IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A Research on Increased Bioavailability of Dapsone in Rats

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Abstract

Piperine, an alkaloid present in a number of piper species, selectively enhances the bioavailability of structurally and therapeutically different drugs, either by increasing the absorption or by delaying the metabolism of the drug or by a combination of both processes. Dapsone, a widely used anti-leprosy drug , is known to produce methaemoglobinaemia as a serious side effect. Based on the reported interaction of piperine with drug metabolising enzymes, the present investigation was undertaken to study changes in bioavailability of dapsone and possible reduction in methaemoglobinaemia in the presence of piperine in rats.

A C_{max} value of 2.4 ± 0.12 ug /mL was obtained with dapsone alone (10 mg/Kg) ,compared with 3.90 ± 0.16 ug/mL obtained with a combination of dapsone (10 mg /Kg) and piperine (10 mg/ Kg). This represents an increase of 62% in peak plasma levels caused by the presence of piperine. Reduction in total clearance from 4.80 ± 0.31 to 3.81 ± 0.20 ml/h and a volume of distribution from 4.61 ± 0.19 to 3.08 ± 0.12 L resulted in a net increase of 35% in AUC (34.55 ± 1.83 TO 46.70 ± 3.14) in the presence of piperine .

We conclude that piperine significantly ($p<0.001$) enhances the bioavailability of dapsone.

Keywords: Bioavailability, Dapsone, Piperine, methaemoglobinaemia etc.

Introduction

Reported inhibition of arylhydrocarbon hydroxylase by piperine may help reduce formation of methaemoglobin due to hydroxylation of dapsone. A survey of the Ayurvedic literature resulted in identification of a group of common species as a frequent component of a large number of remedies. A systemic study by Atal *et al* (1981) provided the basis for suggesting that these herbs were acting as bioavailability enhancer. More detailed studies resulted in isolation and characterization of the alkaloid piperine as the chemical entity responsible for bioavailability enhancing activity.

The compound was established as being able to increase the bioavailability of a large number of drugs (Atal *et al* 1981: Bnao *et al* 1987: 1991). This bioavailability enhancing effect of the compound seemed to be drug dependent. Piperine is active at low doses and is devoid of any toxic manifestations, as well as having the unique property of interacting with the biosystem both at transport (Johri *et al* 1992) and metabolic levels (Atel *et al* 1985) in a dose dependent, reversible manner. The role of piperine in specifically increasing bioavailability of a variety of structurally different drugs has generated much interest, and the concept is being put into pharmaceutical practice for possible reduction in doses of various antimicrobial compounds.

Dapsone, a widely used anti-leprosy drug, and useful in the treatment of a large number of other skin problems and in arthritis, unfortunately is also haemolytic mainly due to N-hydroxyl metabolites (Zuidema *et at* 1986).

As part of continuing programme to investigate the influence of this compound on the bioavailability of various antimicrobial compounds, dapsone was used as the model drug for the present study. Based on the reported inter action of piperine with drug metabolising enzymes, oxidation, hydroxylation and gluccuronidation (Atal *et al* 1985: Singh *et al* 1986) alteration in dapsone therapy can be expected by way of both reduction in dose and in reduction of dose related side effects.

Materials and Methods

Chemicals and analytical methodology

HPLC grade acetonitrile and methanol were obtained from Merck (India). All other chemicals used in the study were of analytical grade. Piperine was prepared in our laboratory by elution of pepper oleoresin with chloroform on neutral alumina to a purity of 99.9% (mp 129^{o} C). Purity of the compound as a single entity was confirmed by thin layer chromatography.

Analysis was carried out on a Gilson high pressure liquid chromatography. The plasma sample analysis was carried out as a described by Edstein (1984) for quantification of anti-malarial drugs. The standard curve ranged from 0.045 to 4.5 µg /mL.

Animals

Charles Foster male rats, 120-150 g, bred at the institute's animal house and maintained on pelleted diet (Lipton, India), were fasted overnight, with free access to water. Rats were placed into three groups (6 animals/group, one group for each time interval) group 1 received vehicle (water)only, and was used for obtaining control plasma: group 2 was administered dapsone at a dose of 10 mg/kg and group 3 received a combination of dapsone (10 mg /kg) and piperine (10 mg/kg). Animals were killed at predetermined time intervals (0.25, 0.5, 1, 2, 4, 6, 8, 16, 24and 36 h). Blood was collected in heparinised tubes to prepare plasma, which was extracted and analysed on HPLC.

Student *t* test was applied to the data for determination of statistically significant differences.

Pharmacokinetic analysis was carried out using the TOPFIT (V.2.0) kinetic programme using non compartmental analysis following the linear trapezoidal rule for calculation of AUC.

Results and Discusion

Plasma levels of dapsone for the different regimens are presented in figure 1. A Cmax value of 2.41 ± 0.12 µg/ml at 2.0 h was achieved when dapsone was administered alone, while the Cmax after administration with piperine was 3.90 ± 0.16 µg/ml, representing an increase of 62%. Higher dapsone plasma concentrations were found in piperine experiment at every time point up to 6.0 h after administration. Other pharmacokinetic parameters comparing the bioavailability of the two formulations are given in table 1.

Table 1. Comapartive pharmacokinetic parameters of dapsone alone and dapsone with piperine in rats.

Parameter	Dapsone	Dapsone with piperine
Cmax (µg Ml^{-1})	2.41 ± 0.05	3.90 ± 0.31
Disposition half life (h)	9.68 ± 0.76	9.73 ± 0.51
Total clearance (mL h^{-1})	4.80 ± 0.31	3.81 ± 0.20
Volume of distribution (L)	4.61 ± 0.31	3.08 ± 0.20
AUC (µg mL^{-1} h^{-1})	34.55 ± 1.83	46.70 ± 3.14

Rats received dapsone (10 mg kg^{-1}) alone and a combination of dapsone (10 mg kg^{-1}) with piperine (10 mg kg^{-1}). Values are mean ± SE (n=6).

