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Influence of menthol on first pass elimination

[Influencia del mentol sobre la eliminación de primer paso]

Ayse GELAL

Dokuz Eylul University Medical Faculty, Department of Pharmacology. Inciralti, 35340 Izmir Turkey.

*Contact: E-mail: ayse.gelal@deu.edu.tr

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Abstract

Menthol is one of the most widely consumed essential oils. In vitro and in vivo studies indicate that menthol induces or inhibits drug metabolizing activities of liver or gut; thus it could decrease or increase serum drug concentrations. In vitro studies demonstrate that menthol has a relaxant effect on the gastrointestinal tract, thus it could influence the rate of drug absorption. Also in vitro Caco-2 model study results suggest that peppermint oil (30-55% of which is menthol) has inhibitory effect on the functionality of intestinal P-glycoprotein related efflux carriers, which could affect the amount of absorbed drug. This paper will focus on the effect of menthol on the first pass elimination of drugs. This issue is stressed, because it could change pharmacological responses of various drugs.

Keywords: Menthol, Essential oils, Metabolism, Drug-interactions.

INTRODUCTION

Menthol (C_{10}H_{20}O; mol. wt 156.27) is a monocyclic terpene alcohol present as a major constituent of peppermint oil (Mentha piperita) and cornmint oil (Mentha arvensis). Menthol has three asymmetric carbon atoms in its cyclohexane ring (Fig. 1), and therefore occurs as four pairs of optical isomers: (-)- and (+)-menthol, (-)- and (+)-neomenthol, (-)- and (+)-isomenthol, and (-)- and (+)-neo-isomenthol (Eccles, 1994). (-)-menthol (also called l-menthol or (1R,2S,5R)-menthol) is the main form of menthol occurring in nature and one of the most important flavoring chemicals. The majority of natural (-)-menthol is obtained by freezing the oil of Mentha arvensis to crystallize the menthol present (Anonymous, 2007).

Menthol is used extensively in many commercial products (pharmaceuticals, cosmetics, toothpastes, chewing gum, and other toilet goods as well as in cigarettes) and foods. In 2007, worldwide consumption of (-)-menthol, by product area, was estimated to be (Clark, 2007): Oral hygiene, 28.0%; pharmaceuticals, 26.6%; tobacco, 25.3%; confectionaries, 11.0%; shaving products, 7.0%; miscellaneous, 2.1%. With regard to its medicinal purposes, menthol is currently available in both prescribed and over-the-counter...
(OTC) medications for gastrointestinal disorders, common cold and respiratory conditions, musculoskeletal pain and dermatological problems. The current annual world production of menthol is estimated to be in excess of 19,000 metric tons (natural menthol at 12,870 metric tons and synthetic menthol at 6,300 metric tons for a total of 19,170 metric tons) (Anonymous, 2007).

**Figure 1.** Chemical structure of (-)-menthol

Bioavailability of an orally administered drug is comprised of the individual fractions that survive the various barriers encountered by the drug during its first passage from the gut lumen to the sampling site (Kwan, 1997):

\[ F' = F_X \times F_G \times F_{IH} \]

\( F' \) is oral bioavailability fraction. \( F_X \) is the fraction absorbed (i.e. net transport of unchanged drug into and around the absorptive cells of the gastrointestinal tract), \( F_G \) is the fraction that is not metabolized in a single passage through the gut wall, \( F_{IH} \) is the fraction that is not extracted during the first passage through the liver.

\( F' \) is less than 100% of the active ingredient in the oral dose for four reasons (Benet et al, 1998):

1. drug is not absorbed out of the gut lumen into the cells of the intestine and is eliminated in the feces
2. drug is absorbed into the cells of the intestine but back-transported into the gut lumen
3. drug is biotransformed by the cells of the intestine (to an inactive metabolite)
4. drug is eliminated by the cells of the liver, either by biotransformation and/or by transport into the bile.

The main topic of this paper is the effect of menthol on the bioavailability of the coadministered drugs through the above mentioned first pass elimination mechanisms. The studies investigating whether or not menthol, which is consumed widely all over the world, causes natural product-drug interaction will be discussed.

