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UNIVERSIDADE ESTADUAL PAULISTA - "JÚLIO DE MESQUITA FILHO"
INSTITUTO DE BIOCIÊNCIAS DE BOTUCATU – IBB
PROGRAMA DE PÓS-GRADUAÇÃO EM FARMACOLOGIA E BIOTECNOLOGIA

ANA CAROLINA CASALI REIS

"INFLUÊNCIA DA EXPOSIÇÃO *IN UTERO* A ONDANSETRONA: POSSÍVEIS EFEITOS TERATOGÊNICOS E REPERCUSSÃO TARDIA EM PARÂMETROS REPRODUTIVOS E COMPORTAMENTAIS EM RATOS MACHOS"

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Orientador: Prof[a]. Dr[a]. Arielle Cristina Arena

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Epígrafe

"Nada na vida deve ser temido, somente compreendido.
Agora é hora de compreender mais para temer menos."
(Marie Curie)

Resumo

A ondansetrona é um antagonista altamente seletivo do receptor de serotonina 5HT3, utilizado na prevenção e tratamento de náuseas e vômitos. É considerada uma droga de categoria B, contraindicada para mulheres grávidas sem orientação médica ou do cirurgião dentista, no entanto é amplamente utilizada para aliviar náuseas e vômitos na gestação. Poucos dados avaliando o uso deste medicamento durante a período gestacional estão disponíveis na literatura. Dessa forma o objetivo é avaliar os possíveis efeitos teratogênicos e impactos tardios da ondansetrona em parâmetros reprodutivos e comportamentais na prole masculina após exposição intrauterina. Para isso, ratas Wistar com diagnóstico de prenhez foram alocadas em três grupos (n=20/grupo), sendo um grupo controle (água destilada) e dois grupos tratados com diferentes doses de ondansetrona (1,7 ou 2,5 mg/kg/dia, via oral). Parte dos animais n=10/grupo foi exposta ao medicamento do 6° ao 15° dia de prenhez (período correspondente a organogênese), e a outra parte foi exposta durante todo o período de prenhez, abrangendo o primeiro pico de testosterona, essencial para o processo de diferenciação sexual hipotalâmica. Os resultados gerados indicam que ondansetrona não foi capaz de alterar significativamente o processo de diferenciação sexual hipotalâmica, não havendo alterações em marcadores de masculinizacão e puberdade respectivamente: distância anogenital e separação prepucial. Demais parâmetros espermáticos e férteis avaliados permaneceram inalterados, limitando seus impactos a vida peripubere alterando o padrão de comportamento social. Avaliações do caráter teratogênico não indicou que o uso de ondansetrona durante a organogênese aumenta o risco de malformações externas, viscerais ou esqueléticas. No entanto mudanças em parâmetros bioquímicos e histológicos de ratas prenhas tratadas do dia de prenhez 6 ao 15 apontaram para lesão renal.

Palavras-chaves: náuseas e vômitos na gestação, hiperêmese gravídica, teratógenos, diferenciação sexual hipotalâmica, lesão renal.

Abstract

Ondansetron is a highly selective serotonin 5HT3 receptor antagonist used in the prevention and treatment of nausea and vomiting. It is considered a category B drug, contraindicated for pregnant women without medical or dental surgeon guidance, however, it is widely used to relieve nausea and vomiting during pregnancy. Few data evaluating the use of this drug during pregnancy are available in the literature. Thus, the objective is to evaluate the possible teratogenic effects and late impacts of ondansetron on reproductive and behavioral parameters in male offspring after intrauterine exposure. For this, Wistar rats diagnosed with pregnancy were allocated into three groups (n=20/group), being a control group (distilled water) and two groups treated with different doses of ondansetron (1.7 or 2.5 mg/kg /day, orally). Part of the animals n=10/group was exposed to the drug from the 6th to the 15th day of pregnancy (period corresponding to organogenesis), and the other part was exposed throughout the entire pregnancy period, covering the first peak of testosterone, essential for the process of hypothalamic sexual differentiation. The developed results indicate that ondansetron was not able to significantly alter the hypothalamic sexual differentiation process, with no changes in masculinization and puberty markers, anogenital distance, and preputial separation respectively. Other sperm and fertile parameters evaluated remained unchanged, limiting their impacts on peripubertal life, altering the pattern of social behavior. Assessments of teratogenicity did not indicate that the use of ondansetron during organogenesis increases the risk of external, visceral, or skeletal malformations. However, changes in biochemical and histological parameters of pregnant rats treated from pregnancy day 6 to 15 pointed to kidney injury.

key words: nausea and vomiting during pregnancy, hyperemesis gravidarum, teratogens, hypothalamic sex differentiation, kidney injury.

