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Renal Blood Flow and Pelvic Pressure After 4 Weeks of Total Upper Urinary Tract Obstruction in the Pig

The Effect of a TxA2 Synthetase Inhibitor on Active Preglomerular Vasoconstriction

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Summary. In 8 female pigs complete unilateral ureteral obstruction was investigated over a 4 weeks period. The pigs were monitored with intrapelvic pressure measurements and by 131-I-hippuran scintigraphy twice a week; one group without and one with TxA_2 blocking, UK-38,485 [3-(1H-imidazol-1-yl-methyl)-2methyl-1H-indol-1-propanoic acid], which is a well-known selective thromboxane synthetase inhibitor. During the course of obstruction there was an ipsilateral linear reduction of split function to background level and a net reduction in total hippuran clearance in both groups. On the obstructed side there was a linear reduction of hippuran clearance from 116 ± 26 ml/min to 11 ± 3 ml/min during the first 2 weeks of obstruction. The TxA_2 synthetase inhibitor, 5 mg/kg reduced se-TxB_2 to almost zero for at least one hour after i.v. administration. One week after obstruction the pelvic pressure was 45 ± 5 cm H_2O) administration of the TxA_2 synthetase inhibitor. The pelvic pressure remained elevated throughout the period of observation. The study confirmed earlier work which showed that total ureteral obstruction caused complete cessation of kidney function within a few weeks, but contradicts previous studies because there was no increase in renal blood flow after thromboxane blockade. These differences may be explained by several mechanisms. The continuing increase in pelvic pressure suggested that it was not only a preglomerular vasoconstriction which was responsible for the renal flow reduction, but that there was also a postglomerular vasoconstriction.

Key words: Unilateral complete ureteric obstruction – Renal blood flow – Preglomerular vasoconstriction – Thromboxane inhibition

Reconstruction of uncomplicated chronic dilatation of the upper urinary tract is performed to relieve symptoms and to stabilize or even improve ipsilateral kidney function.

Experimental studies in animals have revealed that there are 3 phases of change in the ipsilateral renal blood flow and the pressure in the ureter after unilateral total obstruction of the ureter: 1) 0–1.5 h there is an increase in both RBF and ureteral pressure, 2) 1.5–5 h there is a decrease RBF while the pressure in the ureter still increases, and in 3) 5–18 h there is a decrease in both the ureter pressure and RBF [21]. The explanation of these time-dependent observations could be that in 1) there is a vasodilatation [1, 21, 36], in 2) there is a postglomerular increase in the vascular resistance, and in 3) there is a preglomerular vasoconstriction [21].

Several investigations suggest that the vasoconstriction seen in the third phase is active and of a preglomerular nature alone [4–7]. Studies on rats, rabbits and dogs have suggested that thromboxane-A_2 (TxA_2) may be an important factor in the development of preglomerular vasoconstriction and a subsequent renal blood flow reduction in the course of urinary tract obstruction. Huland et al. found [13, 14] that administration of 2-benzyl-2-imidazole (tolazoline), which is a TXA_2 antagonist, was able to reverse RBF to preobstruction values, without changing the RBF on the contralateral side. However corresponding investigations did not produce corroborative results. Hope and Clausen [11] and Balint et al. [4] found that in rats and also in dogs there was no change in RBF after administration of a TxA_2 inhibitor to an animal with unilateral urinary tract obstruction.

One obstacle in enterpreting these data might be species differences, and any parallel to the human situation might be ameliorated by studying an animal with a kidney structure similar to man. Therefore we undertook a study to see if a well-tested non-toxic thromboxane A_2 synthetase inhibitor UK-38,485 did have any effect on RBF and ureteral pressure in the chronically obstructed multicalyceal system in pigs.

Material and Methods

Eight female pigs of the Danish landrace, mean weight 22.5 kg were allocated to a control-(C) and a UK-38,485 group (D). All investiga-

