# The impact of acute phase response on the plasma clearance of antipyrine, theophylline, phenytoin and nifedipine in rabbits

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The impact of acute phase response (APR) on the plasma clearances of antipyrine, theophylline, phenytoin and nifedipine was studied using 50 female rabbits. APR was induced by a bolus intramuscular injection of *Escherichia coli* lipopolysaccharide (LPS, 50 μg/kg). No abnormal findings, other than an increase in rectal body temperature and the plasma concentration of interleukin-6 (IL-6), were observed in the LPS-treated animals. Twenty-four hours after LPS injection, the pharmacokinetic parameters of the four drugs were obtained following intravenous administrations of antipyrine (7 mg/kg), theophylline (5 mg/kg), phenytoin (10 mg/kg) and nifedipine (1 mg/kg). Total body clearances of antipyrine, theophylline, phenytoin and nifedipine in LPS-treated rabbits decreased, and terminal elimination half-life and the mean residence time of these drugs increased compared with those in the control rabbits. The apparent volume of distribution for phenytoin and nifedipine increased after the LPS injection, although the binding percentage of the drugs with plasma protein did not change. These results suggested that APR appears to decrease the plasma clearances of these drugs in rabbits, which may be due to the suppression of the activity of cytochrome P450 enzymes.

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## INTRODUCTION

Acute phase response (APR) is defined as a pathophysiological condition induced by many causal factors, i.e. infection, inflammation, tissue damage, neoplastic growth or immunological disorders. The APR induces many metabolic (Kushner, 1982; Van Miert, 1991, 1995) and systemic changes, which include fever, increased lassitude, loss of appetite and synthesis and secretion of acute phase hepatic proteins (Van Miert, 1991, 1995). Proinflammatory cytokines, such as tumor necrosis factor-α, interleukins and interferons, are produced vigorously during APR, which leads to a direct suppression of the microsomal cytochrome P450 (CYP)-dependent activity in the liver (Wright & Morgan, 1991; Chen *et al.*, 1992; Abdel-Razzak *et al.*, 1993), in turn possibly to alter the pharmacokinetic profile of some drugs.

We previously induced the APR using successive intravenous injections of *Escherichia coli* lipopolysaccharide (LPS) in rabbits, and we demonstrated the suppression of CYP-dependent activities during APR. Subsequently, the inhibition of CYP-dependent activities was characterized by a decrease in maximum velocity ($V_{max}$) of CYP enzymes (Saitoh *et al.*, 1999). So it may be reasonable to consider that the drug disposition of certain drugs is altered during APR, suggesting that the dosage regimen of some drugs are subject to modification during APR. In fact, many reports have described the impairment of clearance in several drugs during APR in pigs (Monshouwer *et al.*, 1995, 1996), in rabbits (Saitoh *et al.*, 1999) and in humans (Shedlofsky *et al.*, 1994, 1997; McKindley *et al.*, 1997).

In the present study, using antipyrine, theophylline, phenytoin and nifedipine as probes we examined the impact of suppression for CYP-dependent activity on drug disposition in rabbits during APR.

 

*Drugs and chemicals*

*Escherichia coli* LPS (O111:B4), theophylline and 7β-hydroxypropyltheophylline were obtained from Sigma Chemical Company (St. Louis, MO, USA). Antipyrine, phenacetin, phenytoin, 5-(4-methylphenyl)-5-phenylhydantoin, nifedipine and nitrendipine were purchased from Wako Pure Chemical Industries, Limited (Osaka, Japan). Phenytoin sodium (Aleviatin® injection, 50 mg/mL) was obtained from Dainippon Pharmaceutical (Osaka, Japan).

*Animals and treatments*

Fifty female rabbits (Japanese white), 4 months old, were obtained from Kitayama Labes Company, Limited (Nagano, Japan). These rabbits were randomly divided into five groups. One group was used for the measurement of rectal body temperature and plasma interleukin-6 (IL-6) concentration, and four groups were used for pharmacokinetic analysis. Each group consisted of five saline-treated (control) and five LPS-treated female rabbits. All animals were allowed free access to food and water during the study and the animals were housed in individual stainless steel cages on a 12-h light/dark cycle. Room temperature and relative humidity were maintained between 19 and 22 °C, and between 30 and 70%, respectively. LPS was dissolved in saline (0.25 mg/mL) and the rabbits, weighing 3.3–4.0 kg, received an intramuscular injection of LPS (50 μg/kg) to induce APR. Control rabbits received an equal volume of saline. This experiment was approved by the animal care and use committee of Tokyo University of Agriculture and Technology.