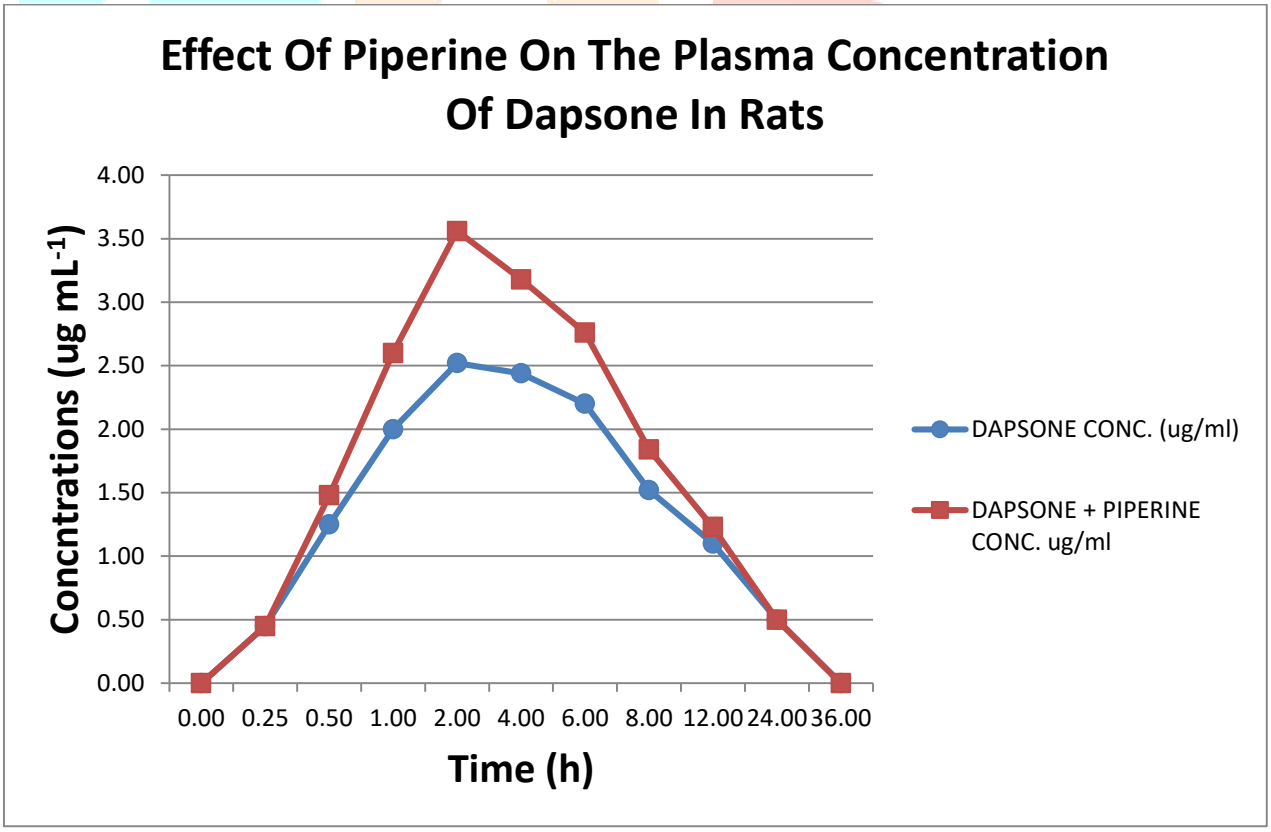

Figure 1. Effect of piperine on the plasma concentration of dapsone in rats given both compounds.
Dapsone alone (10 mg kg^{-1})
■ dapsone (10 mg kg^{-1}) with piperine (10 mg kg^{-1}).

A higher Cmax value reduced total clearance and reduced volume of distribution contributed to an apparent increase of about 35% in AUC. The elimination half life, however, remained unchanged. Colemon *et al* (1992) reported similar findings with a cimetidine dapsone trimethoprim combination, possibly as a result of drug-drug interaction leading to inhibition of metabolizing enzymes. he modification in the kinetics of

dapsone as affected by piperine, may be due to increased absorption as well as reduced metabolism. The bioenhancer studied has been reported here to increase the uptake of amino acids and other moieties (Johri *et al* 1992), and to interact with enzymatic drug biotransformation reactions in vitro and in vivo (Singh *et al* 1986 : Reen and Singh 1991). The compound is reported to inhibit arylhydrocarbon hydroxylation, ethylmorpjhine –N-demethylation and 7- methoxycoumarin -o-deethylation (Atal *et al* 1985) and also impairs glucuronidation (Singh *et al* 1986). Inhibition of hydroxylation prove helpful in dapsone therapy by reducing the most serious side effects of methaemoglobinaemia due to dapsone .cimetidine an inhibitor of drug metabolism, in the presence of trimethoprim has been reported to reduce dapsone induced methaemoglobinaemia (Coleman *et al* 1992).

Conclusion

It can be concluded that the dapsone – piperine combination may result in a reduced strength dosage form with reduced side effects, in particular methaemoglobinaemia.

Acknowledgements:

The Author thanks to Vinayaka College of Pharmacy, Garsa, Kullu for financial support, Innovative College of Pharmacy, knowledge park II Greater Noida, Gautam Buddha Nagar, . for animal studies and School of Vocational Studies and Applied Sciences, Gautam Buddha University, Greater Noida, Gautam Buddha Nagar. Uttar Pradesh. .

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