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UNIVERSIDADE ESTADUAL PAULISTA “JÚLIO DE MESQUITA FILHO”
INSTITUTO DE BIOCIÊNCIAS DE BOTUCATU
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Investigação de parâmetros reprodutivos em ratos machos expostos ao psicoestimulante Lisdexanfetamina do período juvenil a peripuberdade

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Botucatu – SP
2023

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Dissertação apresentada ao programa de pós-graduação em Farmacologia e Biotecnologia do Instituto de Biociências de Botucatu da Universidade Estadual Paulista "Júlio de Mesquita Filho" (UNESP), para obtenção do título de Mestre em Farmacologia e Biotecnologia

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1. Reprodução. 2. Psicoestimulantes. 3. Toxicidade sistêmica. 4. Hepatotoxicidade.

Palavras-chave: Hepatotoxicidade; Lisdexanfetamina; Psicoestimulantes; Toxicidade reprodutiva ; Toxicidade sistêmica.

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LISTA DE ILUSTRAÇÕES

LISTA DE ABREVIATURAS E SÍMBOLOS

5-HT: Serotonina

ANVISA: Agência Brasileira de Vigilância Sanitária

APA: Associação Americana de Psiquiatria

ASC: Área sob a curva

CID10: classificação Estatística Internacional de Doenças e problemas Relacionados com a Saúde, décima edição

$C_{máx}$: Concentração plasmática máxima

DA: Dopamina

D-AMF: Dextroanfetamina

DAT: Transportador de dopamina

DHT: Di-hidrotestosterona

DL50: dose-letal para 50% dos invidíduos

DPN: Dia pós-natal

DSM-5: Manual diagnóstico e estatístico de transtornos mentais, Quinta edição

FDA: food and Drug Administration

FSH: Hormônio Folículo Estimulante

GABA: Ácido gama-aminobutírico

GH: Hormônio do crescimento

GnRH: Hormônio liberador de gonadotrofina

HPG: Eixo hipotálamo-pituitária-gonadal

LDX: Dimesilato de lisdexanfetamina

LH: Hormônio Luteinizante

MOA: Monoamina oxidase

MPH: Metilfenidato

NA: Noradrenalina

NAT: Transportador de noradrenalina

NOAEL: nível de efeitos adversos não observáveis

NOEL: nível de efeitos não observáveis

PEPT1: Transportador de peptídeos 1

SERT: Transportador de serotonina

SNC: Sistema nervoso central

$T_{1/2}$: tempo de meia-vida

TAAR1: Receptor associado a traços de aminas do tipo 1

TDAH: Transtorno de déficit de atenção e hiperatividade

$T_{máx}$: Tempo para se atingir a Cmáx

VMAT2: Transportador de monoamina vesicular 2

RESUMO

O transtorno de déficit de atenção e hiperatividade (TDAH) é um distúrbio do neurodesenvolvimento comum em crianças e adolescentes, com maior incidência de diagnósticos no sexo masculino. Desatenção, hiperatividade e impulsividade em níveis acima do esperado são os principais sintomas do TDAH, afetando negativamente a vida diária dos pacientes. O tratamento adequado é essencial e baseia-se numa estratégia multimodal, com intervenções cognitivo-comportamentais e tratamento farmacológico, geralmente com medicações estimulantes. Um dos principais medicamentos utilizado é o Dimesilato de Lisdexanfetamina (LDX), uma formulação de liberação prolongada, pois é uma pró-droga da dextroanfetamina, hidrolisada no interior dos eritrócitos. Sua ação é mediada pelo aumento dos níveis de catecolaminas, principalmente dopamina e noradrenalina, nas fendas sinápticas. Como os neurotransmissores influenciam o controle hormonal e atuam diretamente nas gônadas, a LDX poderia interferir no desempenho reprodutivo. O período juvenil e a peripuberdade são janelas críticas do desenvolvimento, mais susceptíveis ao efeito de substâncias exógenas. Assim, o objetivo deste estudo foi avaliar os efeitos da exposição ao LDX do período juvenil até a peripuberdade sobre os parâmetros de toxicidade sistêmica e reprodutiva de ratos machos. Ratos Wistar machos (23 dias de idade) foram divididos em um grupo controle (água deionizada) e três grupos expostos a LDX em doses terapêuticas (convertidas para dose animais): 5,2; 8,6 e 12,1 mg/kg/dia. O tratamento ocorreu do dia pós-natal 23 (DPN) ao 53, via gavage. Durante o tratamento, foram avaliados sinais clínicos de toxicidade, peso corporal, ingestão de água e ração, comportamento social de brincar e estabelecimento da puberdade. No dia pós-natal (PND) 54, metade dos animais foi morta para peso dos órgãos, análise hematológica e bioquímica, histologia testicular e estresse oxidativo do testículo. Na vida adulta (PND 90), os animais foram avaliados quanto ao comportamento sexual masculino e parâmetros de fertilidade. No DPN 120, os animais foram mortos para registro do peso dos órgãos, parâmetros hematológicos e espermáticos, contratilidade do ducto deferente, histologia testicular e estresse oxidativo do testículo. Observou-se redução no consumo diário de ração e água durante o período de tratamento. Na avaliação do comportamento social de brincar, os animais apresentaram redução nos comportamentos sociais totais. Nenhum grupo experimental teve o dia da separação prepucial alterado em relação ao controle, mas o peso dos animais do grupo de maior dose foi reduzido neste dia. No DPN 54, vários parâmetros foram alterados, principalmente relacionados à toxicidade sistêmica: redução do ganho de peso corporal, aumento do peso relativo do fígado, baço e glândula seminal, redução da contagem de eritrócitos e leucócitos, redução dos níveis de proteínas totais e

