INVESTIGATIONS ON DISTRIBUTION AND TURNOVER RATE OF $^{14}$C-UREA AND TRITIATED WATER IN RENAL FAILURE

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Problems of urea distribution in renal failure have been repeatedly discussed in the last years (Biro et al., 1965; Blackmore and Elder, 1961; Grossmann and Kopp, 1966; Pecherstorfer, 1966; Shackman et al., 1962). It has been assumed quite often that with renal failure considerable gradients can exist between extracellular and intracellular concentrations of urea and NPN.

Nevertheless the chemical analysis of the concentration gradients between extracellular space (plasma) and intracellular space (muscle tissue checked through biopsy) indicates certain technical difficulties since the test results show differences (Shackman et al., 1962; Pecherstorfer, 1966).

To observe the distribution of urea in the extra- and intracellular compartments of body water in patients with renal failure we have therefore undertaken investigations with radioactive urea and water.

METHOD

Patients with renal failure of different severity were injected simultaneously i.v. with $^{14}$C-urea (50 $\mu$Ci) and tritiated water (200 $\mu$Ci). The radioactivity of $^{14}$C-urea (Walser and Bodenlos, 1959; Robson et al., 1964) and THO (Boling, 1963) was measured in samples of blood and urine, obtained at different times after injection.

In addition, urea-N was determined using the diacetyl-monoxime method. In patients suffering from chronic renal failure, $^{14}$C-urea and THO were injected 3 days prior to dialysis; in cases of acute renal failure, however, the injection was done at least 3 hrs before dialysis. The following parameters were determined:

1. The distribution volume of $^{14}$C-urea and THO.
2. The whole body-content of urea-N and the urea-turnover rate.

The following additional parameters were determined only in dialysed patients:
3. The decrease (half-life time) of $^{14}$C-urea and THO in the blood during dialysis.
4. The changes of $^{14}$C-urea activity in the blood after dialysis.
5. Urea-turnover rate in one patient before and after nephrectomy.

$^{14}$C-urea distribution volume, turnover rate and turnover were calculated by the method of Walser and Bodenlos (1959).

Dialyses were performed with coil kidneys as well as with Kiil kidneys.

RESULTS

re 1. The distribution volumes of $^{14}$C-urea and THO were nearly identical, i.e., even in
patients with a very high pool of urea-N the distribution volume of $^{14}$C-urea did not exceed the volume of total body water. The $^{14}$C-urea/THO-ratio was 0.997 (11 patients) (Table 1).

re 2. The pool of total urea-N was increased in proportion to the degree of renal functional impairment (14 patients). A good correlation was found between the urea-turnover rate and the extent of renal failure as determined by clinical and laboratory data, for instance by endogenous creatinine clearance, when available. Patients with a urea-turnover rate of less than 25%/day required maintenance dialysis (normal values: more than 110%/day) (Fig. 1).

re 3. During the dialysis, $^{14}$C-urea and THO in the blood decreased approx. equally fast. The ratio of the half-life time of THO/$^{14}$C-urea was 0.95 (6 patients). This indicates that $^{14}$C-urea is dialysed approx. with the same speed as tritiated water (Fig. 2).

re 4. Within the first hour after dialysis, the $^{14}$C-urea concentration of the blood increased slightly, presumably as a result of an outflow of $^{14}$C-urea from the intracellular space.

![Graph](image-url)

Fig. 1. Urea turnover rate in chronic renal failure. The decrease of specific activity of $^{14}$C-urea demonstrates a simple exponential function with a short half-life time in the normal case and an increased half-life time in the case of renal failure. The turnover rate is obtained as the slope of the line relating log plasma concentration to time using values obtained after equilibration. Patients with a urea turnover rate of less than 25%/day required maintenance dialyses.
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<table>
<thead>
<tr>
<th>Patient</th>
<th>Creatinine</th>
<th>Urea-N</th>
<th>$^{14}$C-urea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C. ml/min.</td>
<td>Se conc. mg/100 ml</td>
<td>BUN mg/100 ml</td>
</tr>
<tr>
<td>I</td>
<td>SCH 35 y.</td>
<td>130</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>GÖ 33 y.</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>II</td>
<td>WÖ*** 63 y.</td>
<td>24.0</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>KO* 57 y.</td>
<td>5.56</td>
<td>9.0</td>
</tr>
<tr>
<td></td>
<td>GR* 45 y.</td>
<td>8.05</td>
<td>8.4</td>
</tr>
<tr>
<td></td>
<td>SI** 44 y.</td>
<td>6.41</td>
<td>8.1</td>
</tr>
<tr>
<td>III</td>
<td>LO 45 y.</td>
<td>4.65</td>
<td>14.0</td>
</tr>
<tr>
<td></td>
<td>ST 45 y.</td>
<td>20.9</td>
<td>152</td>
</tr>
<tr>
<td></td>
<td>TRW 35 y.</td>
<td>7.26</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>GA 42 y.</td>
<td>23.0</td>
<td>161</td>
</tr>
<tr>
<td></td>
<td>BO 38 y.</td>
<td>18.0</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>FR 47 y.</td>
<td>8.5</td>
<td>67.6</td>
</tr>
<tr>
<td></td>
<td>AL 59 y.</td>
<td>2.5</td>
<td>14.9</td>
</tr>
</tbody>
</table>

I. Normal kidney function.
II. Impairment of kidney function due to Polycyst. Dis.*, C.G.*, and C.P.***
III. Patients requiring maintenance dialysis (Data determined before first dialysis with the exception of AL and FR).