Rectal body temperatures were measured and blood samples were collected from the auricular vein just before (pre-treatment, 0 h) and at 2, 4, 8 and 24 h after the saline and LPS injections. The heparinized plasma, which was used for the determination of IL-6, was separated from blood samples by centrifugation ($1500 \times \boldsymbol{g}$, 15 min) at 4°C and stored at − 70 °C until analysis.

The rabbits received antipyrine (dissolved in saline, 35 mg/mL) at a dose of 7 mg/kg, phenytoin sodium (Aleviatin® injection, 50 mg/mL) at a dose of 10 mg/kg and nifedipine at a dose of 1 mg/kg intravenously at 24 h after the saline and LPS injections in control and LPS-treated rabbits, respectively. Nifedipine was dissolved in ethanol/polyethylene glycol 400/distilled water (15/35/50) at 60 °C to obtain a concentration of 2 mg/mL. Blood samples were collected from the auricular vein at 0.5, 1, 2 and 3 h after the drug injections. The rabbits received theophylline (dissolved in saline, 20 mg/3 mL) at a dose of 5 mg/kg intravenously at 24 h after the saline and LPS injections in control and LPS-treated rabbits, respectively. Blood samples were collected from the auricular vein at 0.5, 1, 3, 5 and 7 h after the theophylline injection. The heparinized plasma, used for the determination of plasma concentrations of the four drugs, was separated by centrifugation ($1500 \times \boldsymbol{g}$, 15 min) at 4 °C and stored at − 70 °C until analysis.

*Plasma analysis*

IL-6 was determined by an enzyme-linked immunosorbent assay system for mice IL-6 (Amersham International plc, Buckinghamshire, UK) using a microplate photometer (Model MTP-22, Corona Electric Company, Limited, Ibaragi, Japan).

Antipyrine plasma concentration was analyzed by a high-performance liquid chromatography (HPLC) method described by Teunissen *et al.* (1983). Theophylline plasma concentration was analyzed by a HPLC method described by Saitoh *et al.* (1999). Samples for the determination of theophylline plasma concentration were prepared according to the OASIS® *Sample Extraction Applications Notebook* (Waters Corporation, MA, USA). Briefly, 7β-hydroxypropyltheophylline was added to plasma (0.5 mL) as internal standard. The plasma was applied to an OASIS™ HLB cartridge (Waters Corporation, MA, USA). Before use, the OASIS™ HLB cartridge was rinsed twice with 1 mL of methanol (MeOH) and then rinsed twice with 1 mL of distilled water. After applying the plasma, the cartridge was washed with 1 mL of distilled water and was eluted with 1 mL MeOH. The eluate was evaporated to dryness under nitrogen at 40 °C and the residue was dissolved in 0.2 mL of the mobile phase. This solution (40 μL) was injected into the HPLC system. Samples were chromatographed at 40 °C and monitored at 278 nm. The mobile phase was a mixture of MeOH (17%) and distilled water (83%) (adjusted to pH 3 with phosphoric acid) at a flow rate of 1.0 mL/min. Phenytoin plasma concentration was analyzed by a HPLC method described by Tanaka *et al.* (1995). Nifedipine plasma concentration was determined by a HPLC method described by Grundy *et al.* (1994) with some modification. The calibration curve was linear from 25 ng/mL to 5 μg/mL ($r > 0.999$) with the detection limit of 25 ng/mL ($S/N = 5$). Briefly, 1 M sodium hydroxide (0.1 mL) and 0.02 mL of nitrendipine (100 μg/mL, dissolved in MeOH as internal standard) were added to 1 mL of plasma. After 5 mL of methyl *tert*-butyl ether/isooctane (75/25) was added, the solution was mixed on a shaker for 5 min and centrifuged at $1500 \times \boldsymbol{g}$ for 5 min. The organic layer was collected and evaporated to dryness under nitrogen at 30 °C. The residue was dissolved in 0.2 mL of the mobile phase. This solution (50 μL) was injected into the HPLC system. Samples were chromatographed at 30 °C and monitored at 240 nm. The mobile phase was a mixture of MeOH (65%) and distilled water (35%) (adjusted to pH 4 with glacial acetic acid) containing 0.03% triethylamine at a flow rate of 0.8 mL/min.

