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Terbinafine and its adverse Hepatic effect:

Terbinafine hydrochloride a synthetic allylamine antifungal agent, is indicated both orally and topically for dermatophytic infections of the toenail or fingernail that is caused by onychomycosis, and also for **Tinea Capitis and Tinea Corporis**. It may be particularly useful in patients who cannot tolerate azole antifungal agents such as itraconazole, ketoconazole ….etc, or when there are concerns regarding possible drug interactions between azole antifungal agents and other drugs the patient is receiving [1]. However, liver failure (sometimes leading to death or liver transplant) has been rarely reported in patients with or without preexisting liver disease who were receiving terbinafine for the treatment of onychomycosis, according to Novartis Lamisil® tablets' prescribing information.

Hepatitis was firstly reported to be associated with the use of terbinafine at 1993[2], that was followed by several reports in the following years[3-8].Risk factors for this adverse effect were addressed by Munoz et al, 2003 [9] , the authors found that most of the reported cases were;

- Age > 50.
- Used the drug for at least 3 weeks before presentation.

The mechanism of terbinafine hepatotoxicity is unknown. However many authors have proposed mechanisms for this effect[10, 11].

One of the proposed mechanisms is thought to be the same for its fungicidal effect which is; selective inhibition of the fungal enzyme squalene epoxidase, a key enzyme for fungal cell ergosterol synthesis. The enzyme inhibition leads to ergosterol deficiency in the fungal cell wall and in turn to toxic levels of intracellular squalene. Squalene epoxidase, the target of terbinafine, is also present in humans. However, squalene epoxide of mammalian cells is less susceptible to inhibition by terbinafine compared with fungal cells[10]. Furthermore, because of the rare and unpredictable nature of the terbinafine hepatic adverse reaction, the mechanism of toxicity has also been hypothesized to be either an uncommon immunological or metabolically mediated effect. Terbinafine-A(TBF-A), the allylic aldehyde metabolite of terbinafine formed by liver enzymes, has been recently proposed to be a direct hepatotoxin, furthermore, TBF-A probably modifies the canalicular proteins, leading to cholestatic dysfunction[11].

This month,**Paredes** et al 2007 [12], reported a case of terbinafine-induced autoimmune hepatitis in a patient with chronic hepatitis B infection. The 57-year-old male, with chronic hepatitis B virus (HBV) used terbinafine 250 mg once daily for dermatophyte toenail onychomycosis. At the beginning of terbinafine administration the patient's liver enzyme levels were within normal limits, but prior to the end of 12th week of treatment course, he developed ascites and jaundice. The patient was taking no other medications or herbal

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Article summary

- Terbinafine (Lamisil®) is available for both oral and topical routes of administration.
- Tebinafine is effective for the treatment of toenail and fingernail onchomycosis.
- The drug has good safety profile in general.
- Rare but serious hepatotoxic effect has been reported with terbinafine use.
- The mechanism is not well understood but reports suggest autoimmune induced response.
- Patients with underlying hepatic dysfunction should avoid the use of terbinafine.

supplements, did not drink alcohol, and did not appear to suffer a flare of HBV infection. The diagnosis as autoimmune- induced hepatitis was supported by the presence of transient autoantibodies and a liver biopsy. Three weeks after terbinafine was discontinued, liver enzymes were very high and he developed thrombocytopenia. Later the patient's liver function studies began to normalize 6 weeks after terbinafine was discontinued. The authors have used 2 different scales in order to assess the association relation ***(Naranjo probability scale, and Roussel Uclaf Causality Assessment Method)***

Both scales revealed a probable relationship between the patient's hepatitis and terbinafine. They proposed a mechanism which is likely involving hapten-carrier complex and the cytochrome P450 isoenzymes. The chronic HBV carrier state may have predisposed him to this autoimmune reaction.

The author concluded that the recommendation of the manufacturer to avoid the use of the drug in case of underlying liver dysfunction should be followed strictly [12].

This case represents the first case of autoimmune hepatitis supported by serologic, biochemical, and biopsy results. However terbinafine was also reported to induce other autoimmune diseases such as;

- Induction of Cutaneous Lupus Erythematosus after at least 1 month of therapy, in patients with pre-existing autoimmune disease[13-17].
- Psoriatic eruption, the clinical manifestations of which occurred days to weeks during and after treatment.[18]

Conclusion:

Terbinafine is a synthetic fungicidal agent of the allylamine class that is available for both oral administration and topical application. Generally it has a good safety profile; side effects appear in about 10% of patients treated with the common oral daily dosage of 250 mg and are usually mild, such as gastrointestinal disturbances, coetaneous symptoms or malaise. However it may induce rare, but serious adverse hepatic effect that is presented as cholestatic hepatitis. Although the mechanism is unknown, some authors proposed direct toxic effect of its metabolite, and it was only recently for terbinafine to be proposed as a cause for autoimmune liver injury effect. Whatever the mechanism by which terbinafine induced this adverse effect it is prudent to avoid its use in patients who have underlying liver disease such as viral Hepatitis B and C, both active diseases and carriers.

