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Interstitial Handling of Aminoglycoside Antibiotics and Radiographic Contrast Media in the Kidney

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Summary

Lymphatics of the mammalian kidney originate in the loose connective tissue around large blood vessels. This paravasal tissue drains the interstitium. The intrarenal lymphatic system consists of interlobular, arcuate, and interlobar vessels according to the architecture of the arterial system. The interlobar vessels drain into the hilar lymph vessels. Capsular lymphatics are connected with the interlobular lymphatics inconsistantly. The renal medulla is drained by the venous vasa recta exclusively – there are no lymphaties in the medulla.

Lymphatic fluid is mainly formed along the small renal veins as vascular transudate.

After i.v. bolus injection concentrations of aminoglycosidic antibiotics in renal lymph reflect plasma values closely. Radiographic contrast media in renal lymph also showed a close correlation with plasma values with some indication of tubular secretion.

This paper reports our results on radiographic contrast media (CM) and aminoglycosidic antibiotics appearance in renal lymph. Knowledge about the distribution patterns of different substances in different compartments not only aids therapeutic considerations but also furthers basic understanding of lymphodynamics of the kidney. In addition – as a result of extensive light- and electronmicroscopic studies – a brief anatomical overview on the renal lymphatics is given.

I. *Biodynamic Availability*

There are many examples that in the light of newly arising considerations old disciplins are revaluated. This applies for problems being discussed under the topic "biodynamic availability" and lymphology. Any therapist – if administering antibiotic or cytostatic substances – has to comply with complex pharmacocinetic considerations: how does the substance enter the organism, how and at which quantity and quality does it reach the receptor, and how is it eliminated. There are very few compartments accessable for uncomplicated and routine concentration determination. Those compartments are blood, urine and feces. In case that the receptor is not located within the bloodstream the half time as measured in the blood – for example – may differ from the half time at the place of action. Similar considerations apply for toxicity of different substances: blood and urine levels may appear subtoxic whereas toxic amounts may be accumulated at particular tissues or structures. Investigation of different substances appearance in the body lymph therefore may contribute new aspects to the view of pharmaco-dynamics.

II. *Anatomical Remarks*

The problem of kidney lymph formation includes composition of lymph as well as location of origin. Since conclusions drawn from lymph composition closely depend on site of lymph production the intrarenal pattern of the lymphatics is of major interest.

In the mammalian kidney lymphatics are found in the vicinity of large blood vessels exclusively. They are located in the loose connective tissue – or paravasal tissue – which surrounds especially the arteries. *Kriz* (1) demonstrated India ink particles in the paravasal tissue of the interlobar arteries after subcapsular injection. Therefore it may be concluded that the paravasal tissue represents an important link of the fluid drainage from the interstitium to the lymph vessels. However, extensive light- and electronmicroscopic studies of *Kriz* and *Dieterich* did not reveal lymphatic vessels in

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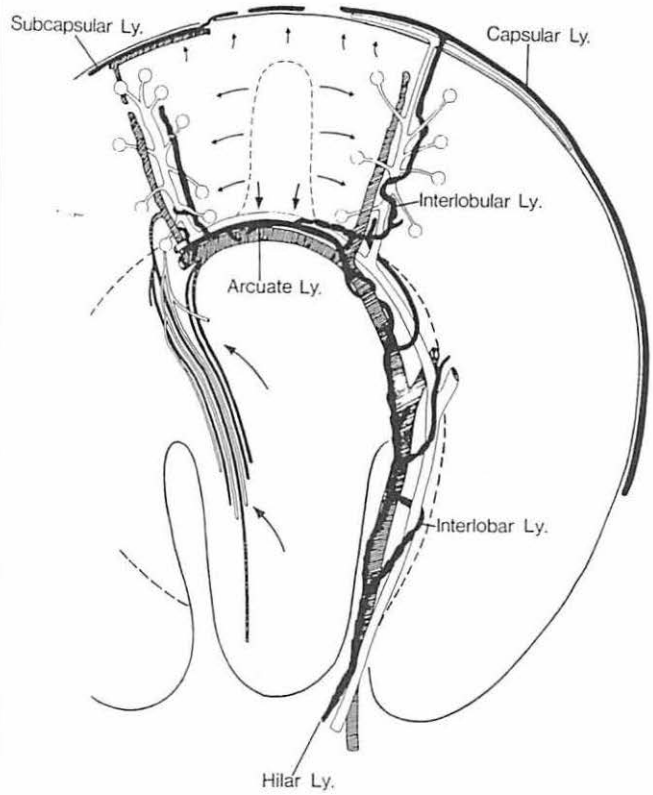

