METHYLPHENIDATE: THE OBEDIENCE'S DRUG USED TO TREAT ATTENTION DEFICIT AND HYPERACTIVITY DISORDER (ADHD)

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ABSTRACT

The recently most largely prescribed drug to treat Attention Deficit and Hyperactivity Disorder (ADHD) is methylphenidate. Methylphenidate is a drug that works by stimulating the "Alfa" and "Beta" adrenoceptors, in direct and indirect ways, through the liberation of Dopamine and Noradrenalin, acting in similarity to the amphetamines, which stimulates the growth and concentration of Dopamine on the synapses process. There are serious controversies regarding the effects of this substance in a long term use, since it can cause physical and psychological dependency; it can also lead to other illicit drugs addiction and in some cases have driven people to commit suicide. Professional guidance to patients that are using or will be using methylphenidate is crucial, because several patients have died as consequence of its use. The methodology used in the development of this study, was based in bibliographical references with theoretical fundaments and above all, in books and electronic documents, referents to the contents related to the methylphenidate. The results of this research looks to contribute with technical information for health professionals, that can on other hand transmit this information to parents and professors and help them to make sure this substance will be used in a very careful an rational manner.

KEYWORDS: Methylphenidate, Attention Deficit, Hyperactivity Disorder.

1. INTRODUCTION

The methylphenidate is currently the most widely prescribed for the treatment of disorder and attention deficit hyperactivity disorder (ADHD) psychostimulant. The methylphenidate helps people with ADHD blocking reuptake of dopamine and thus increasing synaptic uptake of dopamine, possibly in critical regions of the brain related disorders¹. It is well known that psychostimulant can cause neuro-chemical and behavioral changes, chronicling-mind when used. The mechanisms responsible for the therapeutic and adverse effects of this drug are still largely unknown. Studies have shown that methylphenidate alters brain metabolic activity. Most of the energy is obtained by oxidative phosphorylation in the mitochondrial respiratory chain. Tissues with high energy demand, such as the brain, have large amounts of mitochondria².

The mechanism of action may be through stimulation of alpha and beta adrenoceptors directly, or by the release of dopamine and noradrenaline from synaptic indirectly terminals. Its action occur about 30 minutes before administration; the peak of concentration occur at 1 - 2 h, and has a half-life of 2 - 3 h^{1,3}. This transporter regulates dopamine concentration in the synaptic cleft, which is proportional to the magnitude and duration of nerve impulse transmission. The blockade of dopamine transporter (DAT) causes an increase in dopamine levels, amplifying the signal that arises in response to nerve transmission dopa and thereby the extracellular concentration remain active for longer, significantly increasing the density of these transmitters in the synaptic gap⁴.

Some neuroimaging studies specifically evaluating the effect of methylphenidate on brain metabolism. In children with ADHD the methylphenidate is associated with an increase of perfusion in the frontal lobes in the thalamus and caudate⁵.

The methylphenidate is widely used in the treatment of this disorder, and the use of this drug has increased dramatically in recent years, formed especially by children and teenagers⁶. The increase in the use of methylphenidate led to questions about the consequences, in the long term, the use of this drug in children with ADHD⁷; this medication indiscriminately and improperly takes the individual to a mental addiction and often looking for other illicit substances and even suicide.

The aim of this paper is to present the use of methylphenidate as medication for ADHD; its pharmacological characteristics, as well as its adverse effects. We intend to insert the pharmacist as an active and indispensable agent, since its role is related to provide optimal support for the patient, the community and the family, in order to ensure the best quality of life, ensur-

ing a correct and effective treatment. We know that education to patients is of paramount importance, since this drug may cause the patient to death.

2. MATERIAL AND METHODS

In the present study the guiding question of the integrative review was: contribute to technical information for professional health care in order that they may be passed on to parents, teachers and patients taking this measure displacement, or will make use of it, ensuring the rational use of methylphenidate.

Bases (Latin American and Caribbean Literature on Health Sciences) LILACS, SciELO (Scientific Electronic Library on Line) and PubMed (- NCBI US National Library of Medicine National Center for Biotechnology Information) were consulted. Studies that have addressed the thematic, published from 1987 to 2011, regardless of the languages of publication were included.