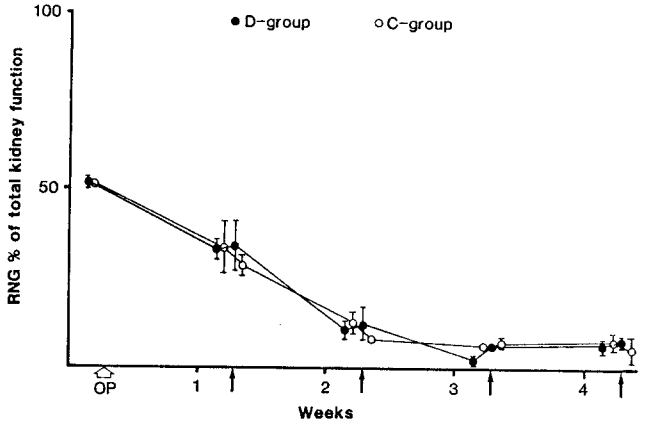

Fig. 1. The figure shows the renographical split function (mean ± SEM) in relation to time during the four weeks of obstruction in both the C- and the D-group. Arrows indicate administration of UK-38,485 to the D-group

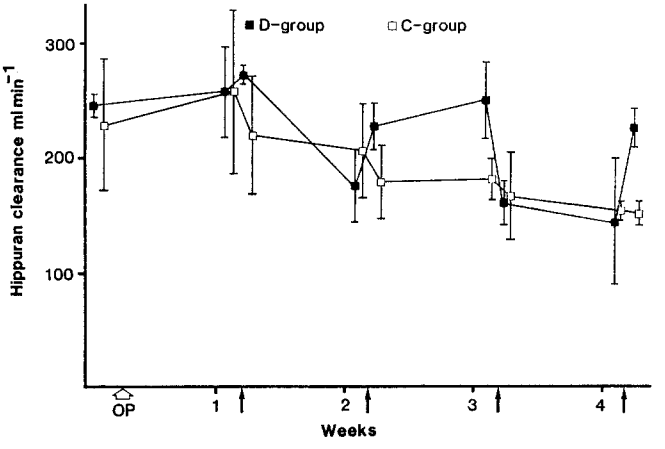

Fig. 2. The figure shows total hippuran clearance (mean ± SEM) in relation to time during the four weeks of obstruction in both the C- and the D-group. Arrows indicate administration of UK-38,485 in dhe D-group

tions throughout the study was performed under geneal anaesthesia induced by 10 mg Ketalar^R (ketamin NFN) per kg b.w. i.m. and maintained with Halothane 0.5–1.5% with the pig on spontaneous respiration in a semi-closed system.

Renal blood flow data were derived from 131-I-Hippuran scintigraphy. An initial scintigraphy was performed to ensure normal function and drainage.

Through a midline incision from the symphysis pubis to the xiphoid process the right kidney, the renal pelvis and the proximal part of the ureter were exposed extraperitoneally. Through a ureterotomy on midureter a Port-A-Cath^R (Pharmacia) silastic catheter was guided into the ureter until the tip with side- and endholes were placed in the pelvis. The ureter was ligated around the catheter which was connected to the infusion chamber. Ureter was also ligated distally to the ureterotomy. The chamber was placed in a subcutaneous pouch in the right groin and fixed to the underlying fascia with 4 prolene 3-0 sutures. Next an incision was made in the right regio femoralis and canalis adductorius and the femoral vessels were localized. Through the right femoral vein another Port-A-Cath^R silastic catheter for injection of drugs and blood sampling for hippuran clearance estimations was guided up into the inferior caval vein by the Seldinger tecnique. The catheter was connected to the chamber, which was sutured to the underlying femoral muscle

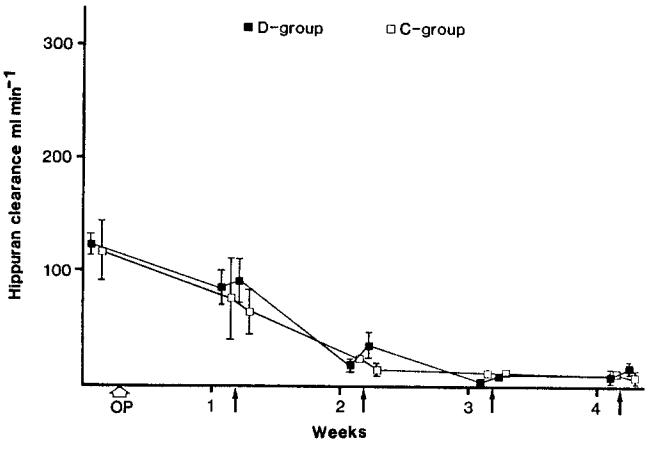

Fig. 3. The figure shows hippuran clearance at total ureter obstruction (mean ± SEM) in relation ot time in both the C- and the D-group. Arrows indicate administration of UK-38,485 in the D-group

fascia. Both Port-A-Cath^R systems were filled with a solution of heaprinized saline.