The HPLC system consisted of a model 79852A pumping system, a model 79853A variable wavelength detector and a model 79855A autosampler from Hewlett-Packard Company (Palo Alto, CA, USA), and a TSKgel ODS-120T (5 μm, Tosoh Company, Tokyo, Japan) reversed-phase column was used. The chromatographic data were processed by a model LC100W/F workstation (Yokogawa Analytical Systems, Tokyo, Japan).

A one-compartment open model was used for pharmacokinetic analysis of antipyrine, theophylline, phenytoin, and nifedipine. The area under the concentration–time curve (*AUC*) from time zero to infinity, the elimination rate constant

($k_{el}$), the apparent volume of distribution ($V_d$) and the mean residence time (*MRT*) were obtained by using the computer program MULTI (Yamaoka *et al.*, 1981). Total body clearance ($Cl_{tot}$) and terminal elimination half-life ($t_{1/2}$) were calculated as follows: $Cl_{tot} = \text{Dose}/AUC$ and $t_{1/2} = 0.693/k_{el}$.

### *Drug–protein binding assay*

Heparinized plasma was collected at 24 h after the saline and the LPS injection in control and LPS-treated rabbits, respectively. Free fraction of theophylline, phenytoin and nifedipine was separated using the Centrifree® micropartition device (Amicon Incorporated, MA, USA). A 2-mL sample of plasma, mixed with a drug solution, was incubated at 37 °C for 10 min. Final concentrations of theophylline, phenytoin and nifedipine in the plasma were 60, 100 and 20 μg/mL, respectively. The plasma was pipetted into the ultrafiltration device and centrifuged ($1500 \times \boldsymbol{g}$) for 60 min at 4 °C. The filtrate was analyzed immediately after centrifugation. The percentage of plasma protein binding was calculated using the following equation:

$$\text{Binding percentage (\%)} = \frac{(\text{Total concentration} - \text{Free concentration})}{\text{Total concentration}} \times 100$$

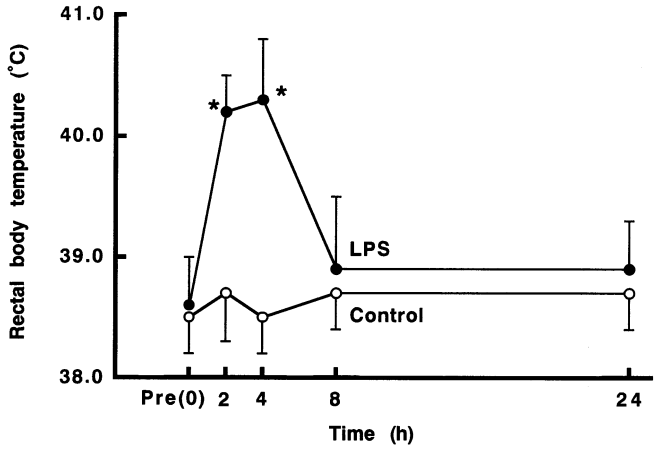


**Fig. 1.** Rectal body temperatures following saline or LPS injection in rabbits. LPS was administered intramuscularly by an injection of 50 μg/kg (0 h). Control rabbits received an equal volume of saline. Rectal body temperatures were measured just before (pre, 0 h) and at 2, 4, 8 and 24 h after the saline and LPS injections. Values represent mean ± SD of control ($n = 5$) and LPS-treated rabbits ($n = 5$). *Significantly different from control group at $P < 0.05$.