3. LITERATURE REVIEW

The ADHD is one of the most common disorders that occur in children. Currently, ADHD is described as a neurobehavioral syndrome. The hyperactivity of genetic origin is an uncontrolled severe motor, which causes the child has sudden and inappropriate movements, mood swings and emotional instability. ADHD is a set of symptoms, causes and personal and environmental factors that arise in child development and behavior as a whole^{1,8}.

The core features of the ADHD is a problem of inattention, hyperactivity, impulsivity, or a combination thereof. Affect the academic life, family and social relationships. In addition to these basic symptoms there is comorbidity with learning disabilities, mood disorders and anxiety, and abuse of drugs and alcohol. The presence of comorbidity often makes the prognosis, long time, even worse⁹.

ADHD is a very common syndrome, identified the individual who does not arouse interest and concentration in its activities, as much as we strive always ends up diverting their attention. Due to these factors, one realizes that there is no single form of ADHD.

According with Amorim (2012)¹⁰ there are three main types of ADHD, according to the current classification of the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders): ADHD Inattentive Type, ADHD Hyperactive-Impulsive Type and ADHD Mixed Type. The ADHD can occur with or without hyperactivity.

In ADHD Inattentive Type the most common characteristics are: inattention, resistance to distraction, difficulty in sustaining the effort in more demanding activities and perception of time passing. In the ADHD Hyperactive-Impulsive Type the characteristics are: agitation, hyperactivity, impulsivity, are most striking. Hyperactivity may be a problem, since disturbs the environment around. The constant search for stimulation, impulsivity and difficulty thinking before acting can bring consequences, both children and adults. The ADHD mixed Type, simultaneously displays the characteristics of the types of ADHD inattentive and hyperactive-impulsive are presents. A complete diagnosis can only be performed by a specialist for detailed diagnosis¹⁰.

Methylphenidate use for the treatment of ADHD

According Itaborahy & Ortega (2011)¹¹, the methylphenidate was synthesized in 1944 and patented in Switzerland in 1954. His first appointment was as mild psychostimulant, not requiring a prescription for purchase. Marketing in Brazil, according to National Health Surveillance Agency, began in 1998.

Methylphenidate is now the most consumed psychostimulant in the world, more than all the other added stimulants. According to the report of the United Nations on production of psychotropic drugs, its global production rose from 2.8 tons in 1990 to almost 38 tons in 2006. From 38 tons produced in 2006, 34.6 were produced by the USA, which are also the largest consumers of the stimulant. In 2011, global consumption of methylphenidate was 35.8 tons, 82.2% were consumed by the USA. According to the report, the large increase in the consumption of methylphenidate, mainly in the USA, is due to its connection to ADHD and the intense publicity the drug targeted directly to American consumers¹¹.

In 1970, about 150,000 American children used the drug. In 1987, this estimate increased to 750,000 schoolchildren. In 1995, this number reached more than 2.6 million. In Brazil, the consumption is also growing over the years. In 2000, domestic consumption of methylphenidate was 23 kg⁶. The Brazilian production increased from 40 kg in 2002 to 226 kg in 2006. Also in 2006, Brazil imported 91 kg of stimulant¹¹.

Some hypotheses for the growth of production and consumption of methylphenidate are presented. One, are the changes in diagnostic criteria that always tend to expand the group of people who fall within the diagnosis of ADHD, thus increasing potential users of stimulants. Moreover, the pressure on the children's performance would disproportionately increased social support given to them¹¹.

One of the most controversial points in relation to ADHD refers to treatment, and disturbing the overall growth of the use of psychostimulants, which appear in the literature as the drugs of first choice. Methylphenidate is the most used and object larger number of surveys prescribed in about 90% of cases¹².

Methylphenidate is widely used in the treatment of this disorder, and the use of this drug has increased dramatically in recent years, especially by trained child and adolescent public⁶. The increase in the use of methylphenidate led to questions about the consequences, in long-term, chronic use of this drug in children with ADHD⁷. The drug is a psychostimulant prescribed mainly for the treatment of children diagnosed with ADHD. Being a stimulant related to amphetamines (like cocaine), if consumed in the right dosage, it is argued that would help the performance of students and academic tasks, it increases the activity of executive functions, increasing concentration, besides acting as attenuator the fatigue¹³. This medicine comes with a promise to calm the circle of impulsivity and restlessness, resulting in better concentration and motor coordination. For this reason is one of the most common alternatives prescribed to treat ADHD.

