

α -MSH. This hormone is formed out of the pro-hormone POMC, which is being controlled by dopamine and serotonin. The exact role of serotonin in the hypothalamic gland, however, has not yet been elucidated. It is possible that the increase in the serotonin levels, induced by the use of SSRIs, causes an increase in the secretion of α -MSH. Animal experiments in which the 5-HT receptors are directly activated by the serotonin agonist MK-212 show an increase in the secretion of α -MSH. Administration of fluoxetine, on the other hand, did not influence the secretion of α -MSH.

Conclusion: Reports to the Netherlands Pharmacovigilance Centre Lareb suggest a possible association between hyperpigmentation and the use of selective serotonin reuptake inhibitors.

P075. Post-menopausal bleeding induced by *Vitex agnus castus* L. (Verbenaceae)

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Introduction: Vitamin supplements are generally considered safe. In The Netherlands, regulations only concern the allowed maximal dosages per capsule. Vitamins can be obtained not only from pharmacies and chemists, but also from supermarkets. We report a case of irregular post-menopausal bleeding in a 65-year-old woman, starting one month after having started a multivitamin preparation (Davitamon Femfit?) once daily. Ultrasound and diagnostic curettage revealed no abnormalities. The bleeding resolved after discontinuation of the vitamin preparation, containing *agnus castus*, several months later.

Aim of the study: Description of an adverse event case, involving a multivitamin supplement with phytotherapeutic additives probably causing the adverse event.

Methods: Analysis of the adverse event report, followed by a literature search

Results: Analysis of the report and subsequent searches in literature point to *Vitex agnus castus* L. as probable causal agent for post-menopausal bleeding. This conclusion is strongly supported by the well-documented report, including a description of the gynaecological diagnostic procedures that exclude other causes for post-menopausal bleeding. It is also supported by literature data, indicating that *agnus castus* is supposed to influence menstrual problems resulting from corpus luteum deficiency, including pre-menstrual symptoms, spasmodic dysmenorrhoea, insufficient lactation and certain menopausal conditions. In animal studies *agnus castus* diminished the release of follicle stimulating hormone and increased the release of luteinising hormone and prolactin. In humans *agnus castus* has been found to restore progesterone concentrations, prolong the hyperthermic phase in the basal temperature curve and restore the LH-RH test to normal.

Conclusion: The phytotherapeutic additive to the multivitamin supplement is believed to have caused an adverse event, which has required major diagnostic procedures. Physicians should be aware that multivitamin supplements might contain phytotherapeutic additives, which may cause adverse events

P076. Hepatotoxicity of antibiotics. Overview of spontaneous reports.

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Introduction: Several antibiotics are hepatotoxic. Although hepatic side effects are less frequent than gastrointestinal or cutaneous disorders and the underlying illness may also be associated with significant hepatic injury, the potential severity of hepatic side-effects must be stressed. This abstract presents spontaneous reports in the Netherlands concerning hepatic side effects of antibiotics.

Reports:

- beta-lactam antibiotics: Natural penicillins are a rare cause of, mostly cytolytic, hepatic injury. Semisynthetic penicillins a more frequent cause. The liver injury results from an idiosyncratic, possible immunoallergic, reaction. Cephalosporines of the first generation rarely induce hepatitis, cephalosporins of the third generation can cause mild abnormalities in liver function tests. The Netherlands Pharmacovigilance Centre (Lareb) received most reports on amoxicilline/clavulanic acid, the majority concerned (cholestatic) hepatitis and jaundice. On cephalosporins 6 cases of liver injury were reported.
- macrolide antibiotics: Cholestatic injury during use of macrolide antibiotics are frequently described: hepatitis occurs in about 2% of patients treated over two weeks, subclinical elevation of liver enzymes in up to 15%. Some facts (e.g. eosinophilia, the usual lag period, rechallenge) favour an immunoallergic process. Lareb received 21 reports on macrolide antibiotics, concerning a variety of types of liver injury.
- tetracyclines: Tetracyclines are the only antibiotics with a direct, predictable effect on the liver. They can cause steatosis, but some cases of hepatitis are also described. The mechanism of liver injury lies in the inhibition of tetracycline of the mitochondrial oxidation of fatty acids. Lareb received 14 reports concerning liver injury as suspected adverse event of doxycycline or minocycline. The type of liver injury was diverse.
- sulphonamides (with trimethoprim): Hepatotoxicity of sulphonamides occurs in 0.06% of recipients and results commonly in both cholestasis and necrosis. Subclinical elevation of serum aminotransferases is more frequent. In most cases hepatotoxicity has been ascribed to the sulphonamide components. Liver injury

results from an idiosyncratic, possibly metabolite-dependent mechanism. The Lareb received 19 reports of hepatic injury on sulfamethoxazol/trimethoprim and 5 on trimethoprim, most of them concerned (cholestatic) hepatitis.