On the other hand people with pre – existing autoimmune diseases such as rheumatoid arthritis, psoriasis, Auto-immune thrombocytopenic purpura ….etc. are at risk for developing subacute cutaneous lupus erythematosus with terbinafine use.

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Green tea and stroke prevention:

Tea (Camellia sinensis, Theaceae) is second only to water in worldwide popularity as a beverage. There are three major types of tea that differs according to manufacturing process and consequently in their composition[1];

Green tea

Oolong tea

Black tea

The green tea contains a number of compounds such as flavonoids and theanine that possess strong antioxidant properties, many of the health benefits have been attributed to the polyphenolic components: Epigallocatechin-3-gallate (EGCG) and the related catechins have been the most widely studied in terms of disease prevention and treatment, such as heart diseases, diabetes, neurodegenerative disorders, and cancer[1].

Our focus in this article will be on the beneficial effect of green tea in preventing stroke.

Stroke is the third leading cause of death and the leading cause of serious long-term disability in the United States; it consists of three main subtypes, ischemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage, with ischemic stroke accounting for the majority of cases[2-4]. Epidemiological studies examining the preventive effects of tea on stroke have generated inconsistent results. However, two published studies on green tea reported positive findings [5, 6].

A cohort study conducted in Japan first reported an inverse association between tea consumption and stroke. It specifically examined the relationship between green tea consumption and stroke in 5910 women aged 40 years and over. The incidence of stroke was 5.5 times higher for women drinking no green tea relative to those drinking five or more cups daily.[5] This result was supported recently (2004), in a cross-sectional study that was conducted in China[6], the authors examined tea drinking habits including dose and type of tea consumed by 14,212 people who aged 35—60 years, an inverse association was also found between tea drinking and stroke. The adjusted odds ratio (OR) was 0.60 (95% CI: 0.42—0.85) for drinkers of tea (no special type) compared with non-drinkers which represents a 40% risk reduction of stroke in those who drink tea. The corresponding dose response relationship was also significant. A significant decrease in stroke prevalence was similarly observed when green tea consumption was assessed separately, the adjusted OR being 0.35 (95% CI: 0.18—0.72) for green tea drinkers versus non-drinkers which represents a 65% risk reduction for green tea. Although consumption of black and other teas also appeared to incur a decrease in stroke prevalence, their effects did not reach statistical significance[6].

Mechanisms that were proposed for the stroke prevention effect:

Although mechanism is not completely understood, there is evidence to suggest that green tea could reduce hypertension, atherosclerosis and thrombogenesis which in turn are important risk factors for stroke.[7] The vascular protecting properties of polyphenols were recently reviewed by Curin and Andriantsitohaina[8], which included the antioxidant potential of tea flavonoids and their free radical scavenging effects, leading to lower low-density lipoproteins (LDL) oxidation and platelet aggregation. Polyphenols are also able to modulate the generation of nitric oxide from vascular endothelium and to interfere with the mechanisms leading to inflammation and endothelial apoptosis, therefore contributing to the prevention of the endothelial dysfunction, which is known to play a central role in the pathogenesis of cardiovascular diseases including stroke[8].

As we reached this point in describing the benefits of green tea, it is worthy to mention other studies which give green tea other attributes such as; iron chelating property, in a study by Somdet et al 2006[9], which was performed to investigate the ability of green tea extracts to reduce plasma Non-transferrin-bound iron (NTBI) concentration and oxidative stress. In vitro; the author found that Iron III was found to bind to green tea crude extract and form a complex. Green tea crude extract time- and dose-dependently decreased plasma NTBI concentration and counteracted the increase of oxidative stress in both Fe2+-EDTA-treated human plasma and erythrocytes therefore the authors concluded that green tea is a bi-functional natural product that could be relevant for management of iron overload and oxidative stress, which are complications of B – thalasthemia, obviously, by decreasing the gastrointestinal iron absorption[9].

Therefore, normal population should avoid drinking green tea directly after food or concomitantly with iron supplement so that they could benefit from iron and prevent iron deffi-ciency anemia and at the same time benefit from green tea drinking.

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Rosiglitazone (Avandia®) may increase the risk of Heart Attacks:

A recent meta - analysis study that appears on New England Journal of Medicine. June 14, 2007 showed that rosiglitazone is significantly associated with increased risk of heart attacks, when compared with other antidiabetic drugs. The analysis was based on a review of over 40 existing clinical studies of approximately 28,000 patients. It showed that diabetic patients taking rosiglitazone raised their risk of heart attack to 28.9% from the 20.2% risk of an average diabetic over a seven-year period. [1]

In the editorials and the correspondence sections on 5 and 14 June 2007 issues of the journal many authors expressed their belief that the study raised serious concerns, however readers should realize that the research method used in the study left the results open to interpretation.[2-5]

The FDA in response to the study issued a public safety alert that advised those patients taking the drug to consult their doctors about the potential cardiovascular risks. On the other hand, Glaxo, the manufacturer released a statement that they disagree with the study and that it was based on incomplete evidence. Glaxo and the F.D.A. also disclosed that they knew about the potential cardiovascular risk since last August as a result of their own analysis that was submitted by Glaxo to the FDA.

For more information from FDA, follow the link;

http://www.fda.gov/consumer/updates/avandia052507.html

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