One week after operation and during the following 4 weeks the pigs underwent a scintigraphy twice a week together with pelvic pressure measurements. Before scintigraphy the pigs were anaesthesized as described above. Through an ear vein the pigs recieved 500 ml isotonic NaCl during the investigation. The I-131-hippuran scintigraphy was made using a gamma-camera (Siemens ZLC 7ɔ00) and data collected in an on line computer (Nodecrest V76-600). The dose was 11 MBq/pig administrated intravenously. Computer data was collected in a 64 x 64 matrix, 80 frames of 20 s. The ROI's over the two kidneys and the abdominal aorta were defined and the time-activity curves and the background curve generated. From the time-activity curves renal split function was determined. Estimation of total hippuran clearance was done from blood sampled immediately after scintigraphy and the rate constant obtained from the generated data. Hippuran clearance on each side was total hippuran clearance multiplied by renal split function.

Pelvic pressure was measured during scintigraphy by a Siemens strain gauge 746 transducer and amplifiers. A catheter (Portex^R) connected the Port-A-Cath^R system which was implanted in the right pyeloureter, to the transducer placed at kidney level.

The pigs in the D-group had an intravenous injection of 5 mg UK-38,485/kg 15 min prior to their second weekly scintigraphy. Analysis of serum thromboxane was done with the method described by Nielsen et al. [27].

Results

All pigs had normal bilateral kidney function preoperatively. One pig in the C group was sacrified after 14 days because of urine leakage.

Studies of split function in total obstructed renal systems in the C-group showed that there was an almost linear reduction in functional share to about 10% during the first 2 weeks after obstruction. The split function stabilized at this low level during the following two weeks (Fig. 1).

Total hippuran clearance in the C group decreased gradually from a mean of 230 ± 57 ml/min to a mean of 150 ± 10 ml/min during the four weeks (Fig. 2). On the obstructed side there was a linear decrease during the first two weeks from 116 ± 26 ml/min preoperatively to 11 ± 3 ml/min (Fig. 3). On the contralateral side the preoperative

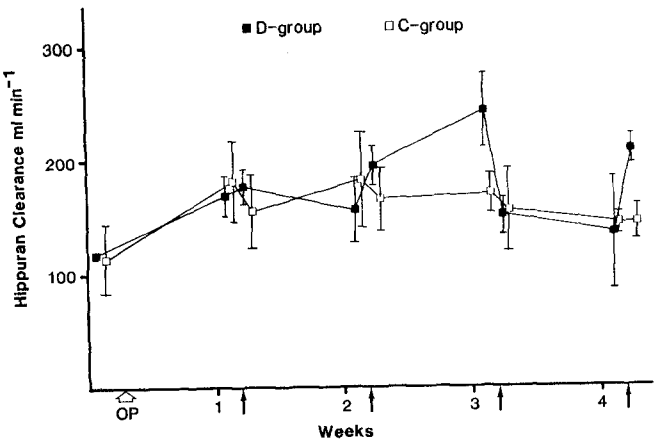

Fig. 4. The figure shows hippuran clearance on the controlateral unobstructed side (mean ± SEM) in relation to time in both the C- and the D-group. Arrows indicate administration of UK-38,485 in the D-group

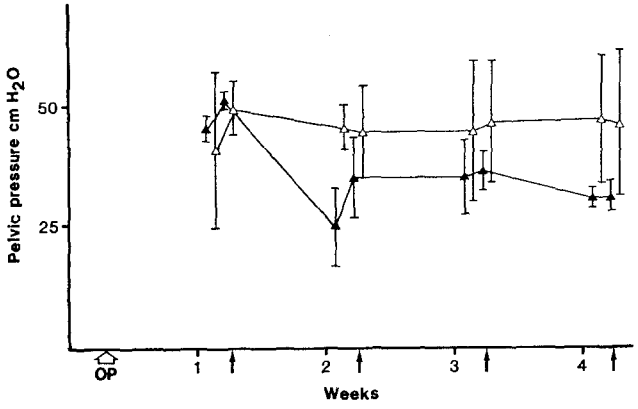

Fig. 5. The figure shows the pelvic pressure (mean ± SEM) in relation to time in both the C- and D-group. Arrows indicate administration of UK-38,485 in the D-group

clearance was 113 ± 30 ml/min (Fig. 4) and increased to 181 ± 73 ml/min and during the third and fourth week after obstruction the mean clearance stabilized at 142 ± 21 ml/min.

