NALIDIXIC ACID KINETICS IN RENAL INSUFFICIENCY

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1 A pharmacokinetic study of nalidixic acid (NA) and metabolites was carried out in 23 patients with differing renal function so as to determine the influence of renal insufficiency on the excretion and biotransformation rate of this antibacterial agent. Plasma and urine concentration of NA and of its 7-hydroxy (HNA) and 7-carboxy (CNA) derivatives were measured after a single oral administration.

2 Renal insufficiency did not markedly affect the renal clearance of NA while it significantly decreased the elimination rate of HNA, a compound which largely excreted into the urine.

3 Interestingly, CNA which could never be detected in the plasma of patients with normal renal function appeared in that of patients with renal insufficiency. Plasma concentrations of CNA and creatinine were positively related, and the amount of urinary CNA increased with the renal impairment.

4 These results suggest that HNA can still be biotransformed into CNA by the impaired kidney. Since CNA cannot be easily excreted in the urine of patients with renal insufficiency it is hypothesized that this compound back diffuses into the plasma.

5 Finally, the study of the urinary concentrations of NA and metabolites shows that a standard NA dosage can be used, at least in patients with mild renal insufficiency.

Introduction

Nalidixic acid, 1-ethyl-1, 4-dihydro-7-methyl-4-oxo-1, 8-naphthyridine-3-carboxylic acid (NA), is an antibacterial drug still widely used for urinary tract infections (Barlow, 1963; Stamey, 1971). Its two major metabolites are 7-hydroxynalidixic acid (HNA), which exhibits antibacterial properties equal to NA (McChesney *et al.*, 1964; Moore *et al.*, 1965; Portmann *et al.*, 1966) and 7-carboxynalidixic acid (CNA), which is inactive.

By using a specific high pressure liquid chromatographic technique (Cuisinaud *et al.*, 1980) we could demonstrate, in normal humans having received single and repeated oral doses of NA, that CNA accounted for 25% of the total urinary NA and metabolites although it was not detectable in plasma (Ferry *et al.*, 1981). This finding suggests that CNA could be, at least partially, formed within the kidney.

In the present work we studied the kinetics of NA and metabolites in patients with renal insufficiency so as to determine (1) the need of a modification of drug dosage in patients with renal impairment treated for urinary tract infection and (2) the possible alteration of CNA formation by the impaired kidney.

Methods

Subjects

After having received their fully-informed consent, 23 patients, 15 women and 8 men, with a history of urinary tract infection, were divided into three groups according to their plasma creatinine concentration (PCr, $\mu\text{mol l}^{-1}$). Group I consisted of 11 women with normal renal function (PCr < 100 $\mu\text{mol l}^{-1}$) aged from 22 to 34 years and weighing from 45 to 65 kg. Group II consisted of 4 men and 2 women with mild renal insufficiency (PCr between 100 and 300 $\mu\text{mol l}^{-1}$). They were aged 30 to 57 years and weighed between 52 and 89 kg. Group III consisted of 4 men and 2 women with severe renal insufficiency (PCr above 300 $\mu\text{mol l}^{-1}$) who were aged 23 to 52 years and weighed between 50 and 85 kg.

Drug administration

Overnight fasted patients received a single 1 g oral dose of NA (Negram[®]) together with 100 ml tap water at 08.00 h. The first standardized meal was allowed 4 h after dosing.

Blood and urine sampling

According to a time schedule previously determined several 5 ml blood samples were drawn in heparin before and after dosing. For the urine, each micturition was immediately placed at +4°C. The separated plasma and the urine aliquots were kept at -80°C until assayed for their total content of unconjugated NA, HNA and CNA by the technique of Cuisinaud *et al.* (1980).

Calculations and kinetic analysis

Due to the absence of intravenous administration a complete kinetic analysis was not possible. Consequently, only clinically relevant parameters were obtained: maximum concentration ($C_{\max}$, $\mu\text{g ml}^{-1}$), time necessary to reach $C_{\max}$ ($t_{\max}$, h), and area under the plasma concentration time curves ($\text{AUC}_{0-24\text{ h}}$, $\mu\text{g ml}^{-1}\text{ h}$), calculated by the trapezoidal method.

Since the body weight of the patients was widely different the plasma concentration derived parameters, $C_{\max}$ and $\text{AUC}_{0-24\text{ h}}$, were corrected for this variable.

The renal clearance (CL_R) of NA and metabolites was calculated from the AUC and the cumulative urinary excretion observed during 24 h after dosing by the expression:

$$\text{CL}_R (\text{ml/min}) = \frac{\text{urinary excretion } 0-24 \text{ h } (\mu\text{g})}{\text{AUC}_{0-24 \text{ h}} (\mu\text{g ml}^{-1} \text{ min})}$$

Results are expressed as mean $\pm$ s.e. mean with further statistical analysis by the non parametric Wilcoxon sign test.