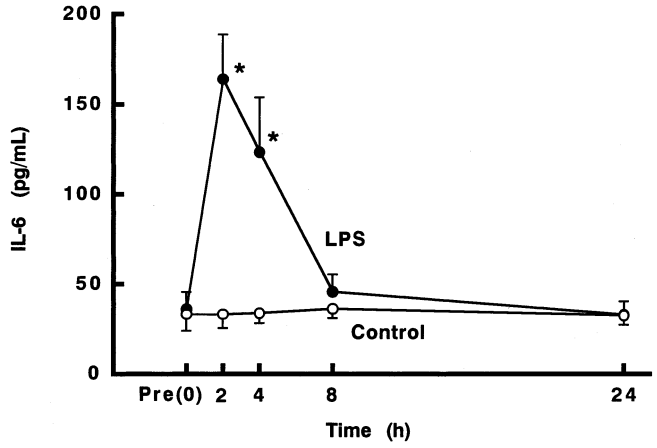


**Fig. 2.** Plasma IL-6 concentrations following saline or LPS injection in rabbits. LPS was administered intramuscularly by an injection of 50 μg/kg (0 h). Control rabbits received an equal volume of saline. Blood samples were collected just before (pre, 0 h) and at 2, 4, 8 and 24 h after the saline and LPS injection. Values represent mean ± SD of control ($n = 5$) and LPS-treated rabbits ($n = 5$). *Significantly different from control group at $P < 0.05$.

### *Statistical analysis*

Data were first analyzed by the *F*-test (Snedecor & Cochran, 1980) for homogeneity of variance with significant levels of 5%. If the test revealed homogeneity of variance, a comparison was made between the LPS-treated and control groups using Student's *t*-test (Snedecor & Cochran, 1980). In the case of heterogeneity of variance, a comparison was made between the LPS-treated and control groups using the Aspin–Welch *t*-test (Snedecor & Cochran, 1980). Differences were considered significant at $P < 0.05$.

## RESULTS

### *APR induction*

After a bolus intramuscular injection of LPS to rabbits, rectal body temperature increased rapidly, and returned to pre-treatment levels at 8 h after the LPS injection (Fig. 1). Plasma concentration of IL-6 after the injection of LPS to rabbits also raised rapidly, and it reached a peak concentration at 2 h after the LPS injection (Fig. 2). No abnormal findings in appearance, such as anorexia, corneal hyperemia or increased lassitude, were observed in the LPS-treated animals.

### *Pharmacokinetic analysis*

Plasma time–concentration curves of antipyrine, theophylline, phenytoin and nifedipine in LPS-treated and control groups are shown in Fig. 3a–d, respectively. These plasma concentrations decreased mono-exponentially in both the treated and control rabbits.

Pharmacokinetic parameters of antipyrine, theophylline, phenytoin and nifedipine are shown in Table 1. $Cl_{tot}$ of these four drugs in the LPS-treated group was significantly lower than that of control group. *AUC*, $t_{1/2}$ and *MRT* of these four drugs in the treated group were significantly higher than those of control group. $V_d$ of phenytoin and nifedipine in the treated group was significantly higher than that of the control group.

### *Binding percentage of the drugs to plasma protein*

Binding percentages of theophylline, phenytoin and nifedipine to plasma protein between the LPS-treated group and the

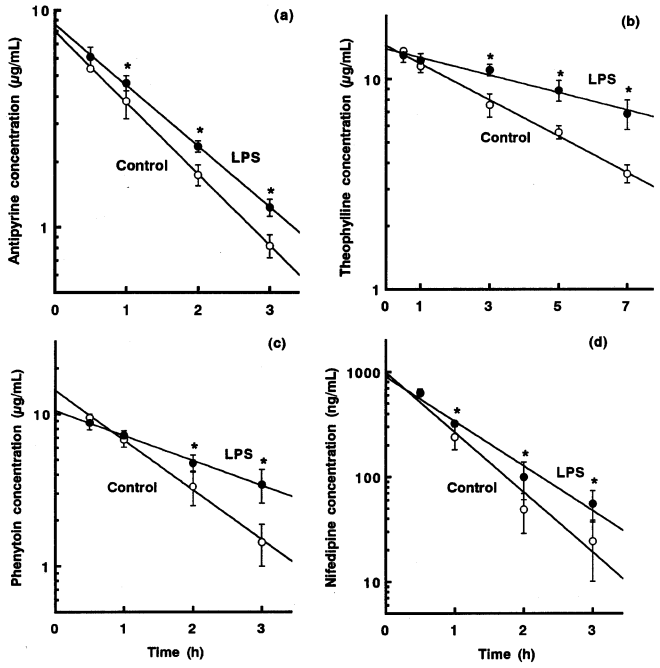


**Fig. 3.** Plasma time–concentration curves of control and LPS-treated rabbits. LPS was administered intramuscularly by an injection of 50 μg/kg. Control rabbits received an equal volume of saline. Antipyrine (a; 7 mg/kg), theophylline (b; 5 mg/kg), phenytoin (c; 10 mg/kg) and nifedipine (d; 1 mg/kg) were given intravenously at 24 h after the saline and LPS injection. Values represent mean ± SD of control ($n = 5$) and LPS-treated rabbits ($n = 5$). *Significantly different from control group at $P < 0.05$.

