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Effects of acute renal failure induced by uranyl nitrate on the pharmacokinetics of intravenous theophylline in rats: the role of CYP2E1 induction in 1,3-dimethyluric acid formation

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Abstract

In rats with acute renal failure induced by uranyl nitrate, the hepatic microsomal cytochrome P450 (CYP) 2E1 and CYP3A23 increased 2–4- and 4-times, respectively, CYP2C11 decreased to 80% of control, but the levels of CYP1A2 and CYP2B1/2 were not changed. It has been reported that theophylline was metabolized to 1,3-dimethyluric acid by CYP1A2 and CYP2E1 and 1-methylxanthine via CYP1A2, which was metabolized further to 1-methyluric acid via xanthine oxidase in rats. Hence, it was expected that the formation of 1,3-dimethyluric acid would show an increase in rats with renal failure as a result of induction of CYP2E1. The pharmacokinetics of theophylline were compared in control rats and rats with renal failure after intravenous administration of aminophylline, 5 mg kg^{-1} as theophylline. In rats with renal failure, the plasma concentrations of theophylline were considerably lower and the resultant total area under the plasma concentration–time curve from time zero to time infinity ($AUC_{0-\infty}$) of theophylline was significantly smaller (2200 vs 1550 μg min mL^{-1}) compared with control rats. In rats with renal failure, the plasma concentrations of 1,3-dimethyluric acid were considerably higher and the resultant $AUC_{0-6\,h}$ of 1,3-dimethyluric acid was significantly greater (44.4 vs 456 μg min mL^{-1}) compared with control rats. Moreover, the $AUC_{0-6\,h,\,1,3\text{-dimethyluric acid}}$/$AUC_{0-\infty,\,theophylline}$ ratio increased from 2.02% in control rats to 29.4% in rats with renal failure. The in-vitro intrinsic 1,3-dimethyluric acid formation clearance was significantly faster in rats with renal failure (734 vs 529 10^{-6} mL min^{-1}) compared with control rats using hepatic microsomal fraction. The results led us to conclude that in rats with uranyl nitrate-induced renal failure after the administration of aminophylline, 5 mg kg^{-1} as theophylline, there was an increase in the formation of 1,3-dimethyluric acid as a result of an increase in CYP2E1 expression.

Introduction

Chung et al (2002) reported that in rats with acute renal failure induced by uranyl nitrate, the hepatic microsomal cytochrome P450 (CYP) 2E1 was induced 2–4-times compared with control rats, based on northern and western blot analyses. Induction of CYP2E1 in rats with renal failure may be accompanied by an increase in urea and L-arginine catabolism and hence mitochondrial dysfunction. Results from our laboratories (unpublished data) showed that in rats with renal failure, the CYP3A23 increased 4-times and CYP2C11 decreased to 80% of control. The CYP1A2 and CYP2B1/2 expressions were not changed by acute renal failure.

Teunissen et al (1985) reported that in rats, theophylline was metabolized to 1,3-dimethyluric acid via CYP1A2 and CYP2E1 and 1-methylxanthine via CYP1A2, which was metabolized further to 1-methyluric acid via xanthine oxidase. Approximately 10% of intravenously administered theophylline was excreted unchanged in urine. After intravenous administration of theophylline, the formation of 1,3-dimethyluric acid decreased significantly (Han & Lee 1999) in rats pretreated with 2-(allylthio)pyrazine (a new chemopreventive agent) since 2-(allylthio)pyrazine suppressed CYP2E1 expression with almost no effect on CYP1A2 (Kim et al 1997). Hence, it could be expected that the

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formation of 1,3-dimethyluric acid could be increased in rats with renal failure due to CYP2E1 induction in the rats.

