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Ondansetron in the first trimester of pregnancy: congenital abnormalities

Quick Read
Based on epidemiological studies of use in pregnant women, it is suspected that ondansetron may cause orofacial malformations when adminsitered in the first trimester of pregnancy.

Ondansetron is iindicated in the control of chemotherapy and radiotherapy induced nausea and vomiting, as well as in the prevention of post-operative nausea and vomiting, in adults and children (depending on the medication and pharmaceutical form used). While its exact mechanism of action is not known, ondansetron is a potent and highly selective central and peripheral neuron 5HT3 receptor antagonist.

Epidemiological studies have pointed to an association between orofacial malformations and ondansetron when this medicine is given in the first trimester of pregnancy. In a **recent cohort study** including over 1.8 million gestations, the use of ondansetron in the first trimester was associated with a slightly increased risk of **cleft palate: 3 additional cases for every 10,000 women treated**. This corresponds to a relative adjusted risk of 1.24 (95% CI: 1.03-1.48).
Evidence regarding **cardiac malformations** has been nuclear and such and association was **not** found in this study.

EMA and Infarmed recommend:

– Ondansetron should not be used during the first trimester of pregnancy.

– Childbearing-age women should consider the use of contraception.

The texts in the SmPCs (Summaries of the Products' Characteristics) and corresponding Information Leaflets will be altered to reflect the above recommendations.

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INDEX CARD

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Spasticity: Overview of potential adverse effects of its pharmacological treatment

Spasticity can be defined as a muscle tonus disorder that is characterised by heightened tonus-dependent speed movement stretch reflexes. It is **one of the most frequent motor disorders** and it is potentially incapacitating in patients with central nervous system (CNS) lesions where there is involvement of the **first neuron** along the cortico-reticula-bulbo-spinal pathway. The pathophysiological mechanisms of this disorder are not totally known. However, some consensus exists regarding loss of descending inhibitory control of the stretch reflex pathways and changes secondary to neuronal plasticity with hyperexcitability of suprasegmental motor neurons.[1]

The clinical picture is characterised by **increased muscle tonus** predominantly involving **antigravitational musculature and exacerbation of deep tendon reflexes**. Other characteristic manifestations of compromise of the cortico-spinal pathway include: decreased muscle strength, clonus, synkinesis, and abnormal plantar reflex (Babinsky reflex elicited).

Treatment should be **multidimensional**, including functional goal based rehabilitation (walking, daily life activities, grooming). Caution needs to be exercised not to affect already established functional capabilities.[2] Pharmacological therapy (oral, focal and intrathecal) has an important role in symptom control. It is essential to bear in mind the adverse effect profile of the most commonly used drugs (Table).[3,4,5,6]

Table. Drugs typically used in the treatment of spasticity and selected characteristic adverse effects

Drug	Mechanism of action	Selected characteristic adverse effects
Systemic therapy		
Baclofen	Centrally acting GABA agonist – pre-synaptic inhibition of spinal interneuron GABAb dos receptors	hypertension, somnolence, dizziness, fatigue, some evidence of negative effects on the post-CNS lesion brain plasticity process
Benzodiazepines	Increased affinity of endogenous GABA for GABA receptors – pre-synaptic inhibition	hypotension, ataxia, somnolence, fatigue, respiratory depression
Clonidine	Alpha-adrenergic agonist with anti-hypertensive and analgesic effects – motor neuron hyperpolarisation and inhibition of excitatory aminoacid release	hypotension, AV block, bradycardia, chest pain, Raynaud's phenomenon, somnolence, confusion, weakness, hallucinations, tinnitus
Tizanidine	Muscle relaxant, centrally acting alfa-2-adrenergic agonist – it inhibits the release of excitatory neurotransmitters from pre-synaptic neurons by binding to alfa-2-adrenergic receptors in the spinal cord	somnolence, fatigue, insomnia and visual hallucinations, hypotension, nausea, dyspepsia, dry mouth, skin rash

Drug	Mechanism of action	Selected characteristic adverse effects
Systemic therapy		
Gabapentin	Alpha-adrenergic agonist causing an increase in GABA in the CNS	hypertension, vasodilatation, ataxia, dizziness, involuntary movements, somnolence, asthenia, amblyopia, leucopoenia, purpura, changes in glycaemia, thyroiditis, gynaecomastia, acne, alopecia, pruritus
Modafinil	Alpha-adrenergic agonist that facilitates transmission of the monosynaptic reflex from sensitive Ia fibres to alpha motor neurons by inhibiting the cortical impulse to the subcortical brainstem and spinal cord areas	hypertension, chest pain, tachycardia, headache, insomnia, dizziness, agitation, auditory hallucinations, orofacial dyskinesia, anorexia, dry mouth, hypersalivation, nausea
Focal therapy		
Botullinic toxin	Similar action to the anaerobic bacterium Clostridium botulinum; it inhibits release of acetylcholine at the neuromuscular plate (junção) with partial neurolysis	pain, local haematoma, antibody formation
Fenol	Chemical axoniotemesis (at concentrations above 3%) with denaturation of the myelin sheath and interruption of nervous conduction and reflex arc	pain, local haematoma, dizziness, nausea, vomiting

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Educational Materials published in the Infomed product information webpage

Click on the links.

INN Medicinal product	Target	Comunication Online publication date
Cholic acid Orphacol	**Physicians:** hepatologists, namely paediatric hepatologists	Safety information 29-10-2019
Atomoxetin Atomoxetina Pentafarma	**Physicians:** paediatrics, neuropaediatrics, psychiatry and child psychiatry	Cardiovascular and cerebrovascular risk assessment and monitoring guide Checklist – pre-treatment Checklist – during treatment Cardiovascular record table 11-10-2019
Propranolol Hemangiol	**Physicians:** potential prescribers, nomely paediatricians and dermatologists	Instructions for use and risk minimisation (includes a tear-out to be handed by physicians to healthcare providers)
	Healthcare providers	Guide Tear-off leaflet 18-10-2019

Compiled by Patrícia Catalão

Farmacovigilância em Portugal: 25 anos ***E-book***

Chapter 7.5. – Gastrointestinal Adverse Reactions

(Ana Paróla, Helena Farinha, Isabel Seves, José Azevedo Rodrigues, Leopoldo Matos)

GI adverse reactions are common and typically produce non-specific manifestations. This can lead to delays in diagnosis and to unnecessary ancillary exams and therapies being undertaken. On the other hand, the clinical manifestations of this type of adverse effects often culminate in the suspension or the discontinuation of an ongoing treatment, which can compromise the effectiveness of the "offending" drug. The main mechanisms of GI toxicity include direct organ lesions, dysbiosis and changes in gut motility, essentially depending on the actual organ being affected.

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