Influence of Resveratrol on the Pharmacokinetics and Pharmacodynamics of Naproxen: Involvement of CYP1A2 Inhibition

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\textbf{Received date:} December 05, 2018; \textbf{Accepted date:} January 19, 2018; \textbf{Published date:} January 30, 2018.

\textbf{Citation this Article:} Prasad Neerati, Maheshwari K, Influence Of Resveratrol on The Pharmacokinetics and Pharmacodynamics of Naproxen: Involvement of CYP1A2 Inhibition. J Pharmaceutics and Pharmacology Research, DOI: \texttt{http://dx.doi.org/10.31579/1.10004}

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\begin{abstract}
The purpose of the present study was to assess the effect of resveratrol (RSV) on the pharmacokinetics of naproxen (NAP) in rats. A single dose of RSV 30mg/kg was administered once during treatment phase. A single dose of NAP 25mg/kg was administered after RSV treatment. The blood samples were collected at predetermined time intervals and analyzed by HPLC. In comparison with the control, RSV pretreatment significantly enhanced maximum plasma concentration (Cmax), area under the curve (AUC), and half life (t1/2) and significantly decreased apparent oral clearance (CL/F) and apparent volume of distribution (Vd/F), while there was no significant change observed in time to reach maximum concentration (tmax) of NAP. The results suggest that the altered pharmacokinetics of NAP might be attributed to RSV-mediated inhibition of CYP1A2 enzyme. Therefore, combination therapy of NAP along with RSV may represent a novel approach to reduce dosage and results in reduced gastrointestinal side effects of NAP.

\textbf{Keywords} \\
Naproxen, Resveratrol, Carrageenan, CYP1A2 enzyme
\end{abstract}

\section*{Introduction}

Naproxen (NAP) (6-methoxy-α-methyl-2-naphthalene acetic acid) is a non-steroidal anti-inflammatory drug effective in rheumatoid arthritis (Bowers et al.1975) and as analgesic (Ruedy and Mcullongh 1973). The efficacy of naproxen is related to its plasma concentrations (Dayet al.1982). Naproxen is well absorbed orally in doses as high as 900mg (Runkel et al.1974) and is concentrated largely in plasma (Runkel et al. 1972) because of extensive binding to plasma albumin (Brogden et al. 1984) Naproxen is a stereochemically pure nonsteroideal anti-inflammatory drug of the 2-arylpropionic acid class. The absorption of naproxen is rapid and complete when given orally. Naproxen is eliminated following biotransformation to glucuroconjugated and sulphate metabolites which are excreted in urine, with only a small amount of the drug being eliminated unchanged. The excretion of the 6-0-desmethylnaproxen metabolite conjugate may be tied to renal function, as accumulation occurs in end-stage renal disease. Naproxen undergoes phase I dealkylation by cytochrome P450 (CYP) to the O-demethylated metabolite, followed by phase II acylglucuronidation. Hence, naproxen is oxidised to 6-0-desmethylnaproxen (6-DMN) and conjugated to naproxen acyl glucuronide and 6-0-desmethylnaproxen acylglucuronide (6-DMNG).

A preliminary report demonstrated that human liver microsomal O-demethylation of S-naproxen was decreased by the CYP2C9-specific inhibitor Sulphenazolme. A subsequent investigation has shown that sulphaphenazole reduced microsomal demethylation of S-naproxen by 47%, and the CYP1A2 inhibitor furafylune decreased O-demethylation of S-naproxen by 28%, suggesting that CYP2C9 and I2A together account for the majority of human liver demethylation of naproxen.