The pharmacokinetic changes of many drugs (either mainly excreted via renal excretion or by hepatic metabolism) have been reported in rats with renal failure. The total area under the plasma concentration–time curve from time zero to time infinity ($AUC_{0-\infty}$) was significantly greater and time-averaged total body (CL), renal (CL_R), and/or nonrenal (CL_{NR}) clearances were significantly slower after intravenous administration of the following drugs (or compounds) to rats with uranyl nitrate-induced renal failure: methotrexate (Park et al 1996), vancomycin (Engineer et al 1981), DA-1131, a new carbapenem (Kim et al 1998b), M1, an active component of a new anthracycline, DA-125 (Kim et al 1996), salicylic acid (Liu et al 1996), azosemide (Park et al 1998), diltiazem (Lee et al 1992), amiodarone (Fruncillo et al 1986), tetraethylammonium bromide and para-amino hippurate (Lin & Lin 1988). Those pharmacokinetic differences were due mainly to differences in the formation of conjugates or liver and/or kidney impairment in rats with uranyl nitrate-induced renal failure based on plasma and urine chemistry data and/or tissue microscopy (Kim et al 1998b and references therein). However, the relationship between pharmacokinetic changes of drugs and changes in CYP isozymes in rats with renal failure was not studied. The $AUC_{0-\infty}$ and CL of (−)-propranolol (Terao & Shen 1984; Lee & Ku 1999), ciclosporin (Lee & Ku 1998), YJA-20379-8, a new proton pump inhibitor (Kim et al 1998a), adriamycin (Lee et al 1996) and tacrolimus (Son et al 2000) were not significantly different between control rats and rats with acute renal failure.

In this study we induced renal failure in rats by administering uranyl nitrate, and then we administered intravenous aminophylline, 5 mg kg^{-1} as theopylline, to enable us to investigate the increase in the formation of 1,3-dimethyluric acid. We measured the maximum velocity (V_{max}), K_m (Michaelis–Menten constant) and intrinsic clearance (CL_{int}) for the formation of 1,3-dimethyluric acid from theophylline in hepatic microsomal fractions.

Materials and Methods

Chemicals

Aminophylline intravenous solution (250 mg/10 mL ampoule) was a product from Daewon Pharmaceutical Company (Seoul, Korea). Uranyl nitrate was obtained from BDH Chemicals (Poole, UK). 1,3-Dimethyluric acid, reduced form of β-nicotinamide adenine dinucleotide phosphate (NADPH) and β-hydroxylethyltheophylline (the internal standard of high-performance liquid chromatographic (HPLC) assay) were purchased from Sigma Chemical Company (St Louis, MO). Other chemicals were of reagent grade or HPLC grade and, therefore, were used without further purification.

Animals

Male Sprague–Dawley rats of 7–8-weeks of age (270–350 g) were purchased from Charles River Company (Atsugi, Japan). The rats were randomly divided into two groups, control rats and rats with uranyl nitrate-induced acute renal failure. Rats were maintained in a clean room (Animal Center for Pharmaceutical Research, College of Pharmacy, Seoul National University, Seoul, Korea) at a temperature between 20 and 23°C, with a 12-h light–dark cycle and a relative humidity of 50%. Rats were individually housed in metabolic cages (Tecniplast, Varese, Italy) under the supply of filtered pathogen-free air and water was freely available. The Animal Care and Use Committee of the College of Pharmacy, Seoul National University, approved the animal study protocol.

Induction of acute renal failure in rats by uranyl nitrate injection

Uranyl nitrate (the uranyl nitrate powder was dissolved in 0.9% NaCl-injectable solution to make a concentration of 0.5%), 1 mL kg^{-1} (5 mg kg^{-1}), was injected once via the tail vein of rats to induce acute renal failure (Kim et al 1998b and references therein). Control rats were injected with the same volume of 0.9% NaCl-injectable solution.

Measurement of V_{max}, K_m and CL_{int} for the formation of 1,3-dimethyluric acid from theophylline in hepatic microsomal fraction

On the fifth day, the livers of control rats (n = 5) and rats with renal failure (n = 5) were homogenized in an ice-cold buffer of 0.154 M KCl/50 mM Tris-HCl in 1 mM ethylenediamine tetraacetate (EDTA), pH 7.4. The homogenate was centrifuged at 9700 *g* for 30 min and the supernatant fraction was further centrifuged at 100 000 *g* for 90 min. The microsomal pellet was resuspended in buffer of 0.154 M KCl/50 mM Tris-HCl in 1 mM EDTA, pH 7.4. Protein content was measured using the method of Lowry et al (1951). The microsomal fraction (equivalent to 1 mg protein) was incubated with 400-μL 100 mM phosphate buffer (to have substrate concentrations of 0.5, 1, 5, and 10 mM as theophylline) and 50-μL 1.2 mM NADPH in a final volume of 500 μL in a thermomixer kept at 37°C and at a rate of 50 oscillations min^{-1}. The reaction was terminated by addition of 0.1-mL ice-cold 8% $ZnSO_4$ after 30-min incubation. The 1,3-dimethyluric acid formed was determined by HPLC analysis (Kwaskatsu et al 1989). The kinetic constants V_{max} (maximum velocity) and K_m (Michaelis–Menten constant, the concentration at which the rate is one-half of V_{max}) for the formation of 1,3-dimethyluric acid from theophylline were calculated using the Lineweaver–Burk plot (Lineweaver & Burk 1934) by linear regression and the method of least squares. Intrinsic 1,3-dimethyluric acid formation clearance (CL_{int}) was calculated using V_{max}/K_m.