Fig. 1 Scheme of the renal lymphatics: 1) Intrarenal lymphatic system, originating as lymphatic capillaries in the area of the interlobular arteries continuing as arcuate lymphatic vessels and interlobar lymphatic vessels altogether forming few hilar vessels. Note: There are no lymphatic vessels in the medulla. 2) Capsular lymphatic system drains the renal capsule. 3) Subcapsular lymphatic system, may be found in the dog sometimes, anastomosing with the capsular system. 4) Connections of intrarenal and capsular/subcapsular lymphatics are developed in the dog kidney inconsistantly. Arrows show direction of lymph drainage. Lymphatics black, arteries white, veins oblique shaded.

the parenchyma between the tubules of cortex and medulla (2, 3).

Lymphatic capillaries in the area of the interlobular arteries are the origin of the *intrarenal lymphatic system* (fig. 1). The wall of these lymphatic capillaries consists only of a thin layer of endothelial cells without a basement membrane. At the cortico-medullary boundary the lymphatic capillaries drain into the arcuate lymphatic vessels, a postcapillary vessel type, which is provided with valves and a wall consisting of endothelium only. These vessels continue as similarly structured interlobar lymphatic vessels forming fewer hilar lymphatic vessels.

The *capsular lymphatic system* drains the renal capsule connective tissue. It seems most likely that they join the paraaortal lymphatics.

A subcapsular lymphatic system can be found in the cat kidney regularly and in the canine kidney occasionaly. In these species a very well developed system of superficial renal veins is accompanied by lymphatics towards the hilus. *Connections* between capsular and subcapsular lymphatics are regularly found. In the kidney of the dog and of Meriones shawii, a desert rodent, there are individual capsular arteries being distal portions of the interlobular arteries reaching and supplying the renal capsule. In some cases these arteries are accompanied by lymphatics. In some individuals these lymphatics establish the only connections between the intrarenal and the capsular lymphatic system.

III. *Lymphatic Drainage*

The renal cortex is drained mainly by interlobular lymph vessels in cooperation with the loosely structured paravasal tissue. Only a minor part of the cortical tissue fluid is drained by the arcuate lymphatic vessels and by the capsular and subcapsular lymphatic system (fig. 1). Absorption of cortical fluid is not res-

tricted to these vessels exclusively. In addition there may be some absorption by the postcapillary arcuate and interlobar lymphatics in cooperation with paravasal tissue. Any lymphatic outflow from the *renal medulla* via lymph vessels seems highly unlikely since lymphatics in this region of the kidney could never be detected by different means otherwise established for visualization of lymphatics (2,3). Besides, any extensive interstitial drainage of the medulla by lymphatics would deeply disturb the osmotic processes of the countercurrent consent multiplication system for final urine concentration. The lymphatic drainage of the medulla is organized via the blood vascular system, especially by the venous vasa recta (fig. 1). The fact that there are no medulla lymphatics may have some clinical relevance since it is generally accepted that the medullary physiology makes this area of the kidney more vulnerable to pyelonephritis. Furthermore, it should be kept in mind that lymph as derived from cortical or hilar renal lymphatics represents renal cortical interstitium mainly and may contain medullar portions as drained along the vasa recta.

IV. Lymph Composition

As far as composition of renal lymph is concerned concentrations of electrolytes do not seem to differ from blood plasma, whereas protein concentration is approximately half of that of the plasma. In contrast concentrations of urea, inulin and especially paraaminohippuric acid (PAH) were lower in renal lymph than arterial plasma. This might suggest a possible association with nephron function.

