of renal function reliably, a simple and accurate method to determine GFR and ERPF had to be worked out. The use of radiopharmaceuticals, thought to be excreted by glomerular filtration (e.g. $^{125}$I-iodoantipyrine) or by glomerular filtration and tubular secretion (e.g. $^{131}$I-hippuran), simplifies the measurement of GFR and ERPF respectively. A routine estimation of GFR and ERPF becomes attractive if also the need for accurate urine collection by catheterization of the bladder can be eliminated. In chapter 1 such a method is described. In this method GFR and ERPF are determined simultaneously with radiopharmaceuticals whereby the necessity of bladder catheterization is obviated. An additional advantage of the use of radio-iodinated hippuran is the impossibility to exceed the maximal tubular secretory rate of hippuran by the doses normally used. No precautions in this respect are necessary in patients with very low GFR. Special testing must be carried out to assure that the free iodine content is minimal and patients should have thyroid-blocking doses of lugol’s solution the day before the study (with the exception of patients with a known sensitivity to iodides). The radiation that patients receive from the described procedure is minimal because the radioactivity is rapidly excreted. The estimated radiation dose (rads) in patients with normal GFR amounts to [1–4]:

<table>
<thead>
<tr>
<th>Compartment</th>
<th>$^{125}$I</th>
<th>$^{131}$I</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidneys</td>
<td>0.050</td>
<td>0.010</td>
<td>0.060</td>
</tr>
<tr>
<td>Urine bladder</td>
<td>0.020</td>
<td>0.005</td>
<td>0.025</td>
</tr>
<tr>
<td>Gonads</td>
<td>0.005</td>
<td>0.001</td>
<td>0.006</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1.0</td>
<td>0.2</td>
<td>1.2</td>
</tr>
<tr>
<td>after lugol</td>
<td>0.020</td>
<td>0.005</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Using radiopharmaceuticals, in chapter 2–4 it is shown that indomethacin decreases GFR (and FF) in normal individuals and in patients with renal disease, especially when they are sodium depleted. Moreover, administration of indomethacin is shown to cause sodium and water retention and a fall in PRA. These results are attributed to inhibition of the renal prostaglandin synthesis. It may be asked whether this explanation fits in with the physiological role of the renal prostaglandin synthesis.

It is generally accepted that blood pressure is maintained to a large extent through peripheral vasoconstriction, regulated by the sympathetic vasoconstrictor tone, the secretion of catecholamines and the renin-angiotensin system. In low output and low pressure states, the renal vascular bed is relatively free of vasoconstriction in order to preserve urine production and for instance the homeostasis of potassium or pH. The renal ability to withstand vasoconstriction seems to be caused by the renal prostaglandin synthesis. This synthesis, mainly located in the renal medulla, is
promoted by renal ischemia, itself largely a result of an increased renin release in the renal cortex. Thus, endogenous angiotensin II increases renal prostaglandin synthesis just like exogenous angiotensin II. On the other hand, prostaglandins increase renin release, directly or secondary to their vasodilator effect. An equilibrium between these two vasoactive systems might be achieved by prostaglandin 15-hydroxy dehydrogenase. This enzyme, present in the renal cortex, possibly inactivates the prostaglandins that are synthesized in the renal medulla. In this way the related renin-angiotensin and prostaglandin productions together can determine ultimately the blood flow in outer and inner renal cortex and in the renal medulla, thereby influencing the sodium and water balance.

From this point of view it is explainable that inhibition of the renal prostaglandin synthesis by indomethacin is accompanied by a decrease in GFR, a retention of sodium and water and a fall in PRA. It is also understandable that these effects are more pronounced when the renin-angiotensin system has been stimulated. In vivo, inactivation of prostaglandin 15-hydroxydehydrogenase by furosemide (already demonstrated in vitro), will result in an immediate increase in PRA, as in this condition the vasodilatory prostaglandins influence the cortical nephrons unopposed. As shown in chapter 6, this effect of furosemide on PRA can be abolished by a preceding prostaglandin synthesis inhibition. Normally this will not be accompanied by a clearly diminished excretion of sodium and water as furosemide inhibits sodium transport along the whole nephron. Only in Bartter's syndrome and in patients with severe nephrotic syndrome, conditions both characterized by hyperreninemia and hyperaldosteronism, a preceding prostaglandin synthesis inhibition by indomethacin results in a diminished natriuretic and diuretic activity of furosemide. Probably in these patients cortical hyperemia by furosemide, an effect enhanced by the already elevated prostaglandin synthesis and resulting in diminished proximal tubular sodium reabsorption, attributes to the saluretic activity of the drug.