Pretreatment of rats

In the early morning of the fifth day each rat received either intravenous administration of uranyl nitrate or 0.9% NaCl-injectable solution. Under light ether anaesthesia,

the jugular vein (for drug administration) and the carotid artery (for blood sampling) of each rat were cannulated with polyethylene tubing (Clay Adams, Parsippany, NJ). Both cannulae were exteriorized to the dorsal side of the neck where each cannula was terminated with long Silastic tubing (Dow Corning, Midland, MI). To allow free movement of the rat both the Silastic tubings were inserted into a wire. Each rat was housed individually in a rat metabolic cage (Daejong Scientific Company, Seoul, Korea) and was allowed 4–5 h to recover from the anaesthesia before the study began. The rats were not restrained during the experimental period.

Intravenous infusion study

Aminophylline, 5 mg kg^{-1} as theophylline, was administered by intravenous infusion over 1-min via the jugular vein (total injection volume was approximately 0.6 mL) of control rats (n = 10) and rats with renal failure (n = 10). A blood sample (approximately 0.12 mL) was collected via the carotid artery at 0 (to serve as a control), 1 (at the end of the infusion), 5, 15, 30, 45, 60, 90, 120, 180, 240, 300 and 360 min after administration of the drug. After centrifugation, a 0.05-mL plasma sample was stored in a −70°C freezer (Revco ULT 1490 D-N-S; Western Mednics, Asheville, NC) until HPLC analysis of theophylline and 1,3-dimethyluric acid (Kwaskatsu et al 1989). Approximately 0.3-mL heparinized 0.9% NaCl-injectable solution (20 units mL^{-1}) was used to flush the cannula immediately after each blood sampling to prevent blood clotting. At the end of 24 h, as much blood as possible was collected via the carotid artery and the plasma was stored at −70°C for the measurement of plasma protein binding. At the same time (24 h) the entire gastrointestinal tract (including its contents and faeces) was removed, transferred into a beaker containing 100 mL methanol (to facilitate the extraction of theophylline) and cut into small pieces using scissors. After stirring with a glass rod, two 0.05-mL samples of the supernatant were collected from each beaker and stored at −70°C until HPLC analysis of theophylline and 1,3-dimethyluric acid (Kwaskatsu et al 1989). At the same time (24 h), the whole kidney and liver of each rat were excised, rinsed or perfused with 0.9% NaCl-injectable solution, blotted dry with tissue paper and weighed. Small portions of each organ were fixed in 10% neutral phosphate-buffered formalin and then processed for routine histological examination with haematoxylin-eosin staining.

Plasma protein binding study

The binding of theophylline to plasma protein of control rats and rats with renal failure was determined using an equilibrium dialysis technique (Lee & Lee 1995). One millimeter plasma was dialysed against 1 mL isotonic Sørensen phosphate buffer (pH 7.4) containing 3.0% dextran to minimize volume shift, with a 1 mL dialysis cell (Fisher Scientific, Fair Lawn, NJ) and Spectral/Por 4 membrane (molecular weight cut-off of 12000–14000; Spectrum Medical Industries Inc., Los Angeles, CA). To reduce equilibration time, theophylline 5 $\mu g\ mL^{-1}$ was added into the plasma side (Guentert & Øie 1982). The dialysis cell was then incubated for 24 h in a water-bath shaker kept at 37°C and at a rate of 50 oscillation min^{-1} (Lee & Lee 1995).