V. *Lymph Formation*

Physiological findings of *Keyl* et al. (4) stress our anatomical findings as outlined above. They argue that one would expect differing concentrations of ions in renal lymph when the osmolality of urine is altered since the concentration of ions in the medulla is directly related to renal concentrating ability. In addition PAH extraction is high in the cortex and low in the medulla. Though, one would expect PAH concentration of medulla lymph to come near to arterial blood plasma. But experiments in anesthetized and conscious animals showed constant renal lymph composition under varying renal concentration ability. PAH concentrations in renal capsular and hilar lymph were identical. Only when the renal vasculature was maximally dilated by acetylcholine PAH concentration of hilar lymph surpassed that of cortical lymph. These findings suggest that the renal cortex is the main site of lymph formation. Renal medulla may partly contribute to lymph formation under particular circumstances via the vasa recta.

Swann (5), a physiologist, contributed a very interesting particularity of the kidney which gives some strong explanation on the relatively high renal lymph production which may be as high as urine output: there are connective tissue rings at the outlet of the small renal veins that maintain pressures at 25 mm Hg average – much higher than pressures usually recorded in the main renal vein. In the view of renal lymph production it is interesting to note, that it takes about 25 mm Hg venous pressure to produce edema in extremities under experimental conditions and this same pressure also approximates the oncotic pressure of the blood plasma. Thus, renal lymph represents a vascular transudate the quantity of which is mainly venous pressure dependent. Whereas elevation of main renal vein pressure leads to an almost uniform increase of renal lymph production there are different reactions to ureteral obstruction. In the dog for example there is a renal lymph flow increase whereas in the calf renal lymph output remains constant during ureteral obstruction. Anatomical studies indicate that this is due to obstruction of the main renal vein by the congested renal pelvis. This finding objects the so called safety valve function of renal lymphatics.

Material and Methods

Renal lymph – hilar and/or capsular – as well as cisterna chyli lymph was obtained from 12 male mongrel dogs under Nembutal anesthesia. Blood and urine samples have been taken additionally. All samples have been obtained simultaneously starting with baseline samples and samples following i.v. bolus injection of

10 mg/kg Sisomicin (4 dogs), Tobramycin (4 dogs) and Gentamicin (4 dogs) accordingly. The antibiotic samples were asseyed by an agar well diffusion method (6).

In another study 125 J labelled Na-diatrizoate (5 dogs) and methylglucamine diatrizoate (5 dogs) was i.v. bolus injected. Samples were obtained according to a technique described previously (7). Particular care was taken to minimize sampling intervalls. The samples were asseyed with a well type scintillation counter.

Results

Aminoglycosides

Figures 2, 3 and 4 show that the substances investigated build up high concentrations in plasma and very high concentrations in urine. Kidney and cisterna chyli lymph concentrations do not reveal significant concentration differences. The overall results of Sisomicin are somewhat lower as compared to Tobramycin and Gentamicin because of an different arrangement of the bio assey. Two hours after application and thereafter lymph concentrations are practically identical with plasma concentrations. Shortly after application of the antibiotics kidney lymph concentrations of Sisomicin and Gentamicin reach 80% of the corresponding plasma values whereas corresponding Tobramycin levels reach 50%. Cisterna chyli lymph concentrations do not significantly deviate from plasma values.

Contrast Media

No differences were seen in the appearance of the curves in the two groups of animals. Therefore only one curve is shown in fig. 5. By comparing the results of dogs with differing renal lymph flow rates it becomes apparent that the peak of cm concentration in renal lymph shifts towards the plasma peak with the lymph flow increasing. When renal lymph flow rate is taken into consideration and the curve corrected accordingly there is no visible difference between the curves for plasma and renal lymph CM concentration. Note the almost instantaneous appearance of CM in renal and cisterna chyli lymph (fig. 5).