Results

The mean plasma concentrations of NA, HNA and CNA observed are shown in Figure 1 and the calculated pharmacokinetic parameters in Table 1.

Concerning NA, renal insufficiency induced a decrease in $C_{\max}$ body weight and in $\text{AUC}_{0-24\text{ h}}$ body weight, which was associated with an increase in $t_{\max}$. Since the apparent elimination rate of NA was not markedly altered by the renal impairment these changes would suggest either a decrease in the absorption of the drug, or an increase in its distribution volume. This latter hypothesis would appear more probable since NA is largely bound to plasma proteins (Moore *et al.*, 1965) which are known to be altered in renal insufficiency.

$C_{\max}$ body weight and $t_{\max}$ for HNA were significantly increased in patients with renal impairment. Otherwise in each of the three groups of patients $t_{\max}$ for HNA was observed 1 h after that of NA which indicates that the rate of hydroxylation of NA was not altered. Contrarily to NA, a marked increase in the

Figure 1 Plasma concentrations (mean $\pm$ s.e. mean) of NA (a), HNA (b) and CNA (c) following a single 1 g oral dose of NA in patients with normal renal function ($\blacktriangle$), mild ($\circ$) and severe ($\blacksquare$) renal insufficiency.

$\text{AUC}_{0-24\text{ h}}$ body weight and a decrease in the apparent elimination rate, the urinary excretion and the renal clearance of HNA were observed in patients with renal insufficiency. A positive significant relationship was found between $\text{AUC}_{0-24\text{ h}}$ body weight values for HNA and those of plasma creatinine ($r = 0.754$; $n = 23$; $P < 0.001$).

When considering CNA, the major finding was its appearance in the plasma of patients with renal insufficiency, while it was not detectable in those with normal function. In addition, $C_{\max}$ body weight and $\text{AUC}_{0-24\text{ h}}$ body weight for CNA were positively related with the plasma creatinine values ($r = 0.848$; $n = 12$; $P < 0.001$ and $r = 0.858$; $n = 12$; $P < 0.001$ for $C_{\max}$ body weight and $\text{AUC}_{0-24\text{ h}}$ body weight respectively). The amount of CNA excreted in the urine increased with renal insufficiency, where it represented 18%, 32% and 52% of the total urinary excretion of NA and metabolites in patients of groups I, II and III respectively. Finally, there was a close

Table 1 Pharmacokinetic parameters for NA, HNA and CNA in the three groups of patients studied (mean $\pm$ s.e. mean).

	Group I (n = 11)	Group II (n = 6)	Group III (n = 6)
<i>Plasma creatinine</i> ($\mu\text{mol l}^{-1}$)	79 $\pm$ 2	184 $\pm$ 9 ^a	600 $\pm$ 110 ^{a,b}
<i>Naladixic acid</i>			
t_{max} (h)	1.5 $\pm$ 0.2	1.9 $\pm$ 0.1	3.4 $\pm$ 0.7 ^a
C_{max} body weight ($\mu\text{g ml}^{-1} \text{ kg}^{-1}$)	0.63 $\pm$ 0.06	0.42 $\pm$ 0.09 ^a	0.28 $\pm$ 0.06 ^a
AUC _{0-24h} body weight ($\mu\text{g ml}^{-1} \text{ h kg}^{-1}$)	1.6 $\pm$ 0.14	1.1 $\pm$ 0.21 ^a	1 $\pm$ 0.22 ^a
U _{NA0-24 h} (mg)	32.8 $\pm$ 12	24.2 $\pm$ 2.5	18 $\pm$ 8.7
CL _R (ml min ⁻¹)	6.5 $\pm$ 2.4	6.5 $\pm$ 1.7	4.5 $\pm$ 1.7
<i>Hydroxynalidixic acid</i>			
t_{max} (h)	2.5 $\pm$ 0.3	3 $\pm$ 0.4	4.5 $\pm$ 0.5 ^{a,b}
C_{max} body weight ($\mu\text{g ml}^{-1} \text{ kg}^{-1}$)	0.19 $\pm$ 0.03	0.15 $\pm$ 0.04	0.27 $\pm$ 0.06 ^a
AUC _{0-24 h} body weight ($\mu\text{g ml}^{-1} \text{ h kg}^{-1}$)	1.1 $\pm$ 0.16	1.1 $\pm$ 0.31	2.7 $\pm$ 0.62 ^{a,b}
U _{HNA0-24 h} (mg)	123 $\pm$ 23	62 $\pm$ 24	30.7 $\pm$ 9.5 ^a
CL _R (ml min ⁻¹)	39.1 $\pm$ 7.3	14.5 $\pm$ 5.8 ^a	4.6 $\pm$ 1.7 ^{a,b}
<i>Carboxynalidixic acid</i>			
t_{max} (h)		4.9 $\pm$ 0.8	7.3 $\pm$ 0.8 ^b
C_{max} body weight ($\mu\text{g ml}^{-1} \text{ kg}^{-1}$)		0.02 $\pm$ 0.005	0.1 $\pm$ 0.03 ^b
AUC _{0-24 h} body weight ($\mu\text{g ml}^{-1} \text{ h kg}^{-1}$)		0.09 $\pm$ 0.03	0.88 $\pm$ 0.39 ^b
U _{CNA0-24 h} (mg)	39.9 $\pm$ 6.8	47.2 $\pm$ 11.7	61.3 $\pm$ 3 ^a
CL _R (ml min ⁻¹)		140.3 $\pm$ 27	36.1 $\pm$ 8.7 ^b