Analytical procedure

The concentrations of theophylline and 1,3-dimethyluric acid in plasma samples were analysed by the HPLC method of Kwaskatsu et al (1989); acetonitrile 300 μL (containing 2 $\mu g\ mL^{-1}$ internal standard, β-hydroxyethyl theophylline) was added to a 50-μL plasma sample. After vortex-mixing and centrifugation, a 300-μL sample of supernatant was evaporated under N_2 gas. The residue was reconstituted with 100 μL mobile phase and 50 μL supernatant was injected directly onto HPLC column. The mobile phase, 10 mM acetate buffer (pH 5.0) : acetonitrile : tetrahydrofuran (94 : 5 : 1, v/v/v), was run at a flow rate of 1.0 mL min^{-1} and the column effluent was monitored by a UV detector set at 280 nm. The detection limits for theophylline and 1,3-dimethyluric acid in rat were 100 and 50 ng mL^{-1}, respectively. The coefficients of variation of the assay (within- and between-day) were generally low (below 8.90%).

Pharmacokinetic analysis

The $AUC_{0-\infty}$ for theophylline and AUC for up to 6 h for 1,3-dimethyluric acid ($AUC_{0-6\,h}$) were calculated by the trapezoidal rule method; this method utilized the logarithmic trapezoidal rule (Chiou 1978) for the calculation of the area during the declining plasma-level phase and the linear trapezoidal rule for the rising plasma-level phase. The area from the last data point to time infinity (for $AUC_{0-\infty}$) was estimated by dividing the last measured plasma concentration by the terminal rate constant.

Standard methods (Gibaldi & Perrier 1982) were used to calculate the clearance (CL), area under the first moment of the plasma concentration–time curve (AUMC), mean residence time (MRT) and apparent volume of distribution at steady state (Vd_{ss}) (Kim et al 1993).

The harmonic mean method was employed to calculate the mean values of Vd_{ss} (Chiou 1979), terminal half-life (Eatman et al 1977) and CL (Chiou 1980).

Statistical analysis

A P value of less than 0.05 was considered to be statistically significant using the unpaired t-test. All data are expressed as mean ± s.d.

Results

Induction of acute renal failure

In rats with acute renal failure, the kidney weight (% body weight) was significantly heavier (35.5% increase) com-

Table 1 Pharmacokinetic parameters of theophylline and 1,3-dimethyluric acid (1,3-DMU) after intravenous administration of theophylline, 5 mg kg^{-1}, to control rats and rats with acute renal failure induced by uranyl nitrate.

Parameters	Control	Renal failure
Body weight (g)	336±7.62	297±12.1**
Theopylline		
Terminal half-life (min)	221±83.9	225±89.0
$AUC_{0-\infty}$ (μg min mL^{-1})	2200±836	1550±347*
MRT (min)	335±78.8	313±74.2
CL (mL min^{-1} kg^{-1})	2.27±0.860	3.23±0.794*
Vd_{ss} (mL kg^{-1})	762±78.8	992±175**
$GI_{24\,h}$ (% of intravenous dose)	BD	BD
Protein binding (%)	11.9±3.53	14.4±2.02
1,3-DMU		
$AUC_{0-6\,h}$ (μg min mL^{-1})	44.4±10.1	456±127**
Kidney weight (% body weight)	0.812±0.101	1.10±0.104**
Liver weight (% body weight)	3.93±0.422	3.57±0.146

Values are mean (±s.d.), n = 10. BD: below detection limit. *$P < 0.05$, **$P < 0.001$.

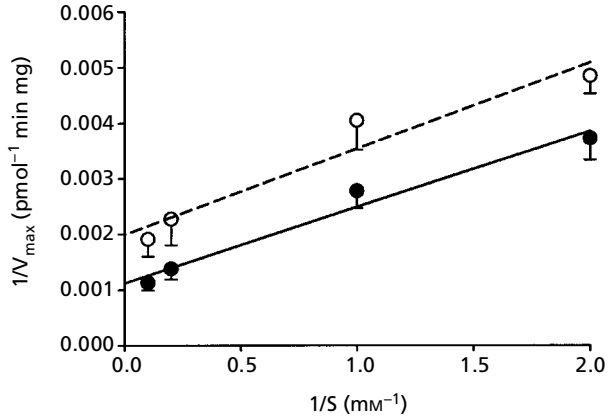

Figure 1 Lineweaver–Burk plot for the formation of 1,3-dimethyluric acid from theophylline in control rats (○, n = 5) and rats with acute renal failure induced by uranyl nitrate (●, n = 5). S represents concentration of theophylline. Vertical bars represent s.d.

