Anaphylactic shock induced by mephenesin
Choc anaphylactique induit par la méphénésine

Mephenesin is an aromatic glycerol ether, which decreases polysynaptic transmission in the spinal cord and brainstem. It is used as a skeletal muscle relaxant in the treatment of multiple sclerosis, Parkinsonism and acute muscle strain [1]. Usually, mephenesin is well tolerated and the common side effects are rashes, flushing of the face, nausea, vomiting, and somnolence [1]. Anaphylactic shock induced by mephenesin is exceptional. We report one case of anaphylactic shock induced by oral intake of mephenesin. This case was notified to the National Centre of Pharmacovigilance of Tunis the 4th of June 2012.

Case report
On May 2012, a 25-year-old man was operated for a fracture of the left lower limb. He has no personal or family history of atopy. For knees pain, he was prescribed ketoprofen (Ketofen 50®) one tablet × 3/day and mephenesin (Decontractyl 500®) one tablet × 2/day.

On September 29th, 2010, he received ketoprofen (1 tablet × 2) without any incident. The last tablet was taken on 9 pm. The next day, (September, 30th) he took one tablet of mephenesin at 9 am for the first time. He did not take ketoprofen. Ten minutes later, he presented facial edema, pruritus and dyspnea. He was hospitalized and physical examination revealed generalized edema without skin eruption, tachycardia and low blood pressure (80/40). The diagnosis of anaphylactic shock was retained.

He had been treated with systemic corticotherapy, adrenaline, and oxygenotherapy, with a good evolution within few hours. Ketoprofen and mephenesin were stopped. On March 2011, prick test (0.5 mg/ml than 5 mg/ml) and intradermal reactions (0.05 mg/ml than 0.5 mg/ml) with ketoprofen were negatives. The patient refused any tests with mephenesin.

Discussion
The role of mephenesin was retained with a possible intrinsic imputability score (or 12) according to the French method of imputability, this score is based on chronologic and semilogic criteria [2]:
• a suggestive delay (few minutes after its intake);
• a good evolution after drug withdrawal;
• a less high score of imputability for ketoprofen (11) or doubtful in front of an only compatible delay (> 12 h);
• the negative skin tests with ketoprofen.

Untoward reactions to mephenesin have occurred mainly after prolonged administration or overdoses in the case of Fantom et al., the patient was found dead after a 6-month treatment with mephenesin [3].

In literature, allergic reactions, mainly cases of cutaneous eruption (contact dermatitis, erythema multiforme like eruptions) were notified with mephenesin [4,5]. In those cases, mephenesin were used by topical route. Immune-allergic reactions associated with oral mephenesin were described in one case of fever on the fourth day of mephenesin carbamate administration with positive rechallenge after 24 h [6].

Anaphylactic shock is cited in the summary of product characteristics, but in literature, we only found one case that occurred after rechallenge with mephenesin [7]. This case deals with a 41-year-old woman who presented chest tightness and upper limb numbness while treated by mephenesin, Aspirin–phenaacetin–caffeine (APC) and tetracycline. The rechallenge of mephenesin was positive.

Skin testing is a practical, reliable and well-tolerated method for establishing IgE-mediated diseases [8]. The negative skin tests with ketoprofen and the low intrinsic score of this drug make its role unlikely. We could not undergo mephenesin tests because the patient did not agree.

Conclusion
The mephenesin is used commonly. It can be associated with anaphylactic shock. To our knowledge, only one case of anaphylactic shock was described in literature.

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References

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Serotonin and yawning: A possible adverse drug reaction during antidepressant therapy

Sérotonine et bâillements : un effet indésirable possible lors d’un traitement par antidépresseur

Yawning is a common but complex stereotyped reflex poorly understood. Different physiologic (hunger, hypoglycaemia, sedation) and pathologic (Eustachian tube disorders, travel sickness, infectious diseases, neurological diseases,iatrogene) states can induce yawning. Among drugs known to induce yawning, serotoninergic agents are frequently cited, such as selective serotonin reuptake inhibitors antidepressants [1]. Yawning induced by other class of antidepressants, such as noradrenalin and serotonin reuptake inhibitors or imipraminic antidepressants have also been described in literature [2,3]. We report here the case of a young woman who presented repetitive excessive yawning induced successively by paroxetine, a selective serotonin reuptake inhibitor, clomipramine, a tricyclic antidepressant and Saint John’s wort (Hypericum perforatum). Interestingly, the yawns regressed during agomelatine treatment.

Case report
An 18-year-old woman presenting depression was first treated with minalcipran, a noradrenalin and serotonin reuptake inhibitor antidepressant. The treatment was well tolerated but was stopped because of a lack of efficacy and induced insomnia. Then, the patient received a selective serotonin reuptake inhibitor, paroxetine 20 mg daily, but, some days later, she experienced abnormal excessive daytime yawning lasting up to several seconds, associated with contractures of the jaws. These yawns were disturbing, and disabled the patient while working and bothered her to speak. Paroxetine was discontinued and her yawning completely disappeared. Paroxetine was replaced by a tricyclic antidepressant, clomipramine 25 mg daily, which rapidly induced the same symptoms. Clomipramine was stopped and, as previously, yawning rapidly regressed. After one week, this treatment was substituted by Saint John’s wort but yawning reappeared after the first dose, and disappeared the day after discontinuation. Agomelatine, a melatonin receptors agonist, was then introduced, without causing yawning after few weeks of therapy.

Discussion
Yawning is known to be under the control of several neurotransmitters and neuropeptides, such as serotonin, dopamine, acetylcholine, nitric oxide, excitatory amino acids, ACTH and oxytocin [4]. Yawning induced by serotonin reuptake inhibitors antidepressants, such as paroxetine, or tricyclic antidepressants, such as clomipramine, is a rare but known adverse drug reaction. In 2007, Sommet et al. study the observations of yawning in the French Pharmacovigilance Database [1]. Among the 38 reports recorded from 1985 to 2004, 12 involved serotonin reuptake inhibitors (paroxetine n = 5, fluoxetine n = 4, sertraline n = 3). The delay of occurrence ranged from 1 day to 8 weeks. Drug was withdrawn in 8 cases and the resolution was observed in 9 cases. In this study, the serotonin reuptake inhibitors were the main pharmacological class involved, followed by dopaminergic drugs, confirming the implication of serotonin and dopamine in yawning.

In the other cases reported in literature, yawning appears during the days following the introduction of the treatment, and regresses or disappears after dose reduction [3,5–7]. Some case reports have suggested that yawning behaviour might be dose-dependant.

Yawning is considered as an unwanted effect during antidepressant therapy but for few authors, it is considered as beneficial in the regulation of brain homeostasis [8,9]. Indeed, there is a strong connection between yawning and thermoregulation, and a yawn would promote cerebral cooling. Thus, when serotonin, a vasoactive compound implicated in thermoregulation, induces brain and core temperature, it is counter-balanced by excessive yawning.

No case of yawning induced by Saint John’s wort is described in literature, but his mechanism of action passing by the serotoninergic way could explain his involvement in this case. Up to now, no case of yawning induced by agomelatine is reported in literature, probably because no direct action on 5HT increase is associated with this drug. To note, this drug is a melatonin receptor agonist (MT1-MT2) and a 5-HT2C receptor antagonist (but without effect on extracellular serotonin concentrations).