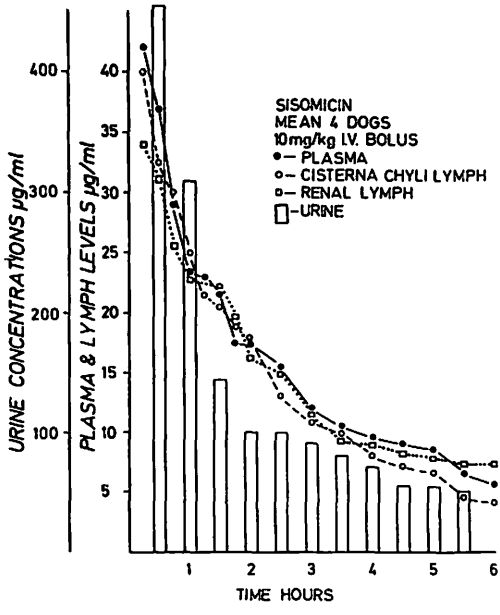

Fig. 2 Sisomicin levels in body fluids after i.v. bolus injection.

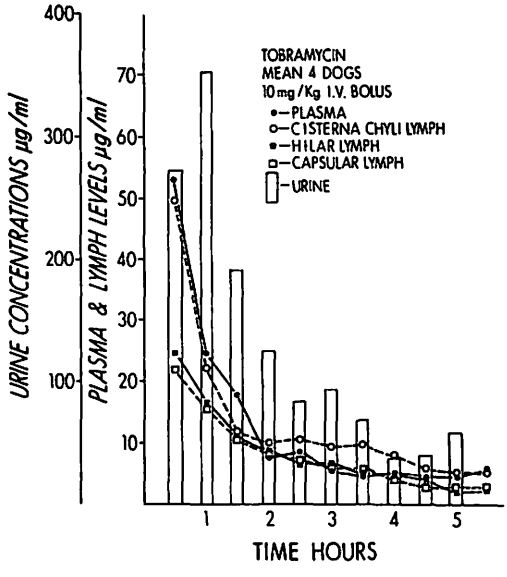

Fig. 3 Tobramycin levels in body fluids after i.v. bolus injection.

In the first 45 minutes after injection the concentration in both renal lymphatic compartments are almost identical to plasma levels while the concentration in the cisterna chyli

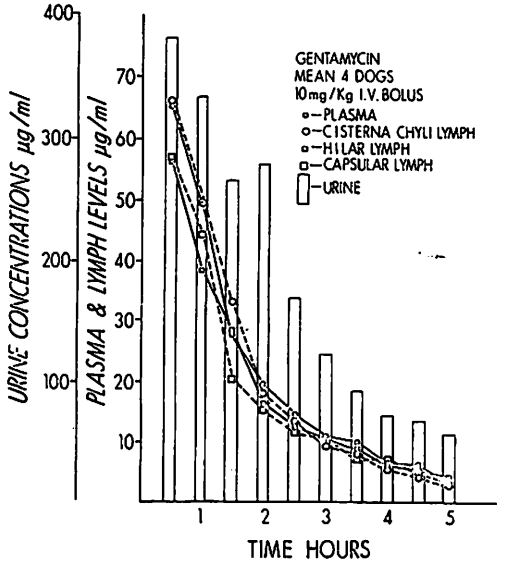

Fig. 4 Gentamicin levels in body fluids after i.v. bolus injection.

remains slightly above the plasma concentration. In the period there-after both renal lymphatic compartments decline below plasma concentration while cisterna chyli lymph contains slightly more CM than plasma. A statistical comparison between both renal lymph concentrations and cisterna chyli levels showed a significant difference ($.005 < p < .01$).

Discussion

Our data on dogs show Sisomicin and Tobramycin as well as Gentamicin to appear in high concentrations in the systemic lymph as represented by cisterna chyli lymph and in the kidney interstitium as characterized by renal lymph (12). This is an important finding since pyelonephritis in its early stages is considered to be located in the interstitium.

Presuming that our experimental findings reflect the pharmacodynamic situation of the human kidney this would give the clinician a good estimate of what tissue concentration he may achieve at a given peripheral venous blood concentration. Regarding the aminoglycosides investigated doses of 1 mg/kg would build up reliable tissue levels (8). The marked concentration decay of the drugs investigated in all compartments following the injection should be kept in mind making constant infusion mandatory in cases were more constant concentrations are desired. By comparing the aminoglycoside lymph levels to those of Penicillin G a very significant difference becomes evident (9, 10). Under administration of clinical doses Penicillin G only reaches lymph levels half as high as the plasma levels. This is important to know when treatment of renal infection is attempted.