Table 2 V_{max}, K_m and CL_{int} for the formation of 1,3-dimethyluric acid from theophylline in hepatic microsomes of control rats and rats with uranyl nitrate-induced acute renal failure.

Parameters	Control	Renal failure
V_{max} (pmol min^{-1} mg^{-1})	555±97.4	903±138**
K_m (mM)	1.08±0.220	1.23±0.0970
CL_{int} (10^{-6} mL min^{-1})	529±129	734±72.5*

Values are mean±s.d., n = 5, *$P < 0.05$, **$P < 0.001$.

pared with control rats (Table 1). Impaired kidney function in rats with renal failure was supported by kidney microscopy; the cortical distal convoluted tubules underwent complete necrosis whereas proximal convoluted tubules and glomeruli were intact. Medullary distal tubules were severely degenerated, but still viable. Collecting ducts were largely intact and contained numerous protein casts. The renal papilla and blood vessels were unremarkable. Impaired kidney function in rats with uranyl nitrate-induced acute renal failure has also been reported elsewhere (Kim et al 1998b and references therein). No significant findings were found by kidney microscopy in the control rats. In rats with renal failure, the livers were unremarkable except for mild patch degeneration at the centrilobular area and no evident necrosis was present. No significant findings were found by liver microscopy in the control rats.

Measurement of V_{max}, K_m and CL_{int} for the formation of 1,3-dimethyluric acid from theophylline in hepatic microsomal fraction

Figure 1 shows the Lineweaver–Burk plot, and the V_{max}, K_m and CL_{int} values are listed in Table 2. In rats with renal failure, the V_{max} values for the formation of 1,3-dimethyluric acid from theophylline in hepatic microsomal fraction were significantly faster (62.7% increase) compared with control rats; however, the k_m values were not significantly different between the two groups of rats (Table 2). As a result, the intrinsic 1,3-dimethyluric acid formation clearance, CL_{int}, in hepatic microsomal fraction was significantly faster (38.8% increase) in rats with renal failure (Table 2) indicating that the formation of 1,3-dimethyluric acid increased in rats with renal failure.

Pharmacokinetics of theophylline and 1,3-dimethyluric acid after intravenous administration of theophylline

Many investigators have reported dose-dependent metabolic disposition of theophylline in man (Lesko 1979; Birket et al 1984; Massey et al 1984) and in rats (Teunissen et al 1985). Therefore, theophylline (5 mg kg^{-1}) which has been reported to be in the range of linear pharmacokinetics in rats (Teunissen et al 1985) was administered intravenously to rats. The plasma concentrations of theophylline declined in a polyexponential fashion for both groups of rats, with considerably lower levels in rats with renal failure (Figure 2A). This resulted in a significantly smaller AUC of theophylline (29.5% decrease) in rats with renal failure compared with control rats (Table 1). The smaller AUC of theophylline in rats with renal failure could be due to significantly faster CL of theophylline (42.3% increase) (Table 1). In rats with renal failure, the Vd_{ss} was significantly larger (30.2% increase) compared with control rats and this could not be due to an increase in free fraction of theophylline in plasma; the unbound fractions of theophylline were 88.1 and 85.6% for control rats and rats with renal failure, respectively (Table 1). Although the exact reason is not clear, tissues of rats with renal failure had increased affinity for theophylline compared with control