Resveratrol (RSV) (3, 4′, 5-trihydroxystilbene) is a naturally occurring polyphenolic phytoalexin is present in fruits, vegetables, grape skins and especially in red wine. RSV possesses diverse biochemical and physiological properties including anti-inflammatory, immune modulatory activities as well as wide range of health benefits ranging from chemoprevention to cardio protection (Kalantari and Das, 2010; Brisdelli et al., 2009). RSV has recently been shown to exert genoprotective, cytotoxic, antiproliferative and proapoptotic actions in different tumoural cell lines (Romano et al., 2013). RSV exhibits anti-inflammatory activity through the modulation of enzymes and pathways that produce mediators of inflammation. RSV possesses good potential to be used as an adjunctive or alternative therapy for inflammatory diseases (Das and Das, 2007; Udenigwe et al., 2008). In addition, RSV has been shown to produce a low profile of side effects (Cottart et al., 2010). Thus, the combination of NAP along with RSV could be an alternative in the treatment of inflammatory diseases.

NAP is an important anti-inflammatory drug with widespread use, and its administration receiving long-term therapy with herbal compounds or dietary supplements containing RSV may occur. An extensive study of the literature did not reveal any report of an interaction between NAP and RSV. It is therefore relevant to consider the interaction between NAP and RSV. The aim of this study was to evaluate the effect of RSV treatment on the pharmacokinetics of NAP in rats.

\section*{Materials and Methods}

\textbf{Materials}

Naproxen was a gift sample from Aurobindo Pharmaceuticals (Jadcherla, Mahaboobnagar). Carrageenan was obtained from (Sigma Aldrich,Bangalore ). RSV was procured from Navachetan (New Delhi, India).
The AUC0-∞ was calculated using the formula AUC0-∞ = \int_{0}^{∞} C(\tau) \, d\tau + [\text{Cl}\text{ast}/ \text{K.el}] where Clast is the concentration in mg/ml at the last time point and K.el is the elimination rate constant.

**Results**

During the study period, no serious adverse events related to drug were reported. The pharmacokinetic parameters and mean plasma concentration–time profiles of NAP after pretreatment with RSV are shown in (Table 1) and (Table 2), respectively.

| TIME (h) | NAP | NAP+RSV |
|----------|-----|---------|
| 0        | 0±0 | 0±0     |
| 1        | 2.1±0.24 | 2.8±0.29 |
| 2        | 5.6±0.32 | 6.1±0.35 |
| 4        | 8.6±0.72 | 8.3±0.68 |
| 6        | 4.3±0.28 | 8.4±0.31 |
| 8        | 3.2±0.18 | 4.8±0.20 |
| 10       | 2.1±0.9 | 3.5±0.12 |
| 12       | 1.3±0.8 | 2.3±0.2 |

**Table1:** Mean serum concentration (ug/ml) of Naproxen and naproxen in presence of resveratrol (SDT & MDT) in inflammatory rats.

| PK PARAMETER | Naproxen | NAP+RSV |
|--------------|----------|---------|
| Cmax (µg/ml) | 1.8±0.72 | 2.95±0.7 |
| tmax (h)    | 1.4±0.2 | 2.82±0.2 |
| AUC 0-∞ (µg/ml/h) | 4.81±1.8 | 7.61±2.7 |
| t½ (h)      | 10.7±0.05 | 14.3±0.06 |
| Clearance (l/hr) | 14.83±5.45 | 6.01±2.85 |
| Vd (ml)     | 22.92±8.68 | 12.96±7.32 |

**Table2:** Mean Pharmacokinetic parameters of Naproxen in presence of resveratrol in Inflammatory rats

Mean ± SD: ***significant at p<0.001; ** significant at p<0.01; *significant at p<0.05 compared to Naproxen control

The plasma NAP concentrations were increased after RSV pretreatment when compared to control phase. The mean Cmax (1.8±0.72 versus 2.95±0.7µg/mL, p<0.05), mean AUC (4.81±1.8 versus 7.61±2.7µg/mL, p<0.05) and mean t½ (10.7±0.05 versus 14.3±0.06 h, p<0.05) values were increased respectively, after RSV pretreatment as compared to that of control phase. On the other hand, mean CL/F (14.83±5.45 versus 6.01±2.85 L/h, p<0.05) and mean Vd/F (22.92±8.68 versus 12.96±7.32 L, p<0.05) values were decreased respectively, after RSV pretreatment as compared to the control phase. However, there was no significant change observed in tmax of NAP between RSV treatment and control phases. The pharmacodynamic study states that the percentage inhibition of mean paw edema for resveratrol treated group was 51.1±0.1, naproxen treated group was 48.2±0.5, combination of naproxen and resveratrol treated group was 53.1±0.2.