LISTA DE ILUSTRAÇÕES

LISTA DE ABREVIATURAS E SÍMBOLOS

5HT	5- hidroxitriptamina
AVPV	Núcleo Periventricular Anteroventral
DG	Dia Gestacional
FDA	Food and Drug Administration
GABA	Ácido Gama-aminobutírico
hCG	Gonadotrofina Coriônica Humana
HG	Hiperêmese gravídica
NVG	Náuseas e Vômitos na Gestação
SDN-POA	Núcleo Sexualmente Dimórfico da Area Pré-óptica
SNC	Sistema Nervoso Central

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7. CONCLUSÃO

Nossos resultados demonstraram que, neste modelo experimental, a ondansetrona não foi capaz de causar impactos no processo de maturação sexual, não ocasionando mudanças comportamentais, assim como alterações significativas em parâmetros espermáticos ou hormonais na vida adulta. Além disso, avaliações do caráter teratogênico dessa substância não demonstraram elevações dos riscos de malformações diante da administração dessa droga em ratas Wistar durante o periodo de organogênese.

8.ANEXO

CERTIFICADO

Certificamos que a proposta intitulada "Influência da exposição in utero a ondansetrona: efeitos teratogênicos e repercussão tardia em parâmetros reprodutivos e comportamentais em ratos machos.", protocolada sob o CEUA nº 6353250620 (ID 000122), sob a responsabilidade de **Arielle Cristina Arena** *e equipe; Ana Carolina Casali Reis* - que envolve a produção, manutenção e/ou utilização de animais pertencentes ao filo Chordata, subfilo Vertebrata (exceto o homem), para fins de pesquisa científica ou ensino - está de acordo com os preceitos da Lei 11.794 de 8 de outubro de 2008, com o Decreto 6.899 de 15 de julho de 2009, bem como com as normas editadas pelo Conselho Nacional de Controle da Experimentação Animal (CONCEA), e foi **aprovada** pela Comissão de Ética no Uso de Animais do Universidade Estadual Paulista (IBB/UNESP) na reunião de 10/08/2020.

We certify that the proposal "Influence of in utero exposure to ondansetron: teratogenic effects and late repercussions on reproductive and behavioral parameters in male rats.", utilizing 285 Heterogenics rats (males and females), protocol number CEUA 6353250620 (ID 000122), under the responsibility of **Arielle Cristina Arena** *and team; Ana Carolina Casali Reis* - which involves the production, maintenance and/or use of animals belonging to the phylum Chordata, subphylum Vertebrata (except human beings), for scientific research purposes or teaching - is in accordance with Law 11.794 of October 8, 2008, Decree 6899 of July 15, 2009, as well as with the rules issued by the National Council for Control of Animal Experimentation (CONCEA), and was **approved** by the Ethic Committee on Animal Use of the São Paulo State University (IBB/UNESP) in the meeting of 08/10/2020.

Finalidade da Proposta: Pesquisa (Acadêmica)

Vigência da Proposta: de 10/2020 a 05/2022 Área: Ciências Biomédicas

Origem:	Biotério Central da UNESP						
Espécie:	Ratos heterogênicos	sexo:	Machos e Fêmeas	idade:	0 a 5 meses	N:	285
Linhagem:	Wistar			Peso:	4 a 500 g		

Local do experimento: Lugares onde os experimentos e atividades propostas serão realizados: Biotério de mamíferos do departamento de Biologia Estrutural e Funcional Laboratório de toxicologia de produtos naturais e sintéticos

Botucatu, 15 de novembro de 2021

Profa. Dra. Ana Carolina Inhasz Kiss
Coordenadora da Comissão de Ética no Uso de Animais
Universidade Estadual Paulista

Prof. Assoc. Luis Fernando Barbisan
Vice-Coordenador da Comissão de Ética no Uso de Animais
Universidade Estadual Paulista