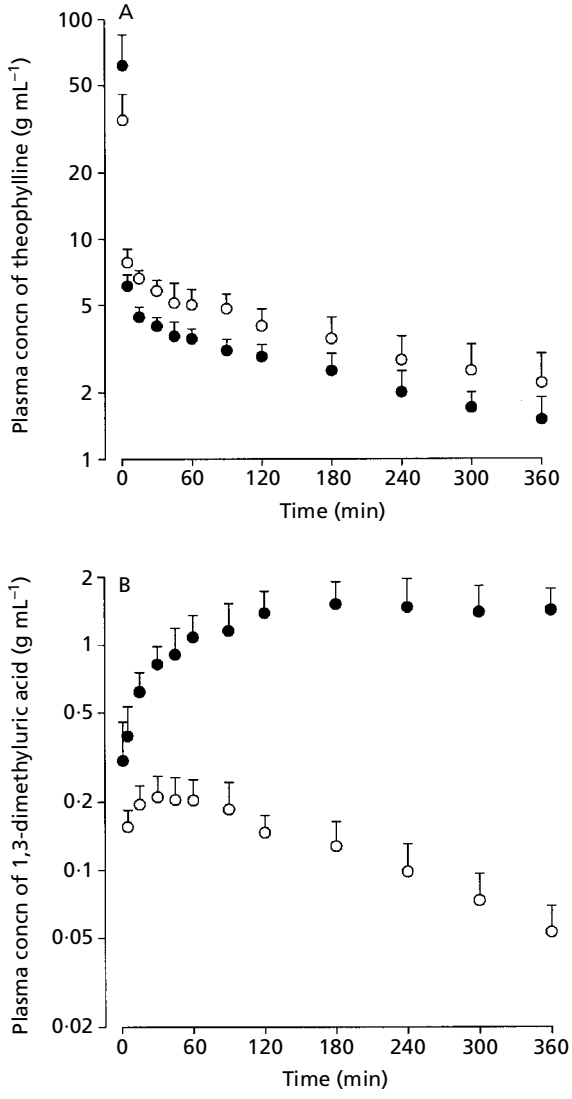

Figure 2 Mean arterial plasma concentration–time profiles of theophylline (A) and 1,3-dimethyluric acid (B) after 1-min intravenous infusion of aminophylline, 5 mg kg^{-1} as theophylline, to control rats (○, n = 10) and rats with acute renal failure induced by uranyl nitrate (●, n = 10). Vertical bars represent s.d.

rats. Unchanged theophylline recovered from gastrointestinal tract at 24 h ($GI_{24\,h}$) was below detection limit for both groups of rats (Table 2). The body weight gain decreased significantly (from 291 g to 297 g) in rats five days after treatment with uranyl nitrate compared with control rats (from 292 g to 336 g).

Formation of 1,3-dimethyluric acid after intravenous administration of theophylline was rapid for both groups of rats; 1,3-dimethyluric acid was detected in plasma from the first or second blood sampling time (Figure 2B). In rats with renal failure, the plasma concentrations of 1,3-dimethyluric acid were considerably higher compared with control rats (Figure 2B) and this resulted in a significantly greater $AUC_{0-6\,h}$ of 1,3-dimethyluric acid (927% increase) compared with control rats (Table 1).

Discussion

The changes of the reported pharmacokinetic parameters of many drugs (or compounds) in rats with uranyl nitrate-induced renal failure were due mainly to changes in the formation of conjugates or impaired kidney and/or liver function in the rats as mentioned earlier. However, the relationship between pharmacokinetic changes of drugs and changes in CYP isozymes in rats with renal failure was not studied.

Teunissen et al (1985) reported that theophylline was mainly metabolized to 1,3-dimethyluric acid via CYP1A2 and CYP2E1 in rats. Since CYP2E1 increased 2–4-times in rats with renal failure while CYP1A2 was comparable between the two groups of rats, it was expected that the formation of 1,3-dimethyluric acid could increase in rats with renal failure due to an increase in CYP2E1 in the rats. This was supported by our results. The plasma concentrations of theophylline were considerably lower (Figure 2A) and the resultant $AUC_{0-\infty}$ of theophylline was significantly smaller in rats with renal failure. This could be due to significantly faster CL of theophylline in the rats (Table 1). The plasma concentrations of 1,3-dimethyluric acid were considerably higher (Figure 2B) and the resultant $AUC_{0-6\,h}$ of 1,3-dimethyluric acid was significantly greater (Table 1) in rats with renal failure compared with control rats. Moreover, the $AUC_{0-6\,h,\,1,3\text{-dimethyluricacid}}/AUC_{0-\infty,\,theophylline}$ ratio increased from 2.02% in control rats to 29.4% in rats with renal failure. Finally, the in-vitro CL_{int} for the formation of 1,3-dimethyluric acid from theophylline in hepatic microsomal fraction was significantly faster in rats with renal failure (Table 2).

In summary, the formation of 1,3-dimethyluric acid from theophylline increased in rats with uranyl nitrate-induced renal failure due to CYP2E1 induction.

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