control group exhibited almost similar values (no significant difference). The values of theophylline, phenytoin and nifedipine in control and LPS-treated group were 52.9 ± 1.0% and 55.3 ± 1.8%, 92.7 ± 0.7% and 91.9 ± 1.0% and 97.3 ± 2.3% and 98.4 ± 0.9%, respectively.

## DISCUSSION

We previously demonstrated that an activity of CYP-dependent enzyme was suppressed during APR in rabbits. In the present study, we examined the impact of suppression on the CYP enzyme activity during APR on drug disposition *in vivo*, using antipyrine, theophylline, phenytoin and nifedipine as probes. As shown in the results, the $Cl_{tot}$ of the four drugs was significantly suppressed at 24 h after the LPS intramuscular injection. Although the symptoms of APR showed less significant clinical signs, the increases of rectal body temperature and plasma concentration of IL-6 were clearly shown, which suggests that the APR can be established in the present study. Consequently, the suppression of CYP enzyme activity during APR was demonstrated *in vivo* with regard to the pharmacokinetic profiles.

As for the APR production, we previously produced the APR model by means of five separate intravenous injections of LPS (17 μg/kg each time, total 85 μg/kg), with an interval of 1 h (Saitoh *et al.*, 1999). Typical symptoms of APR including anorexia, corneal hyperemia, increased lassitude and a rise of rectal temperature were observed. In the present study, we produced the APR by a bolus intramuscular injection of LPS. The symptoms of APR were mild and they showed less significant clinical signs compared with those in the previous study. However, rectal body temperature and plasma IL-6 level increased and $Cl_{tot}$ of antipyrine decreased. It is well known that rectal body temperature and proinflammatory cytokine, including tumor necrosis factor-α, interleukin-1α/β, IL-6 and interferons, rose during APR (Fey & Gauldie, 1990; Van Miert, 1991, 1995). Moreover, comparing the results of present study with results of previous ones, we found that the extent of the decrease in $Cl_{tot}$ of antipyrine during APR was not so different; i.e. a 33% decrease in the previous experiment (Saitoh *et al.*, 1999) and a 23% decrease in the present experiment. We previously demonstrated an approximately 30% decrease in total CYP contents at 24 h after APR induction, which, interestingly, corresponded with the decrease percentages of $Cl_{tot}$ for antipyrine. Therefore, we considered that the activity of CYP-dependent enzymes was suppressed almost to the same extent in both studies.

The elimination of antipyrine, theophylline, phenytoin and nifedipine is dependent upon the metabolism by CYP enzyme. Antipyrine has been used widely as a probe, model drug for the assessment of hepatic oxidative metabolizing ability. Antipyrine was metabolized by CYP1A2, CYP2C and CYP3A, because the three main metabolites of the drug in urine were catalyzed by these CYPs in humans (Engel *et al.*, 1996). Theophylline, phenytoin and nifedipine are catalyzed largely by CYP1A2, CYP2C3 and CYP3A6 in rabbits, respectively. In the present study, we determined that $Cl_{tot}$ of theophylline, phenytoin and nifedipine during APR was decreased by 46, 42 and 19% in rabbits, respectively. The decreases of CYP1A2 (39%) and CYP2C3 activities (33%) were reported in rabbits during APR (Saitoh *et al.*, 1999). Although the activity of CYP3A was not determined, the decrease of $Cl_{tot}$ of these drugs must be due to the decrease of the correspondent enzyme activities. In fact, decreases in CYP-dependent activities, apoproteins and/or mRNA levels of CYP subfamilies during the APR have been shown in rats (Morgan 1989, 1993; Sewer *et al.*, 1996), in pigs (Monshouwer *et al.*, 1996), in rabbits (Proulx & Du Souich, 1995; Saitoh *et al.*, 1999) and in horses (Mills *et al.*, 1997). The decrease in CYP1A2, CYP2C and CYP3A was reported in hepatic disorder patients (Tanaka, 1998).