- chinolon antibiotics: Slight elevation of liver enzymes is described in few percent of patients, but published data are sparse. The only case report of overt (cytolytic) hepatitis has been described for norfloxacin. Lareb received a total number of 13 reports concerning hepatotoxicity of chinolon antibiotics, among which three of overt hepatitis.
- others: Hepatotoxicity of lincomycines is reported mainly after high doses. With the decreasing use of chloramphenicol, reports of hepatic injury are extremely rare. The Netherlands Pharmacovigilance Centre has not received any reports on both groups of antibiotics. Hepatic injury due to aminoglycosides is not well documented. Lareb has received one report on gentamycin, concerning jaundice. Rifamycins may cause hyperbilirubinaemia. Lareb has received 1 report on rifamycin of hyperbilirubinaemia and 4 reports of hepatocellular injury.

Conclusion: Hepatotoxicity, as reported to Lareb, does not always resemble the data published in literature, as is the case with trimethoprim, penicillins and chinolon antibiotics. The number of spontaneous reports in the Netherlands reflects the importance of liver injury due to antibiotics.

P077. Monoplegia following Hepatitis B vaccination: usefulness of careful documentation and follow-up

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Introduction: A close temporal relationship between vaccination and a subsequent adverse event is often viewed as a causal relationship between the two: A careful investigation can often establish that this is not so.

Case: A 38-year-old German health care worker received a dose of recombinant Hepatitis B vaccine (Gen H-B-VaxÒ, Merck & Co. Inc) in February 2000. Though the exact number in series was not reported, this was at least his third dose, and previous vaccinations with the same vaccine had been well tolerated. The next day, he was unable to move his left arm. He was admitted to hospital with the diagnosis of 'acute paralysis of the brachial nerve.' The close temporal association with vaccination suggested a possible causal relationship. However, a follow-up report four months later, allowed the actual cause of the injury to be identified. Following nine days of unusually exhausting work in an emergency unit, the patient had slept for 16 hours lying on the same arm, in which he had been vaccinated the day before. Neurological examination concluded that the clinical signs

and symptoms were related to a compression of the brachial nerve resulting in a mechanical monoplegia, and were definitely not related to vaccination. The patient fully recovered.

Discussion: This case illustrates that a temporal relationship with vaccination is not sufficient to establish causality. It also emphasizes the importance of carefully documenting and following up all adverse events temporally related to vaccination in order to rule out any other possible etiology.

P078. The long-term acceptance of hormone replacement therapy

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Despite well-defined benefits of hormone replacement therapy (HRT), small proportions of postmenopausal women use HRT.

The aims of our study were to investigate: acceptance of HRT in women who have indication for HRT, reasons for non-acceptance or discontinuing and duration of HRT use.

In this study we included 668 women who had indication for HRT. The women were between 36 and 67 years of age (average 50.67 + -5.65). In 434 (64.97%) women the menopause was spontaneous, while in 234 women (35.03%) it was proved surgically. The postmenopause lasted between 6 months and 8.5 years (average 48.91 + -49.01 months). The results showed that 174 women (26.05%) did not accept HRT, 90 of them (13.47%) discontinued after less than 3 months, while 404 of them (60.48%) were taking HRT longer than 12 months. The most prevalent indication for women who took HRT longer than 12 months, were vasomotor disorders and/or psychological problems. In those who did not accept the HRT or discontinued after less than 3 months, the most frequent indication was prevention of cardiovascular disorders or osteoporosis.

The most frequent reasons for non-acceptance of HRT were: fear of unwanted effects of HRT, primarily the breast cancer (28.8%), inadequate physician's advice (24.4%) and price of HRT drugs (23.0%). The most frequent reasons for discontinuing therapy were: inadequate physician's advice (28.9%), unacceptable side effects (vaginal bleeding, headache and vertigo, swelling and tenderness of the breasts)—24.4%, price of HRT drugs (15.6%) and fear of breast cancer (8.9%). The women were taking HRT from 13 to 114 months. The average duration of taking the HRT was about 3.5 years (42.07 + -23.10 months). The correlation between the duration of taking HRT and the number of postmenopausal disorders, which existed at the beginning of the therapy was statistically significant ($r = 0.119$, $p < 0.05$). The results showed that women who had more