Pharmacological characteristics of methylphenidate

After oral administration, the active ingredient (methylphenidate hydrochloride) is rapidly and almost completely absorbed. Owing to extensive first pass metabolism, its systemic availability was only 30% (11-51 %) of the dose. Ingestion with food accelerates the absorption, but has no effect on the amount absorbed. Peak plasma concentrations of around 40 nmol/ L (11 ng/ mL) are obtained on average 2 h after administration of 0.30 mg/ kg. Peak plasma concentrations, however, vary markedly between patients. The area under the plasma concentration curve (AUC) and maximum plasma concentration is proportional to the dose¹⁴.

In blood, methylphenidate and its metabolites are distributed between the plasma (57%) and erythrocytes (43%). The binding to plasma proteins of methylphenidate and its metabolites is low (10-33 %). The apparent volume of distribution is around 10 L/ kg¹⁴.

The methylphenidate resides primarily in the D-enantiomer (based on desired therapeutic effect). D-methylphenidate binds to the DAT in the brain while the L-methylphenidate enantiomer does not bind (base desired therapeutic effect)².

The distribution of D-methylphenidate in the human brain is greater in the basal ganglia, while the enantiomer L-methylphenidate is distributed homogeneously throughout the brain. Both enantiomers have similar rates of uptake, with peak concentrations reached within 10 minutes after administration. However, the rate of clearance of D-enantiomer is significantly slower than that of L-enantiomer ².

Biotransformation of methylphenidate is rapid and extensive. The predominant peak plasma concentrations of the diesterified metabolite, acetic-phenyl-2-piperidin acid are reached at about 2 h after administration of methylphenidate is 30 to 50 times higher than those of unchanged substance. The half-life of the acid-phenyl-2-pipe-ridine acetic is about twice that of methylphenidate and mean systemic clearance is 0.17 L/ h/ kg. Only small amounts of hydroxylated metabolites (eg.: hydroxymethylphenidate and hydroxyritalinic acid) are detectable. The therapeutic activity seems to be mainly due to the parent compound¹⁴.

The methylphenidate has been considered a weak CNS stimulant because the recommended oral dose is metabolized rapidly into ritalinic acid. The metabolite formed has low affinity for DAT, indicating that this drug at therapeutic doses, blocks a large portion of the DAT^{2, 15}. The apparent mean systemic clearance is 10 L/ h/ kg. After oral administration 78 - 97 % of the administered dose is excreted in the urine and 1 to 3% in the faeces as metabolites, in 48 to 96 hours. Only small amounts (<1%) of unchanged methylphenidate appear in the urine. Most of the dose is excreted in the urine as acid-phenyl-2-pipe-ridine acetic (60-86%)¹⁴.

There are no apparent differences in pharmacokinetic behavior of methylphenidate between hyperactive children and normal adults. The data show that elimination in patients with normal renal function, renal excretion of unchanged methylphenidate would be reduced only in the presence of decreased renal function. However, the renal excretion of acid metabolite-phenyl-2-piperidine acetic acid can be reduced¹⁴.

The methylphenidate treatment leads to an amplification of the signal by blocking DAT, whereas the decreases in striatal dopamine neuron after release while the cortical-striatal signal are stronger in striatal cells. This increases the selective amplification signal in target neurons, which could lead to improved care and decreased distraction².

Thereby, it could be speculated that the improvement of the dopaminergic signal induced by methylphenidate causes an increase in the perception of the stimulus for achievement and motivation of the individual to engage in tasks with improved attention and performance. Little is known about the mechanisms that contribute to the effectiveness of stimulants or on neuroadaptacional possible consequence of methylphenidate on its long-term effects of chronic use, especially in children, and its effects on neurochemistry².

Methylphenidate acts as a potent agonist of the alpha and beta-adrenoceptors directly, or indirectly by the release of dopamine and norepinephrine, which is similar to the mechanism of action of amphetamines that stimulate increased concentration of dopamine in the synap $ses^{3, 4, 16}$.

The role of methylphenidate on prefrontal cortex is implicated in the development of locomotor sensitization and behavioral changes. Furthermore, there are studies indicating their association with certain aspects of drugs of abuse. Given the fact that there is great interest in finding out whether there are adverse effects of prolonged use of stimulants on learning and behavior, whereas in children, the CNS is under continuous development and maturation^{2, 3}.