**Pharmacodynamic data**

| Time (h) | Control | RSV | NAP | RSV+NAP |
|----------|---------|-----|-----|---------|
| 0        | 31.2±0.4 | 34.3±0.1 | 35.1±0.4 | 36.2±0.5 |
| 1        | 42.3±0.1 | 51.1±0.1 | 48.2±0.5 | 53.1±0.2 |
| 2        | 60.6±0.1 | 63.2±0.4 | 59.1±0.3 | 64.3±0.9 |
| 3        | 58.2±0.3 | 54.1±0.2 | 55.1±0.1 | 59.3±0.1 |
| 4        | 55.3±0.4 | 52.1±0.3 | 48.5±0.3 | 43.2±0.2 |

**Table 3:** % Inhibition of Mean Paw edema
Discussions

Herbal medicines have been widely used as a complementary or alternative treatment for a variety of diseases, rehabilitation and health care. Herbal medicines contain more than one pharmacologically active ingredient and are commonly used with many prescribed drugs. From the literature it is evident that, RSV was proposed to block the transcription of various CYPs through antagonism of the nuclear aryl hydrocarbon receptor (AhR). On the other hand, inhibition of CYP activity by RSV could lead to safety problems by altering the pharmacokinetics of co-administered drugs.

Thus, the present study evaluated the effect of RSV treatment on the pharmacokinetics of naproxen in rats by using naproxen as a CYP1A2 substrate.

On account of its good tolerance when administered, naproxen represents a promising CYP1A2 probe substrate to assess the CYP1A2 enzyme activity. Alterations in the catalytic activity of CYP1A2 enzyme can change the pharmacokinetics of naproxen. Hence, naproxen is used as a probe drug for assessing the CYP1A2enzyme activity in the study.

Our results suggest that oral administration of RSV significantly altered the pharmacokinetics and enhanced the bioavailability of naproxen through the inhibition of CYP1A2 enzyme in rats. In this study, we found that treatment with RSV resulted in significant increase in mean Cmax, AUC, T1/2 and a significant decrease in mean CL/F, Vd/F of naproxen as compared to control. Although mean Tmax values of naproxen were increased after RSV treatment phase but they were statistically insignificant. The increasing Cmax and AUC values indicate that enhanced exposure of naproxen after RSV treatment. On the other hand, the decreasing CL/F and increasing T1/2 values indicate the inhibition of elimination of Naproxen upon RSV treatment.

Based on these findings, resveratrol acts as an inhibitor of CYP1A2 mediated metabolism of naproxen in rats. Consequently, the bioavailability of naproxen was increased via the inhibition of CYP1A2enzyme activity.

Therefore, combination of naproxen along with RSV may represent a novel approach to reduce the dosage and results in reduced gastrointestinal side effects of naproxen.

The mean percent paw volume in control and drug treated animals was compared. These findings suggest that the inhibition of sustained phase of paw edema following subplantar injection of carrageenan in naproxen and resveratrol treated animals is enhanced compared to only naproxen treated group.

These changes in the pharmacokinetics and pharmacodynamics of naproxen when co-administered with resveratrol may be due to the inhibition of CYP1A2 enzyme by resveratrol.

References

1. Bedada SK, Nearati P. (2015). Effect of resveratrol on the pharmacokinetics of carbamazepine in healthy human volunteers. Phytother Res 29: 701–706.

2. Brouwers JR, de Smet PA. (1994)Pharmacokinetic-pharmacodynamic drug interactions with nonsteroidal anti-inflammatory drugs. *Clinical Pharmacokinetics* 27: 462-485.