The $V_d$ values of phenytoin and nifedipine in LPS-treated rabbits increased in the present study. Phenytoin and nifedipine are acidic drugs and bind to plasma albumin with high affinity. High values of percentages (92–98%) were determined in both control and LPS-treated rabbits. The binding percentage was not affected during APR in rabbits. It is well known that capillary permeability rises during inflammation. Accordingly, it was considered that the reason why $V_d$ increased was due to the transition of albumin, which bound to phenytoin and nifedipine, from plasma to interstitial tissue.

**Table 1.** Pharmacokinetic parameters of antipyrin, theophylline, phenytoin and nifedipine in control and LPS-treated rabbits

| Drugs | $Cl_{tot}$ (mL/h/kg) | $t_{1/2}$ (h) | $V_d$ (L/kg) | *AUC* (μg·h/mL) | *MRT* (h) |
|---|---|---|---|---|---|
| *Antipyrine* (7 mg/kg) | | | | | |
| Control | 797 ± 54 | 0.92 ± 0.09 | 0.88 ± 0.02 | 8.81 ± 0.58 | 1.57 ± 0.17 |
| LPS | 614 ± 47* | 1.10 ± 0.08* | 0.83 ± 0.10 | 11.45 ± 0.83* | 1.80 ± 0.13* |
| *Theophylline* (5 mg/kg) | | | | | |
| Control | 74.9 ± 7.5 | 3.38 ± 0.31 | 0.34 ± 0.01 | 67.2 ± 6.5 | 4.90 ± 0.39 |
| LPS | 40.4 ± 7.6* | 8.73 ± 3.75* | 0.37 ± 0.04 | 127.3 ± 23.4* | 8.78 ± 2.10* |
| *Phenytoin* (10 mg/kg) | | | | | |
| Control | 646 ± 97 | 0.97 ± 0.18 | 0.72 ± 0.06 | 15.8 ± 2.3 | 1.53 ± 0.17 |
| LPS | 374 ± 113* | 1.89 ± 0.48* | 0.95 ± 0.11* | 28.2 ± 6.9* | 3.40 ± 0.97* |
| *Nifedipine* (1 mg/kg) | | | | | |
| Control | 1594 ± 224 | 0.37 ± 0.09 | 0.61 ± 0.15 | 0.64 ± 0.09 | 0.86 ± 0.13 |
| LPS | 1290 ± 122* | 0.57 ± 0.09* | 0.88 ± 0.11* | 0.78 ± 0.07* | 1.14 ± 0.15* |

LPS was administered intramuscularly by an injection of 50 μg/kg. Control rabbits received an equal volume of saline. Antipyrine, theophylline, phenytoin and nifedipine were given intravenously at 24 h after saline (control) and LPS injection. Values represent mean ± SD of control ($n = 5$) and LPS-treated rabbits ($n = 5$). *Significantly different from control group at $P < 0.05$.

APR is a common pathophysiological condition. Suppression of $Cl_{tot}$ for theophylline and phenytoin will occur in many animals during APR. The decreases in clearance and/or elimination of theophylline and phenytoin during APR has been reported in humans as follows; a decrease of theophylline elimination due to viral respiratory infection (Chang *et al.*, 1978), bacterial pneumonia (Vozeh *et al.*, 1978; Sonne *et al.*, 1985) and influenza vaccine inoculation (Renton *et al.*, 1980). In rabbits, a 45% decrease in $Cl_{tot}$ of theophylline was reported during inflammation induced by turpentine (Barakat & Du Souich, 1996). A 33% decrease in $Cl_{tot}$ of phenytoin was indicated in rats with hepatic failure by D-galactosamine (Itoh *et al.*, 1988). The inhibition of systemic clearance for nifedipine was reported in patients with liver cirrhosis (Kleinbloesem *et al.*, 1986). Since theophylline, phenytoin and nifedipine are used commonly as therapeutic drugs, it is nec2essary to pay attention in clinical use.

Consequently, it has been demonstrated that the clearances of antipyrine, theophylline, phenytoin and nifedipine were suppressed during APR in rabbits. The impact was induced by inhibition of CYP-dependent activity. Even if clinical symptoms have not been found after the APR, the clearances of drugs may be potentially downregulated.

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