In the C group the mean pelvic pressure was about 45 cm H_2) during all 4 weeks (Fig. 5).

Control analysis of the efficacy of the blocking of the thromboxane synthesis showed that se-TxB_2 in the untreated animal was 39.5 µg/l (Fig. 6). Administration of 5 mg of UK-38,485/kg reduced se-TxB_2 almost to zero for at least one hour.

Split function studies showed that UK-38,485 administration was not followed by a significant increase in functional share. As in the C group there was an almost linear pattern of reduction during the first 2–3 weeks, and the functional share was less than 10% of total after 4 weeks of obstruction (Fig. 1).

UK-38,485 injection resulted in an increase of total hippuran clearance during the first, second and fourth week after obstruction varying from 15 ml/min to 75 ml/min

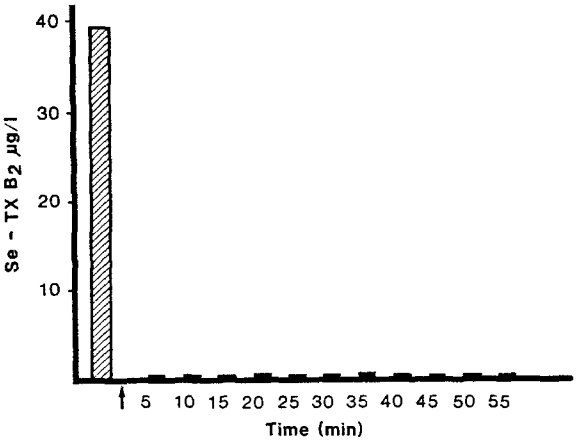

Fig. 6. The figure shows a column diagram of the se-TxB_2 level in relation to time before and after administration of UK-38,485. Arrow indicate UK-38,485 administration

(Fig. 2). In the third week of obstruction there was a decrease in clearance. On the completely obstructed side the preoperative hippuran clearance was 126 ± 13 ml/min (Fig. 3). During the following three weeks there was a linear decrease to 17 ± 8 ml/min. Consistently every UK-38,485 administration was followed by a minor increase in hippuran clearance. On the contralateral side the preoperative hippuran clearance was 117 ± 2 ml/min (Fig. 4). During the first two weeks after obstruction there was a minor increase in mean clearance to 194 ± 29 ml/min, and in the third and fourth week after obstruction the mean clearance varied from 134 ± 69 ml/min to 242 ± 56 ml/min UK-38,485 administration did not result in any consistent changes in hippuran clearance.

After one week of obstruction the pelvic pressure was 45 ± 5 cm H_2O in the D group (Fig. 5). During the four weeks of obstruction the pelvic pressure stabilized at 31 cm H_2O and UK-38,485 injections resulted in no significant pressure increase.

Discussion

Knowledge of preglomerular vasoconstriction in renal blood flow, and of drugs modulating this vasoconstriction has mainly been derived from studies on rats, rabbits and dogs [1, 2, 6, 9, 14, 21, 34, 36, 37]. We chose the pig as experimental animal because of the similarity of the porcine and human kidneys both microscopically and macroscopically.

In the experimental design we put emphasis on non-invasive estimation of RBF changes. Comparative studies in animals have shown that renography is useful in the estimation of kidney blood flow [3, 7, 10, 33]. However it is unknown how implanted prostheses may disturb RBF. By estimating kidney function renographically twice a week it was possible to detect changes in function.

Earlier in vivo [37] and in vitro [22–25] investigations did reveal that vasoactive prostaglandins, among these TxA_2,

are produced in chronically obstructed kidney. Several investigations [2, 9, 16] suggested that the decrease in RBF in the chronically obstructed rat kidney is of preglomerular nature. By blocking TxA_2 with imidazole Huland et al. [14] in reversing the ipsilateral RBF to normal level in dogs with unilateral complete ureteral obstruction for 4 weeks, without affecting contralateral RBF.

In this study we estimated the serum thromboxane level before and after injection of UK-38,485. Analysis of se-TxB_2 showed that UK-38,485 was an extremely potent inhibitor of the thromboxane synthetase in pigs. However, we did not notice any change in the decrease of RBF on the obstructed side. The experimental design did not allow a seperate analysis of the venous kidney blood. Therefore we had no information about the pre- and postobstructive renal TxA_2 level.