3. Casper RF, Quesne M, Rogers IM, Takihiko Shirota, André Jolivet et al. (1999). Resveratrol has antagonist activity on the aryl hydrocarbon receptor: implications for prevention of dioxin toxicity. Mol Pharmacol 56:784–790.

4. Chow HH, Garland LL, Hsu CH, Donna R, Vining, Wade M. Chew et al. (2010). Resveratrol modulates drug- and carcinogen-metabolizing enzymes in a healthyvolunteer study. Canc Prev Res 3: 1168–1175.

5. Cottart CH, Nivet-Antoine V, Laguillier-Morizot C, Beaufreux JL.. (2010). Resveratrol bioavailability and toxicity in humans. Mol Nutr Food Res 54: 7–16.

6. Das S, Das DK. (2007). Anti-inflammatory responses of resveratrol. Inflamm Allergy Drug Targets 6: 168–173.

7. Day RO, Francis H, Vial J.(1995) Naproxen concentrations in plasma and synovial fluid and effects on prostanooid concentrations. *Journal of Rheumatology* ; 22: 2295-2303.

8. Davies NM, Anderson KE. (1997). Clinical pharmacokinetics of diclofenac. Therapeutic insights and pitfalls. Clin Pharmacokinet 33: 184–213.

9. Detampel P, Beck M, Krähenbühl S, Huwyler J. (2012). Drug interaction potential of resveratrol. Drug Metab Rev 44: 253–265.

10. Hippisley-Cox J, Coupland C, Logan R. (2005). Risk of adverse gastrointestinal outcomes in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case–control analysis. BMJ 331: 1310–1316.

11. Kalantari H, Das DK. (2010). Physiological effects of resveratrol. BioFactors 36: 401–406.

12. Rajarayana K, Venkatesham A, Krishna DR. (2007). Bioavailability of diclofenac sodium after treatment with diclofenac in healthy volunteers. Drug Metabol Drug Interact 22: 165–174.

13. Romano B, Pagano E, Montanaro V. (2013). Novel insights into the pharmacology of flavonoids. Phytother Res 27:1588–1596.

14. Runkel R, Chaplin M, Sevelius J. (1976) Pharmacokinetics of naproxen overdoses. *Clinical Pharmacology Therapeutics* ; 20 (3): 269-277.

15. Ready J and Mcclough W. A comparison of the analgesic efficacy of naproxen and propoxyphene in patients with pain after orthopaedic surgery. *Scandinavian Journal of Rheumatology* 197;2:56-59.

16. Subramanian M, Goswami M, Chakraborty S, Jawali N.(2014) Resveratrol induced inhibition of Escherichia coli proceeds via membrane oxidation andindependent of diffusible reactive oxygen species generation. Redox Biology: 2: 865-872.

17. Sulem P, Gudbjartsson DF, Geller F, Prokopenko I, Feenstra B, et al(2011)variants at CYP1A1-CYP1A2 and AHR associate with coffee consumption. Human Molecular Genetics; 20:2071–

18. Segre EJ, Chaplin M, Forchielli E, et al.(1973) Naproxen-aspirin interactions in man. Clinical Pharmacology Therapeutics ; 15 (2): 374-379.

19. Volans G N.(1978) Drug interactions in rheumatoid disease are there of any clinicalsignificance Rheum Rehabilitation ;112

20. Vree TB, Van Den Biggelaar M, Corriep PWGM, (1993)Pharmacokinetics of naproxen, its metabolite O-desmethylnaproxen, and their acyl glucuronides in humansBiopharmaceutics Drug Disposition ;14: 491-502.

21. Willkens R F, (1985)Worldwide clinical safety experience with diclofenac. Seminars in arthritis and rheumatism: ;15(1):105-110.

22. Winter CA, Risley EA, Nuss Gw.(1962) Carrageenan induced edema in the hind paw of the rat as an assay for anti-inflammatory drugs. Proceedings of the Society Experimental Biology and Medicine ; :544-549.