In chapter 3 and 4 it is also shown that indomethacin administration to patients with a nephrotic syndrome of various origin induces a marked and abrupt decrease in urinary protein loss, associated with an increase in selectivity of the residual proteinuria. One may postulate that these effects are the result of a change in the glomerular ultrafiltration coefficient \( K_f \), a change in glomerular plasma flow, a change in the effective transcapillary hydraulic pressure difference \( \Delta P \), or a change in the fixed negative charges on the glomerular capillary wall. The latter seems to be unlikely as the effect of indomethacin on proteinuria is enhanced by sodium depletion, while sodium depletion itself does not influence urinary protein loss. As indomethacin inhibits prostaglandin synthesis and decreases PRA immediately, a decrease in the effective transcapillary hydraulic pressure difference, possibly restricted to the juxtamedullary nephrons, would explain the decrease in proteinuria by this anti-inflammatory drug in the same way as a renin – or angiotensin-induced increase in the intraglomerular pressure induces an increase in (macromolecular) proteinuria (accompanied by an increase in FF) [6]. The decrease in FF, pointing to (an increase of) filtration pressure disequilibrium, is in support of this hypothesis. Measurement of glomerular plasma flow, average effective transcapillary hydraulic pressure difference and average effective oncotic pressure difference \( \Delta \pi \), before and after indomethacin administration to nephrotic animals, seems to be of prime importance in the evaluation of the mechanism that underlies the indomethacin-induced decrease in transglomerular passage of plasma proteins.

A possible favorable long-term effect of indomethacin on the course of some types of renal
diseases, e.g. by inhibition of the chemotactic migration of leucocytes or of the maturation of T-lymphocytes and/or by stabilization of lysosomal membranes [7] warrants controlled trials. A modification of the natural history of the renal disease by an inhibition of the platelet aggregation seems to be unlikely as mounting evidence suggests that urinary fibrin-fibrinogen-related antigen excretion in glomerulonephritis is derived predominantly from increased filtration of plasma fibrinogen rather than from breakdown of intraglomerular fibrin [8]. Therefore, the excretion of fibrin-fibrinogen degradation products in nephrotic patients before and during indomethacin administration has to be related to the selectivity of the proteinuria.

Administration of other prostaglandin synthesis inhibitors such as meclofenamate, diclofenac sodium and ibuprofen to (sodium depleted) patients with nephrotic syndrome, will be helpful to substantiate the assumption that the initial effect of indomethacin on proteinuria depends exclusively on the inhibition of the prostaglandin synthesis. In support of this hypothesis are the renal effects of other potent inhibitors such as aminophenazone (pyramidon®), phenylbutazone, salicylates [9] and fenoprofen [10].

It also would be of importance to measure the total amount of prostaglandins produced in sodium depleted nephrotic patients and to compare this with the prostaglandin production during indomethacin administration. In vitro a 100 per cent inhibition of prostaglandin synthesis was found at an indomethacin concentration of 1.0 μg/ml [11]. The determination of prostaglandin metabolites in 24-hours' urine [12] or the determination of PGE₂ in (renal) blood samples by combined gas-liquid chromatography – mass spectrometry [13] and the determination of indomethacin serum concentrations [14], may be of value to find the optimal prostaglandin synthesis inhibiting dose of indomethacin, especially when GFR is normal.

Peptic ulceration, a serious side effect of prolonged administration of indomethacin, probably can be prevented by 15(R)15 methylprostaglandin E₃ orally. It is not known whether oral administration of this analogue influences GFR or urinary protein loss. The availability of synthetic prostaglandins [15], including PGE₂, makes also possible the study on the effects of oral or intravenous administration of these compounds to (indomethacin treated) animals and patients with nephrotic syndrome.

Finally, the cause of hyperprostaglandinism in Bartter’s syndrome (chapter 5) needs elucidation. As argued in chapter 6, an absence of the prostaglandin inactivating enzyme, at least in one patient with that condition, seems to be unlikely. It is quite possible that the state of hyperprostaglandinism, as expressed among other things by an elevation of urinary PGE₂ [16, 17], is secondary to other physiological abnormalities, i.e. Bartter’s syndrome may be a heterogenous disorder. However, measurement of PGE₂ (and PGF₂α) in peripheral and renal vein blood remains of prime importance in order to establish whether one has to do with a renal or general state of hyperprostaglandinism.

References

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