**Effects of menthol on gastrointestinal motility**

As mentioned above peppermint oil is obtained from the fresh leaves of *Mentha piperita*. The major constituents of the oil are (-)-menthol (30-55%), (-)-menthone (14-32%), (+)- isomenthone (1.5-10%), (-)-menthyl acetate (2.8-10%), (+)-menthofuran (1.0-9.0%) and 1.8 cineol (3.5-14%). Peppermint oil has been used for many years in herbal remedies for the treatment of digestive disorders since it has spasmylytic effect on gastrointestinal tract. Grigoleit’s review shows that peppermint oil is used in an enteric coated form in irritable bowel syndrome, and that it is a safe, efficacious and cost effective symptomatic short term treatment in reducing global symptoms and pain due to its spasmylytic and antiflatulent effects. The antispasmodic effect of peppermint oil is due to (-)-menthol, which acts as a calcium antagonist; however, its antiflatulent effects are currently unexplained (Grigoleit and Grigoleit, 2005a, 2005b).

Menthol has been shown to inhibit histamine and acetylcholine-induced contractions of guinea-pig isolated *Taenia coli*. The inhibitory effect depends on its antagonistic effect on L type calcium channels (Hawthorn et al., 1988; Grigoleit and Grigoleit, 2005c). *In vitro* studies on guinea-pig and human gut smooth muscle indicate that menthol exerts an inhibitory effect on gut smooth muscle by decreasing the influx of extracellular calcium through potential-dependent channels, whilst having no effect on the intracellular mobilization of calcium (Eccles, 1994). The relaxant effect of menthol on the gastrointestinal tract could influence the rate of drug absorption.

Menthol is highly lipid-soluble and is rapidly absorbed from the small intestine when taken orally. We had determined the disposition kinetics of 100 mg menthol capsule and 10 mg menthol containing mint candy or mint infusion (Gelal et al., 1999). Average peak plasma concentrations of menthol (C\text{max}) were 2610±862 ng/ml and 368±115 ng/ml; the time to reach C\text{max} (t\text{max}) were 61±26 min and 30±12 min in the menthol capsule group and mint candy lozenges/mint infusion group, respectively. In our menthol-coffeine interaction study, eleven healthy female subjects participated in a randomized, double-blind, two-way crossover study, comparing the kinetics and effects of a single oral dose of caffeine (200 mg) in coffee taken together with a single oral dose of menthol (100 mg) or placebo capsules, coadministration of menthol caused a significant increase in caffeine t\text{max} and slight
decrease of caffeine $C_{\text{max}}$. We suggested that the relaxant effect of menthol on the gastrointestinal tract could influence the rate of drug absorption by decreasing gastric emptying, which most likely accounts for the slowing of caffeine absorption in our study (Gelal et al., 2003). However, in our other study undertaken to determine whether or not menthol affects the metabolism and pharmacological responses of the calcium channel antagonist felodipine in people, felodipine $t_{\text{max}}$ value did not change in presence of menthol. This indicates that the rate of felodipine absorption into the systemic circulation is unaffected by the coadministration of menthol (Gelal et al., 2005). The lack of effect by menthol on felodipine absorption rate in our study could be related to competitive antagonism between $l$-menthol and [3H]-nitrendipine or the dihydropyridine radioligand [3H]-(+)-PN200-110 binding to intestinal smooth muscle (Hawthorn et al., 1988).

**Effects of menthol on drug metabolism (biotransformation)**

The liver contains many isofoms of cytochrome P450 (CYP) and can biotransform a large variety of substances. The enterocytes lining the lumen of the intestine also have significant CYP activity and this activity is dominated by a single family of isozymes, CYP3A, the most important isofoms in drug metabolism (Benet et al., 1998). Despite widespread human exposure to menthol and other monoterpenes found in essential oils, the effects of these substances on drug metabolism are not well characterized. The effects can be estimated using in vitro and in vivo drug biotransformation measurements.

Some of the terpenoids used in pharmaceutical preparations and as constituents of food induce or inhibit drug metabolizing activities of liver in vitro. Madyastha and Srivastan (1988), for establishing the effect of $l$-menthol on hepatic drug-metabolizing enzymes, administered 800 mg/kg $l$-menthol (as a suspension in 1% methyl cellulose solution, once daily up to 7 days) by gastric intubation to the adult male rats. In this study it was observed that both CYP and NADPH-cytochrome c reductase activity were induced to significant levels. Maximal induction of CYP and its reductase was observed upon 3 days of repeated treatment with $l$-menthol. Further treatment (for 7 days total) reduced their levels considerably, although the levels were still higher than the control values.