$k_0 =$ Urea-turnover rate

Within the next hour at the latest the concentration returned to an equilibrium. The extent of the outflow could be estimated by a comparison of the plasma urea-N concentration immediately after dialysis and at the time, when $^{14}$C-urea had equilibrated. It turned out that this amount was very low and that it concerned only a very low fraction of the total urea-N pool. In 2 patients undergoing RDT the calculated amount was less than 0.5 g, in 1 patient with ARF it was 1.25 g (Fig. 3).

**Fig. 2.** Decrease of THO and $^{14}$C-urea in plasma during dialysis. Ratio $t/2$ THO/$t/2$ $^{14}$C-urea = 0.96. (Pat. BE, 23 y, ☥; dialysis performed with a Kiil kidney. In dialyses performed with coil kidneys the ratio did not alter.)

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Fig. 3. $^{14}$C-urea plasma concentration during and after dialysis. Estimation of the outflow of urea from the intracellular space during equilibration after dialysis:

I. in an approach (without consideration of production and degradation of urea during equilibration)

II. by determination of the remaining $^{14}$C-urea contents in the body after dialysis and its distribution.

Pat. HE, 47 yr, o
BWt = 63.1 kg
TBW = 27.01
ECF* = 12.61
ICF = 14.41

1. Equilibrium time of $^{14}$C-urea after dialysis = 2 hrs

BUN at end of dialysis 176 mg/100 ml
BUN 2 hrs after dialysis 188 mg/100 ml

difference 12 mg/100 ml

$12 \text{mg/100 ml} \times 12.61 \text{(EFC)} = 1.5 g$

UN from ICF → ECF

since excess UN production during 2 hrs was not considered: <1.5 g UN from ICF → ECF

* assumed as 20% of BWt

II. $^{14}$C-urea eliminated during dialysis = 43.9%
remaining = 56.1%

$^{14}$C-urea plasma conc. at end of dialysis = 1.96%/l

$^{14}$C-urea virtual distr. space at end of dialysis = 56.1/1.96 = 28.7 l

Dialysis end:

BUN = 176 mg/100 ml

$\times 28.7 l = 50.5 g \text{ UN in total body}$

$\times 12.61 = 22.2 g \text{ UN in ECF}$

$\times 16.11 = 28.3 g \text{ UN in ICF (A)}$

2 hrs after dialysis:

BUN = 188 mg/100 ml

$\times 27.0 l = 50.70 g \text{ UN in total body}$

$\times 12.61 = 23.65 g \text{ UN in ECF}$

$\times 14.41 = 27.05 g \text{ UN in ICF (B)}$

During equilibrium time $A - B = 1.25 g \text{ UN}$
from ICF → ECF

The urea outflow from intracellular space was a very low fraction of the total urea pool and was discontinued at latest 2 hrs after dialysis. Thus it cannot explain the well-known accelerated rate of rise of the plasma urea concentration during first post-dialysis day.

re 5. A total nephrectomy was performed on one patient, who was treated with maintenance dialysis and who suffered excessive hypertension. $^{14}$C-urea plasma concentration decreased preoperatively with a half-life time of 136 hrs, after nephrectomy $^{14}$C-urea half-life time increased to 204 hrs. In this patient the urea-turnover rate was 12.29%/day preoperatively and 8.15%/day postoperatively (Fig. 4). The turnover rate of 8% per day postoperatively demonstrates extrarenal degradation of urea. This metabolic destruction of urea was calculated to amount to 57.4 mg/hr two hours after dialysis, but 193 mg/hr 3 days after dialysis. The urea degradation decreased with the diminution of the total body urea contents after dialysis and increased with the enlargement of the urea pool during the following days.

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![Graph showing decrease of $^{14}$C-urea and THO plasma concentration before and after nephrectomy.]

*Fig. 4. Decrease of $^{14}$C-urea and THO plasma concentration in a patient in RDT before and after nephrectomy (for explanation see text).*

**CONCLUSIONS**

The investigations with $^{14}$C-urea and THO show that there is no increased urea distribution volume in renal failure. The urea distribution volumes were nearly identical with the volume of the total body water.

Renal failure alone does not lead to a marked intra- and extracellular concentration gradient. During dialysis, however, such a temporary concentration gradient occurs; but it concerns only a minor quantity and the equilibrium is regained within 2 hours of dialysis. The well known temporarily accelerated increase of serum urea concentration during the first post-dialysis day seems to be mainly due to the great decrease of urea degradation that takes place after dialysis, as it could be demonstrated in one patient with total nephrectomy.

**ACKNOWLEDGEMENT**

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**REFERENCES**


ICS 131, Excerpta Medica, Amsterdam.


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