alterações em parâmetros oxidativos. Na idade adulta, o comportamento sexual masculino e a fertilidade não foram alterados. Já no DPN 120, houve aumento de espermatozoides do tipo C (imóvel), diminuição da contagem nos testículos e epidídimos, alterações histológicas nas células de Leydig e nos túbulos seminíferos e alteração dos parâmetros oxidativos. Com base nos dados apresentados, o LDX foi capaz de induzir distúrbios nos parâmetros toxicológicos sistêmicos (principalmente durante o tratamento) e na função reprodutiva (principalmente na vida adulta), indicando que o uso deste medicamento deve considerar esses aspectos.

Palavras-chave: Lisdexanfetamina, psicoestimulantes, toxicidade sistêmica, hepatotoxicidade, toxicidade reprodutiva

ABSTRACT

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in children and adolescents, with a higher incidence of diagnoses in male sex. Inattention, hyperactivity and impulsivity in levels above expected are the main symptoms in ADHD, negatively affecting patients' daily life. Proper treatment is essential and it is based on a multimodal strategy, with cognitive-behavioral interventions and pharmacological treatment, usually with stimulants medications. One of the main drugs is Lisdexamfetamine Dimesylate (LDX), an extended-release formulation since it is a prodrug of dextroamphetamine, hydrolyzed inside erythrocytes. Its action is mediated by increased levels of catecholamines, mainly dopamine and noradrenaline, in synaptic clefts. Neurotransmitters influence hormonal control and act directly in gonads, so LDX could interfere in reproductive performance. Juvenile and peripubertal period are critical windows of development, more susceptible to the effect of exogenous substances. The aim was to evaluate the effects of exposure to Lisdexamfetamine during the juvenile to peripubertal period on parameters of systemic and reproductive toxicity of male rats. Male Wistar rats (23 days old) were divided into a control group (deionized water) and three groups exposed to LDX in therapeutic doses (converted to animal doses): 5.2; 8.6 and 12.1 mg/kg/day. The treatment occurred from post-natal day 23 (PND) to 53, by gavage. During the treatment, clinical signs of toxicity, body weight, water, and food intake, play behavior and puberty onset were evaluated. On postnatal day (PND) 54, half of the animals were killed for organ weight, hematological and biochemical analysis, testis histology and oxidative stress of the testis. In adult life (PND 90), the animals were evaluated in relation to male sexual behavior and fertility parameters. On PND 120, the animals were killed to record organ weight, hematological parameters, sperm parameters, contractile of vas deferens, testis histology and oxidative stress. There was a reduction in the daily food and water consumption during the treatment period. On play behavior evaluation, the animals presented a reduction in total social behaviors. No experimental group had the day of preputial separation altered compared to control, but the weight of the animals in the highest dose group were reduced on this day. At PND 54, several parameters were altered, mainly related to systemic toxicity: reduction in body weight gain, increase in the relative weight of the liver, the spleen and the seminal gland, reduction in the erythrocyte and leukocyte count, reduced total protein levels and a disturbance in oxidative parameters. At adulthood, the male sexual behavior and fertility were not altered. But at PND 120, there was an increase in type C sperm (immobile), reduced sperm count in testis and epididymis, histological alterations in Leydig cells and seminiferous tubules, and oxidative parameters altered. Based on the data presented, LDX was

able to induce disturbances in systemic toxicological parameters (mainly during treatment) and in reproductive function (mainly in adult life), indicating that the use of this medication should consider these aspects.