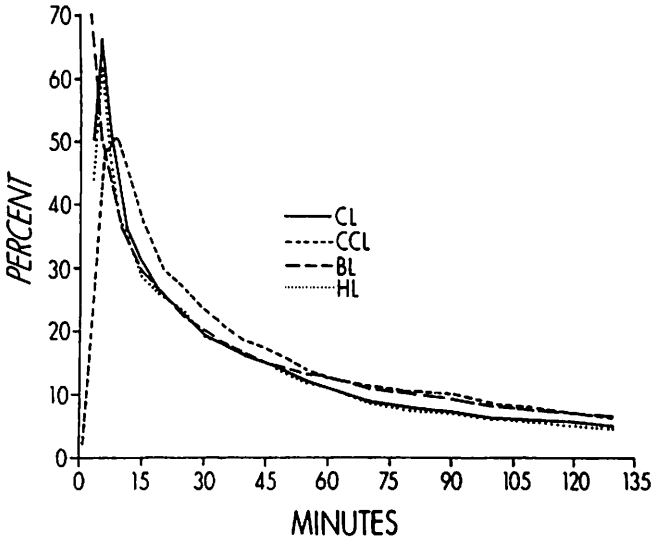

Fig. 5 Average concentrations of sodium diatrizoate after i.v. bolus injection in plasma and lymphatic compartments in 5 dogs with correction for flow rates.

Another interesting finding is the distribution pattern in the different compartments. Renal lymph concentrations were closely related to plasma values, although urine concentrations were up to 20 times higher in some animals. This supports the thesis that vascular transudate contributes the overwhelming part in formation of renal lymph and that renal lymph from cortical and hilar vessels is formed in the cortex. Tubular readsorbate seems to play a minor role or no role at all. The fact that there is no significant difference between capsular and hilar renal lymph despite high concentration gradients of homogenates from cortex and medulla have been demonstrated (11) support this thesis.

Our results suggest that renal interstitial handling of watersoluble CM is comparable to aminoglycoside antibiotics. Both substances are of similar and relatively low molecular weight while protein binding is low. By taking all samples at rather short intervalls we were able to demonstrate an almost instantaneous appearance of the CM in the kidney interstitium. In addition,these findings urge reflections upon the role of the interstitium in the distribution pattern of low molecular substances in the body (13). During the first 30 to 45 minutes, the concentration of CM remains significantly higher (up to 7 per cent) in the cisterna chyli than in plasma. This finding is explicable by the reservoir function of the systemic interstitial fluid (as represented by cisterna chyli lymph) which under a condition of steady state supplies the plasma with CM as it is cleared rapidly by glomerular filtration. Thus, the time required for refilling the intravasal space from the interstitium is a function of the concentration difference in plasma and cisterna chyli lymph.

In contrast renal interstitium (as represented by cortical and hilar lymphatics) CM concentrations showed no significant differences as compared to plasma which is due to an extremly short distance the CM has to traverse by transudation from the postcapillary veins into the interstitium. At the later stage of the experiment, however, renal lymph concentration declined below plasma and systemic lymph values ($.005 < p < .01$).

Though there is no straight explanation at hand for this change of the distribution pattern through the course of the experiment the cause might be found in tubular activity. This does not play a role at high plasma concentration with glomerular filtration of CM highly exceeding "tubular maximal concentration" (Tm) (14, 15, 16). But at the later stage with plasma concentration of CM declining below the Tm level active tubular secretion eliminates CM from the peritubular interstitial space thus reducing the concentration in renal lymph below plasma and cisterna chyli levels.

Thus, it appears that – within the kidney – there is a regional distribution pattern of different substances in terms of medulla and cortex. By cannulation of renal lymphatic vessels – hilar or capsular – composition of the renal cortical interstitial fluid can be studied as well as appearance of different substances administered to the organism. Since the renal medulla interstitium is not drained by lymph vessels this space is not directly accessable by cannulation of lymphatic vessels. Thus, for access of the medulla interstitium methods as micropuncture techniques should be considered.

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