^a Significant difference from mean Group I patients $P < 0.05$.^b Significant difference from mean Group II patients $P < 0.05$.

positive relationship between the urinary excretion of CNA, expressed as percentage of the NA + HNA + CNA urinary excretion and the AUC_{0-24 h} for HNA ($r = 0.85$; $n = 23$; $P < 0.001$) but not for NA ($r = 0.36$; $n = 23$; $P < 0.05$). This result suggests that CNA derives more from HNA than from NA.

In the urine, it appeared that, after a single oral dose of 1 g of NA, the sum of the concentrations of active compounds, i.e. NA + HNA, remained above or near from 5 times the minimum inhibitory concentration, 0.5 to 8 $\mu\text{g/ml}$ for most of the germs responsible for urinary infections (McChesney *et al.*, 1964), for 8 h following dosing in patients with normal or moderately impaired renal function. This was not the case in patients with severe renal insufficiency due to a slowed excretion of NA and HNA.

Discussion

NA is an antibacterial widely used in the treatment of urinary tract infections, which might have to be

administered to patients with impaired renal function.

Having previously described its kinetics (Ferry *et al.*, 1981) it was of interest to determine the influence of renal insufficiency on the elimination of NA and metabolites.

This was achieved, in the present work, After the administration of a single oral dose to patients with varying renal function. Both men and women were used since we have demonstrated that there were no sex-related differences in the kinetics of NA (Ferry *et al.*, 1981). However, due to the large variations in the body weight of our patients, the values of C_{max} and AUC_{0-24 h} were corrected for this factor.

Finally since the i.v. administration of NA is not possible in humans, the precise pharmacokinetics of NA were not known. Therefore only a restricted number of clinically relevant parameters were calculated in this study.

From the present work it appears that the elimination rate of NA is not markedly altered by renal insufficiency. This result confirms that the renal

elimination of NA is less important than its hydroxylation into HNA. The low values found for CL_R of NA are consistent with this statement.

On the contrary, HNA is mainly excreted by the kidney with a renal clearance near from the glomerular filtration rate. Therefore HNA accumulates in the body of patients with renal insufficiency.

Interestingly enough, CNA could be detected in the plasma of patients with altered renal functions, and its plasma concentrations were positively related with those of plasma creatinine. On the other hand, the amount of CNA excreted in the urine increased when the renal functions declined.

The absence of a detectable plasma concentration of CNA in patients with normal renal function could

reflect an hepatic formation of this compound followed by a rapid renal excretion.

However, by using the urinary excretion data, the calculated renal clearance of CNA might have exceeded 5 l/min in order to maintain its plasma concentration below the detection limit of 60 ng/ml.

As a consequence we have hypothesized that CNA could be formed within the kidney (Ferry *et al.*, 1981) and then rapidly excreted in the urine of subjects with normal renal function.

In patients with renal insufficiency, it can be suggested that the tubular formation of CNA is not altered, and the amount of CNA excreted in the urine increases with renal impairment, probably due to a larger amount of HNA which remains available for

Figure 2 Urinary concentrations (mean $\pm$ s.e. mean) of NA (▨), HNA (□) and CNA (■) following a single 1 g oral dose of NA in patients with normal renal function (I), mild (II) and severe (III) renal insufficiency. The dotted line indicates 5 times the level of the minimum inhibitory concentration.

the biotransformation. However the excretion of CNA into the tubular lumen is reduced in renal insufficiency which allows this compound to back diffuse into the plasma.

In conclusion the present work demonstrates that a standard NA dosage (1 g twice daily) can be used, at least in patients with moderate renal impairment since in these patients the urinary concentration of the active compounds—i.e. NA + HNA—remains

above 5 times the minimum inhibitory concentration for at least 8 h following dosage.

In addition the pharmacokinetics of CNA suggested that, in renal insufficiency, there could be a discrepancy between altered excretion processes and unaffected tubular biotransformation pathways.

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