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Very little is known about the neurochemical changes induced by this drug and changes in cell signaling pathways or expression of immediate genes. It is crucial that these data come to know since this drug is widely used in children, period of diagnosis of ADHD, where the indi-vidual is in full neurobiological and psychological development².

Methylphenidate raises alert level in the central nervous system, causing increased production and recycling of neurotransmitters, resulting in improved concentration, coordination and impulse control in patients with ADHD. Some neuroimaging studies specifically evaluating the effect of methylphenidate on brain metabolism. In children with ADHD are methylphenidate associated with an increase of perfusion in the frontal lobes in the thalamus and caudate⁵.

Its mechanism of action has not been completely understood and is still used to treat ADHD. The mechanism by which it exerts its mental and behavioral effects in children is not clearly established, nor is there conclusive evidence showing how these effects relate to the condition of the central nervous system. The L-enantiomer appears to be pharmacologically inactive^{14,17}.

Adverse effects of methylphenidate

The adverse short-term effects, we have to nervousness, decreased appetite and insomnia as major, occur early in treatment and is usually controlled by reducing dosage and omitting the dose in the afternoon or night. There is also less frequently, abdominal pain, headache, drowsiness, dizziness, proneness to crying, tics, nausea, nail biting, talking little, anxiety, indifference, euphoria, irritability, nightmares, sadness, "stopped looking" toxic psychosis sometimes with visual and tactile hallucinations, transient depressed mood, and even suicide wish. In the long term, there are three most important adverse effects: dependence, cardiovascular effects and possible decrease in height^{15,16}.

Other adverse effects of methylphenidate, already described, are visual disturbances, tingling sensations, increased willingness to cramps, to fits of epilepsy and damage to heart vessels, with isolated cases of death¹⁸.

Effects that this substance causes the individuals are extremely worrying. The most talked reaction, and that just nicknaming of "obedience's drug" is the zombie effect that can cause a sort of apathy or lethargy¹⁹.

In the gastrointestinal tract has been reported abdominal pain, nausea, vomiting, dry mouth, which according to literature usually occur early in treatment and may be alleviated by concomitant food intake. Occasionally, tachycardia, palpitations, arrhythmias, changes in blood pressure and heart rate and angina pectoris was rarely observed. May appear on the skin rash, pruritus, rash, fever, arthralgia, alopecia. Isolated cases of thrombocytopenic purpura, exfoliative dermatitis and erythema multiforme. Blood have been reported isolated cases of leukopenia, thrombocytopenia and anemia¹⁴.

These reactions can cause great inconvenience to patients and their families, because in addition to the symptoms of ADHD, will acquire others through the use of the drug. We should take some precautions with treatment using methylphenidate.

> Treatment with methylphenidate is not indicated in all cases of ADHD and should be considered only after detailed survey of the history and evaluation of the child. The decision to prescribe methylphenidate should carry the specification of the severity of symptoms and their appropriateness to the age of the child, considering not only the presence of one or more abnormal behavior characteristics. In which these reactions are associated with symptoms of acute stress, treatment with methylphenidate is usually not indicated¹⁴.

The use of the drug is an alternative that can bring some benefits. Remember that behavioral patterns, skills, abilities, are developed over the years, with practice and persistence. There is a saying: "*Pills do not teach skills*".

"The World Health Organization - WHO classifies Ritalin in the world as the most addictive drug which, due to its high potential for abuse."¹⁸.

[...] Excess methylphenidate may refer to marked tolerance and psychological dependence with varying degrees of behavioral changes. Episodes of frank psychosis may occur, especially with parenteral abuse. Clinical data indicate that children who received methylphenidate have no more possibility of drug dependence compared to teens and adults¹⁴.

This medication indiscriminately and improperly takes the individual to a mental addiction and often the search for other substances such as alcohol, drugs and even suicide. As children clinical data says that the probability of dependency during childhood does not increase, even so be careful when administering methylphenidate in children is the duty of parents and physicians, especially in children under six years of age since the bull itself warns that "should not be used in children under six years of age, since safety and efficacy in this age group have not been established" ¹⁴.

The evidence suggests that methylphenidate should be indicated for children with ADHD over six years, behavioral therapies the treatment of choice until this age, and then six years of age enter as methylphenidate treatment. Even with so many evidences that indicate that methylphenidate for children under six years of age

should not be given doctors continue prescribing this medication, not caring about age. There are cases of children with three or four years old already taking this medication²⁰.