Pelvic pressure measurements along with the RBF estimations showed that despite insignificant changes in pelvic pressure after UK-38,485 administration, there was a continuous presure rise throughout the study. This contrasts with earlier investigations [32, 38].

The results of renal split function and hippuran clearance showed in both groups that the totally obstructed systems had very little function at 4 weeks. This is consistent with earlier investigations [6, 20]. Estimation of split function, showed, that RBF decreases rapidly during the first 2–3 weeks after obstruction. In the non-obstructed systems there was a proportional increase in RBF. Changes in RBF as judged from the renographical curves showed a 20% weekly decrease in RBF on the obstructed side and a proportional increase on the contralateral side. Hope and Clausen [11] found a 50% reduction in ipsilateral RBF and a 36% increase in contralateral RBF 6 days after total unilateral ureter obstruction in rats. Other authors found corresponding results in rats [5] and in dogs [35]. The reduction in ipsilateral split function is compatible with the existence of preglomerular vasoconstriction. But apparently UK-38,485 administrations were not able to reverse the increased resistance, which Huland et al. [13–15] were able to normalize dogs. As mentioned, other authors did not succeed in reproducing these results [11]. There can be several reasons to the observations we made. If total ureteric obstruction caused progressive nephropathy after one week of obstruction, then TxA_2 could not alone be responsible for the reduction in RBF. Also it may be questioned that TxA_2 is the vasoactive substance in the pig kidney. If the preglomerular vasoconstriction is determined by an increased production of TxA_2, then it is possible that the TxA_2 production is determined by Tx-synthetases, which are different from the synthetases inhibited by imidazole and UK-38,485. Patrignini et al. [30] found in vitro that the Tx-synthetase inhibitor Dazoxiben [4(-2-(1H-imidazol-1-y1) ethoxy) benzoic acid hydrochloride] did not equally inhibit the synthesis of TxA_2 in thrombocytes and glomeruli. This can be explained from the existence of so-called isoenzymes, i.e. species differences and tissue differences in TxA_2 synthetases.

Furthermore our results question that it is a preglomerular vasoconstriction which is responsible for the reduction in kidney function preceeding parenchymal atrophy in pigs with ureteral obstruction. The continuing elevation of the pelvic pressure during a 4 week period is not consistent with preglomerular vasoconstriction alone. Very little is known about the renal hemodynamics in the chronically obstructed pig kidney. However, other authors [19, 26] have found the same pressure increase during obstruction of the pig kidney for several weeks. Although we do not know very much about how the tubologlomerular balance is affected in the polycalyceal kidney by complete ureteral obstruction, we do know from rat experiments that this balance remain almost constant [31], but an explanation of the lasting pelvic pressure elevation may in some way be related to a longer postglomerular vasoconstriction than was previously observed in dog experiments [21]. The mechanism behind this possible postglomerular vasoconstriction remain obscure.

Total kidney function estimated by 131-I-hippuran clearance was reduced during the four weeks of obstruction in both groups. In the C-group there was an initial increase in kidney function just after obstruction, but during the 4 weeks of obstruction there was a net decrease in hippuran clearance. After injection of UK-38,485 in the D-group there was an increase in total mean hippuran clearance in the first, second and fourth week after obstruction. These differences can be explained by chance, because there was no consistency between animals in total hippuran clearance after UK-38,485 injections. It is conceivable that implantantion of the catheters may have an influence of RBF and the impact of a non standardized hydration on scintigraphy is yet unknown.

Kidney function in the totally obstructed systems was reduced in both groups during the first 2 weeks. In the non-obstructed systems there was an increase in the first two weeks. This is in accordance with earlier investigations [8, 17]. Why kidney function started to decrease or to stabilize at a lower level during the second week of obstruction is an open question. Compensation occured in both GFR and tubular function, but their relative functional share cannot be calculated in this study. An earlier study did show [18] that during the second week of obstruction there was a deterioration in the already increased GFR on the contralateral side in rabbits with unilateral total ureteral obstruction. According to recent theories it is possible that vasoactive substances produced in the obstructed kidney are able to influence contralateral kidney function [28, 29].

In conclusion the investigation showed that total ureteral obstruction leads to complete cessation of kidney function within a few weeks and that UK38,485 was not able to reverse renal blood flow reduction in pigs secondary to ureteral obstruction. The study thus contradicts previous studies and we believe that the differences could be explained from species- and tissue differences in TxA_2 synthetases or by an even more complex vasoconstriction mechanism than was previously assumed.

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