Austin et al., designed the study to investigate the effects of five terpenoids, including menthol, on the expression of genes coding for components of the CYP2B subfamily of rat liver microsomal membranes. Their research arised from the previous findings that various terpenoids increase the rate of metabolism of penta- and hexabarbital, and decrease the sleeptime induced by these barbiturates suggesting that the action of the terpenoids may be mediated through an increase in the activity of a member of the major phenobarbital-inducible CYP subfamily CYP2B. In their study, the rats were given intraperitoneal injections of menthol or other terpenes at a dose of 40 mg/kg for 3 days. The induction of hepatic CYP2B subfamily was confirmed by radioimmununassay, Western blotting and by nucleic acid hybridization after in vivo treatment of rats with menthol. None of the terpenoids had an effect on the amount of mRNA coding for CYP1A2 (Austin et al., 1988).

De-Oliveira et al. (1999) investigated the inhibitory effects of menthol and some monoterpenoid alcohols on liver microsomal enzymes involved in the biotransformation of xenobiotic substances. They found that (-)-menthol inhibited CYP2B1 activity in vitro, as opposed to previous in vivo studies. They also showed that (-)-menthol had weak inhibitory effect on CYP1A2 activity. In their study, 40 µM menthol decreased rate of $O$-dealkylation by 20%. However, this in vitro finding may not be extrapolated to in vivo results, because menthol is rapidly but incompletely metabolized to menthol glucuronide in vivo and the remainder of menthol is metabolised by hydroxylation (Yamaguchi et al., 1994; Bell et al., 1981). For that reason we carried out a clinical research to determine whether a single oral dose of menthol affects the metabolism of caffeine, a CYP1A2 substrate, and the pharmacological responses of caffeine in people (Gelal et al., 2003). Co-administration of menthol resulted in an increase of caffeine $t_{\text{max}}$ values (as mentioned above) from 43.6±20.6 min (mean ± SD) to 76.4±28.0 min (p<0.05). The $C_{\text{max}}$ values of caffeine were lower in the menthol phase than in the placebo phase, but this effect was not statistically significant (p=0.06). Area under the curve [(AUC)$_{0-24}$, (AUC)$_{0-\infty}$], terminal half-life and oral clearance were not affected by menthol. We concluded that 100 mg menthol did not alter caffeine metabolism in healthy female volunteers.

Some essential oils reduce CYP3A drug biotransformation by acting as an inhibitor of CYP3A activity or as a substrate of CYP3A (Benet et al., 1998). One of the inhibitors identified in this work was peppermint oil. Cyclosporine (CyA) is a potent immunosuppressive agent. It has poor oral bioavaila-
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bility, which can be attributed to presystemic elimination by CYP3A and active eflux of drug by P-glycoprotein (P-gp) to intestinal lumen. The impact of peppermint oil as a bioavailability enhancer on CyA oral bioavailability in male rats was evaluated by Wacher et al. (2002). They compared peppermint oil efficacy with CYP3A inhibitor ketoconazole and the solubility enhancer and Pgp inhibitor D-α-tocopheryl poly (ethylene glycol 1000) succinate (TPGS). Additionally, the in vivo effects of peppermint oil and ketoconazole were compared with their relative activities as CYP3A inhibitors in vitro using liver microsomes. Peppermint oil and TPGS enhanced CyA oral bioavailability. However ketoconazole, a potent CYP3A inhibitor in vitro, was ineffective. They concluded that inhibition of CYP3A may not be the only means by which peppermint oil exerts its effect.

Gastrointestinal muscle relaxant effects (which may account for the significant increase in CyA t_max) and permeability enhancer effects of peppermint oil and menthol may also contribute to the effect of peppermint oil as an enhancer of CyA absorption.