Among the reports listed as the misuse of methylphenidate in children under six years (age range for which the use is expressly contraindicated in bull) that can lead children to serious complications further aggravating the situation you are in because of the association between the drug and the onset of severe adverse reactions, especially cardiovascular events (37.8%) as tachycardia and hypertension, psychiatric disorders (36%) such as depression, psychosis and addiction, as well as the neurological system as dyskinesia, involuntary muscle contractions and spasms, among others²¹.

Recently there have been several criticisms of the very high increase (more than 1,000% in Brazil) in prescribing medication for children, especially methylphenidate. Today, Brazil is the second country that consumes more methylphenidate in the world. In addition, consumption of non-ADHD patients, illegal Internet sales, abuse by young people in ballads or better results in tests or work already assumed frightening proportions and very similar to the other manifestations of drug trafficking²².

The high increase in the prescription of methylphenidate makes Brazil the second largest consumer of this drug in the world, second only to the USA. This drug has been used improperly and incorrectly, both by prescription and illegally by students, businessmen, etc.

Pharmaceutical assistance to patients with ADHD using methylphenidate

Resolution 308 (May 2, 1997) defines the Pharmaceutical Assistance as "*the set of activities and services in order to ensure integrated care, promotion and restoration of health, in public and private establishments that perform project activities, research, handling, production, storage, dispensing, distribution, warranty and quality control, sanitary and epidemiological surveillance of medicinal and pharmaceutical products* "²³. The Pharmaceutical Assistance encompasses a range of activities, from production to the use of medicines by pa*tients*²⁴.

A multidisciplinary team should be part of the monitoring of the patient with ADHD so that there is an complete evaluation and detailed individual from a wide range of factors, such as biological, psychological and educational, for this reason the presence of the pharmacist is essential that staff²⁴.

The pharmacist is essential in the treatment of ADHD, as their role is to provide optimal support for the patient, the community and the family, in order to ensure the best quality of life, ensuring a correct and effective

treatment. Having duty to direct patients to the importance of treatment adherence, explaining about the correct antihypertensive medication use, the purpose, dosage, how to act, and their side effects, drug interactions, such as methylphenidate, the same decreases the effectiveness of the medication used to treat hypertension. The combination with alcohol may intensify adverse effects of the drug in the CNS and clarify the contraindications how to make use of the methylphenidate when patients have the following conditions: hyperthyroidism, cardiac arrhythmia, glaucoma, individuals with bouts of anxiety, tension and agitation, among other cases²⁴.

The methylphenidate hydrochloride is a stimulant drug of the CNS, belongs to the class of amphetamines, a psychotropic substance (narcotic) international control of notifiable prescription type - A3, issued in the form of yellow color. The yellow color indicates the narcotic substance as "*a substance that can result in physical or psychological dependence*"²⁵. The pharmacist acts still stressing the importance of the rational use of medicines, helping to prevent the misuse of drugs used in the treatment of ADHD, which drugs are stimulants, often misused by students seeking better performance in their school and academic activities.

The pharmacist seeks an interaction with the patient, aimed at logic pharmacotherapy, with excellent results-improving the quality of life of patients.

4. CONCLUSION

Would be recommend everyone to know exactly what the indiscriminate use of methylphenidate hydrochloride has been performed frequently by many people, especially in children can lead to serious complications further aggravating the situation you are in because of the association between the drug and the onset of severe adverse reactions, especially cardiovascular events such as tachycardia and hypertension, psychiatric disorders such as depression, psychosis and addiction, as well as the neurological system as dyskinesia, involuntary muscle contractions and spasms, among others; including mostly the people who are not suffering from any disorder use as a device to remain awake, to focus beyond the usual or even lose weight. This practice is not recommended because it is dangerous and can cause serious problems to the usurer medicine. The methylphenidate hydrochloride should be prescribed by a doctor, only with notification recipe yellow A3 list. The increase of indiscriminate use of methylphenidate is associated with immediate effect as a stimulant of the central nervous system, but what most people do not know are the adverse effects caused by this drug. The pharmacist as a health professional should guide users of methylphenidate and enlighten the public that the abuse of this drug

causes adverse reactions from, cardiovascular, central nervous system digestive, psychosis, hallucinations, seizures, drowsiness, anxiety and even desire suicide.

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