Keywords: Lisdexamfetamine, psychostimulants, systemic toxicity, hepatotoxicity, reproductive toxicity

SUMÁRIO

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ABSTRACT

Lisdexamfetamine (LDX) is a d-amphetamine (d-AMP) pro-drug used to treat Attention Deficit and Hyperactivity Disorder (ADHD), a common neurodevelopmental disorder in children and adolescents. Since its action is mediated by increased levels of catecholamines, mainly dopamine and noradrenaline, which influence hormonal control and have direct action in gonads, this drug may interfere with reproductive performance. Thus, this study evaluated the effects of exposure to LDX from the juvenile to peripubertal period (critical windows of development) on parameters of systemic and reproductive toxicity of male rats. Male Wistar rats (23 days old) were treated with 0; 5.2; 8.6 or 12.1 mg/kg/day of LDX from post-natal day (PND) 23 to 53, by gavage. The treatment with LDX provoked a reduction in the daily food and water consumption, as well as a reduction in total social behaviors. The day of preputial separation was unaltered, but the weight of the treated animals was reduced on this day. At PND 54, the treated animals presented signs of systemic toxicity, evidenced by a reduction in body weight gain, increase in the relative weight of the liver, spleen and seminal gland, reduction in the erythrocyte and leukocyte count, reduced total protein levels and disturbances in oxidative parameters. In adulthood, there was an increase in immobile sperm, reduced sperm count, histological changes in the testes, and altered oxidative parameters, without compromising male sexual behavior and fertility of the animals. These results showed that juvenile and peripubertal LDX-treatment induced systemic toxicity immediately after treatment and adversely influenced the reproductive function in adult life, indicating that caution in prescribing this drug on peripubertal period is necessary.

Keywords: Lisdexamfetamine, stimulants, systemic toxicity, hepatotoxicity, reproductive toxicity, sperm disturbances

Abbreviations

ADHD: Attention deficit hyperactivity disorder

ALP: Alkaline phosphatase

ALT: Alanine aminotransferase

ANVISA: Brazilian Health Surveillance Agency

AST: Aspartate aminotransferase

CAT: Catalase

CEUA: Commission for Ethics in the Use of Animals

CONCEA: National Council for the Control of Animal Experimentation

D-AMP: Dextroamphetamine

DAT: Dopamine transportes

DSP: Daily sperm production

$E_{máx}$: Maximal contractions

GEH: Germinal epithelium height

GGT: Gamma-glutamyl transferase

GSH: Glutathione

LC: Leydig cell

LDX: Lisdexamfetamine Dimesylate

LH: Luteinizing hormone

MAO: Monoamine oxidase

MCH: Mean corpuscular hemoglobin

MCHC: Mean corpuscular hemoglobin concentration

MCV: Mean corpuscular volume

MDA: Malondialdehyde

METH: Methamphetamine

NA: Noradrenaline

NET: Noradrenaline transporters

PD: Pregnancy Day

pEC50: -log of the effective concentration at 50%

PND: Post-natal day

SEM: Standard error of the mean

SERT: Serotonin transporters

SOD: Superoxide dismutase

STsD: Seminiferous tubules diameter

TAAR1: Trace amine-associated receptor 1

TBA: Thiobarbituric acid

UNESP: São Paulo State University

VMAT2: Monoamine vesicular transporter 2

Highlights:

- LDX induced systemic toxicity concomitant to treatment period.
- Systemic toxicity alterations were restored to normal levels at adulthood.
- LDX negatively impacted reproductive parameters at adulthood.
- LDX interfered in maturation of male genital system.

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7. CONSIDERAÇÕES FINAIS

Considerando a importância do tratamento adequado do TDAH para melhora na qualidade de vida dos pacientes e que o LDX apresenta boa adesão e melhora dos sintomas envolvidos, um estudo mais aprofundado a respeito de sua segurança, principalmente durante o período juvenil e puberdade mostrou-se de grande necessidade.

O tratamento de ratos machos Wistar durante esta janela crítica do desenvolvimento, que representa o principal período alvo para diagnóstico e tratamento do TDAH em humanos, indicou o potencial do LDX em induzir alterações toxicológicas sistêmicas, principalmente relacionada a hepatotoxicidade, durante e imediatamente ao final do tratamento, com efeitos apresentando um padrão de dose-resposta clássico, ou seja, maiores efeitos conforme o aumento da dose. No entanto, um tempo de recuperação após o término da exposição foi suficiente para restaurar os níveis fisiológicos similares ao controle na vida adulta.

Por outro lado, no que se refere aos parâmetros reprodutivos, algumas alterações foram encontradas logo após o tratamento (DPN 54), mas além disso, os resultados demonstraram que o LDX foi capaz de interferir na maturação do sistema genital masculino durante a puberdade e impactar negativamente o desenvolvimento reprodutivo, levando a danos no sistema genital masculino na vida adulta, mesmo após o término da exposição. Estas alterações apresentaram um perfil diferencial de resposta dependendo do órgão-alvo, levando a um padrão dose-resposta não monotônico, característico de substâncias com potencial de desregulação endócrina. Esta questão reforça que análises hormonais adicionais serão de extrema importância para melhor compreensão dos resultados encontrados e dos mecanismos envolvidos.

Considerando nossas observações, o uso do LDX deve ser feito com cautela, considerando os prós e contras envolvidos, e com melhor entendimento sobre seus possíveis efeitos adversos após uso prolongado durante uma fase crítica de desenvolvimento, o que ressalta a importância de mais estudos clínicos a longo prazo nestes pacientes.