Following the Wacher’s study, Dresser et al. (2002) published the study which investigated the effect of peppermint oil and ascorbyl palminate on CYP3A4 activity in vitro and oral bioavailability of felodipine in humans. Felodipine is a dihydropyridine calcium antagonist. CYP3A4 is the major enzyme for its biotransformation and it is not a substrate for P-gp. So felodipine is the most extensively studied probe for CYP3A4 enzyme activity. Peppermint oil augmented the oral bioavailability of felodipine in this study. The mechanism may involve inhibition of presystemic drug metabolism mediated by CYP3A4. Dresser et al. (2002), suggested that the concentration of menthol in peppermint oil accounts for some portion of the inhibitory effect of the oil on CYP3A4-mediated metabolism in vitro and in vivo. Thereafter, in order to explore the suggestion of Dresser et al.; we planned a study to evaluate the interaction of menthol and felodipine (Plendil®) in healthy subjects. Eleven healthy subjects (10 female, 1 male) participated in a randomized, double-blind, two-way crossover study, comparing the kinetics and effects of a single oral dose of felodipine ER tablet (Plendil®, 10 mg) with menthol or placebo capsules. Menthol was given in divided doses. At the beginning of the study, 100 mg menthol or placebo capsule were given and then in the 2nd, 5th and 7th h of the study, 50 mg, 25 mg and 25 mg menthol or placebo capsules were given, respectively. The results showed that there were no differences in the dehydrofelodipine and felodipine C_max and AUC0-24 values when coadministered with menthol or placebo, indicating that neither the formation nor the elimination of felodipine and dehydrofelodipine (the primary metabolite of felodipine) were affected by the presence of menthol, and also that there was no pre-systemic interaction. Dresser et al. had used 600 mg peppermint oil in their study. Accordingly, subjects received approximately 180 to 300 mg single dose of menthol in this study. We found that pharmacokinetics of felodipine were not altered by 200 mg menthol in divided doses. Divided dose of 200 mg menthol may not constitute an adequate concentration-time profile of menthol at CYP3A4 during the period of absorption or metabolism. However, to conclude that menthol does not affect felodipine pharmacokinetics, further studies are required.

Effects of menthol and other monoterpenic alcohols on propofol induced anesthesia time in mice were investigated (Li et al., 2006). They found that duration of anesthesia was prolonged, primarily due to the inhibition of propofol’s metabolism. Aminopyrine has similar CYP isozyme specificity (CYP2B and CYP2C) with propofol. The effects of menthol on aminopyrine N-demethylation was also tested by Li et al., who showed that menthol significantly inhibited aminopyrine N-demethylation activity preincubated with the microsomes.

In a case report, concomitant ingestion of menthol-containing cough drops (approximately 6 drops/day over 4 days; estimated menthol dose of 42 mg daily) reduced the international normalized ratio (INR) to subtherapeutic range in a patient receiving anticoagulation therapy with warfarin. Clinically available warfarin is a racemic mixture of (R)- and (S)-warfarin, both enantiomers are eliminated extensively via hepatic metabolism. CYP2C9 is almost exclusively responsible for the metabolism of the pharmacologically more active (S)-enantiomer. The Naranjo probability scale was used to assess the causal relationship between the medication and the adverse reaction in the report and was rated 'possible' (Kassebaum et al., 2005).

Menthol is used extensively in cigarettes and one of its major consumption areas is tobacco industry. Benowitz et al. (2004) showed that mentholated cigarette smoking inhibits the metabolism of nicotine. Their data suggest that mentholated cigarette smoking was associated with both a decrease in CYP2A6 activity, as evidenced by a trend towards reduced nicotine clearance via the cotinine pathway, and a significant reduction in glucuronidation, as evidenced by the lower nicotine-glucuronide/nicotine ratio in the
Effects of menthol on P-glycoprotein

P-glycoprotein (Pgp) is a 170 kDa transport protein belonging to the superfamily of the ABC transporters. Drug extrusion is mediated by this active transporter. The efflux mechanism plays a major role in the occurrence of multidrug resistance in the treatment of cancer; it also has an important physiological role in the protection of the body against xenobiotics. Pgp is functionally expressed in the small intestine, renal epithelium, the blood-brain barrier and several other tissues in the human body (Deferme et al., 2002). The essential oil can have properties of being a ligand for Pgp or CYP or a ligand for either proteins (Bennet et al., 1998). Deferme et al. screened standardized food extracts, including mint, to their possible inhibitory effect on the Pgp mediated efflux of 3H-cyclosporine A (CsA) using the in vitro Caco-2 model. Their results included a significantly increased absorptive transport of CsA, together with a significantly decreased secretory transport. The results suggest that the absorption enhancing effect of mint might be due to an inhibitory effect of peppermint oil on the functionality of intestinal Pgp related efflux carriers.

CONCLUSION

Human beings are exposed to menthol, which is commonly used in food, cosmetics, cigarettes and herbal medicinal products. However, our knowledge about this compound is still limited despite its widespread consumption. Research on this natural product-drug interactions is important, since its coadministration with drugs may result in drug toxicity or ineffectiveness.

REFERENCES


