Methylphenidate in Attention Deficit Hyperactivity Disorder

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ABSTRACT:
METHYLPHENIDATE IN ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

Hyperactivity in children (with or without attention disorder) is estimated at approximately 3% of the prepubertal population, occurring more frequently in boys than in girls (9 for 1). Methylphenidate is a psychostimulant drug, which has been used to treat this disorder for more than 25 years in the USA. It has recently been introduced in France. Important controversies occur concerning the use of methylphenidate, as all professionals of health are afraid of a drift. With hindsight on the situation in North America, it has been clearly demonstrated that methylphenidate does not affect children's growth and does not induce addiction, which is always dreaded by Europeans.

Key Words: hyperactivity, attention deficiency, methylphenidate, psychostimulants

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INTRODUCTION

Benzedrine, an amphetamine, was the first psychostimulant drug administered to children in 1937 by Bradley. The advent of World War II sidelined this research and the use of psychostimulants in children.

As far back as 1977 (1), Barkley underlined the major interest of psychostimulant use in hyperactive children, at the very time when more than 500 000 children were treated by methylphenidate in the USA. Such a therapeutic indication may be paradoxical according to the definition of these medications and the over-stimulated behaviour of these children. The concept of hyperactivity has evolved in parallel with the successive editions of the Diagnosis Statistical Manual of the American Psychiatric Association. The precise name for this disease in the northern American current nomenclature is Attention Deficit-Hyperactivity Disorder (ADHD) (DSM-IV, 1994, (2)). This global designation has replaced the former separation between attention deficits with or without hyperactivity mentioned in the DSM-III (1980) (3). Clinical diagnostic criteria are precisely described in the DSM-IV (2). Some European psychiatrists prefer the term psychomotor instability. Such a difference illustrates the great gap concerning the approach and the attitude (4). The prevalence of ADHD in the subject 4 to 20 years old is estimated to range from 1.7 to 17.8 % (5,6). Among children referred to child psychiatrists or psychologists, the boy to girl ratio varies from 3:1 to 9:1 (7,8), whereas in community surveys of school-age children it is closer to 2:1 (9,10). In contrast, among older adolescents, the ratio is 1:1 (10) and among young adults, women predominate with a ratio of 2:1 (11)).

Psychostimulants are often prescribed in children in North America. It is justified by the fact that this disorder may induce serious educational and social consequences if it is left untreated. In France, the prescription is still limited for fear of severe adverse events and of the development of dependence or addiction. These points will be discussed later.

The aim of this article is to take stock of the therapeutic use of methylphenidate in children.

Efficacy of Methylphenidate

Many controlled, short-term studies of children, adolescents and adults have confirmed that psychostimulant drugs have been the drug treatment of choice for children with ADHD. 70% of the patients who suffer from ADHD respond to the stimulant drugs such as methylphenidate, dextroamphetamine or pemoline (12). This improvement includes behavioral symptoms such as inattention, hyperactivity or impulsiveness, as well as educational and psychometric performances and relationships with the circle (parents, teachers, friends) (13,14).

Taylor et al. (15) have focused on the definition of clinical symptoms of hyperactive children, which were

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improved by psychostimulant treatment. They studied the youngest of a group of boys in whom motor agitation was the most predominant symptom (more than provocation, impulsiveness or disobedience) with an attention disorder and ataxia.

The action of methylphenidate is not specific for the hyperactive child. A single dose induces similar behavioral and cognitive effects in both normal and hyperactive children. Thus, a small dose decreases the motor response and improves the ataxia. Concentration, attention and short–term memory are enhanced.

If some of the effects observed in adults are quite similar, it is important to know that the euphoric improvement of the mood does not occur in children. Some clinical studies (16) have highlighted that methylphenidate is efficient chronically but it has not been proven that it notably affects the mental state of the individual, the treatment does not modify intelligence or character.

One study concludes that it is hard to diagnose ADHD in teenagers (17). This difficulty explains why only one study on the efficacy of psychostimulants in adolescents is available. This study shows however that psychostimulants are effective drugs for the treatment of ADHD in teenagers.

Dosage of Methylphenidate and Conditions of Use

Methylphenidate can be prescribed in France in order to treat ADHD firstly by a psychiatrist and then, possibly by a general practitioner on a sheet from a counterfoil book for stupefying drugs. The treatment is limited to 28 days and reserved for children of more than six years old (as recommended by the Food and Drugs Administration), i.e. the legal age for schooling. The lowest doses are generally used but such practices are very controversial. In fact, in animal models, the lowest doses decrease locomotor activity and highest ones increase, conversely, locomotor activity (18). Moreover, efficient doses of psychostimulants are very dependent on idiosyncrasy and the delayed galenic shape of methylphenidate (which is not available in France) is also subjected to individual variability. The increase of the dosage must consequently be gradual until the optimal effect is reached. The use of the smallest efficient dose is also crucial because of the dose dependant relationship of adverse effects.

Nonetheless, it is possible to find some indications about the mean usually effective dosage which is 10 to 20 mg/day (the FDA limits the daily dose to 60 mg).

Considering the mean half-life of this medication, it should be administered twice a day (second administration at lunchtime or at the beginning of the afternoon) to avoid sleep disturbances but if it is not the slow released form that is used, methylphenidate can be administered 4 to 5 hours before the sleep.

Dosages expressed as mg/kg would seem better appropriate for a pedopsychiatric prescription but they are various; for example, in different studies, the dosage of methylphenidate usually fluctuates from 0,3 mg/kg to 0,7 mg/kg by administration without exceeding 0,9 to 2,1 mg/day in 2 or 3 administrations.

Some very recent studies did not confirm the hypothesis proposed in older ones according to which the clinical improvement came with a loss of learning abilities.

The evaluation of cognitive effects according to the dose administered is also a big problem since all the cognitive tasks are not modified in the same way according to the drug and its dose (19).

Pharmacokinetics of Methylphenidate

After oral ingestion, the gastrointestinal absorption of methylphenidate is quick and quite complete. 50% to 90% of the marked drug is eliminated in the urine in 8 hours and 48 hours, respectively. Only 11% to 53% of an oral dose of methylphenidate is bio-available because of the first passage effect. Most of the dose is hydrolysed before entering the systemic circulation. Meals have no significant effects on bioavailability and may even speed up the absorption. Only 15% of methylphenidate is bound to plasma proteins, notably albumin. The ratio between cerebral and plasma concentrations (cerebral/plasma) is 3.4. After oral ingestion, the maximal plasmatic concentration rate is reached in 60 to 120 minutes. The elimination half-life is 2.3 to 4.2 hours.

Dosage of methylphenidate in the blood indicates that discrepancies in inter individual responses to methylphenidate are more dependant on pharmacodynamic differences than pharmacokinetic ones. In fact, for the same plasma concentration, some patients are responders and others are not.

Adverse Events of Methylphenidate

They depend on the dose used.

1- Short term:

The loss of appetite and consequently of weight along with sleep disturbances are the most currently observed adverse effects. Methylphenidate is not administered in the afternoon to avoid these effects on sleep. Anxiety, a depressive syndrome, digestive problems and effects on the peripheral sympathetic nervous system such as a slight increase of the pulse and the systolic and diastolic arterial pressure may also be observed. Finally, a paranoid reaction may rarely appear.

These adverse events disappear when the treatment is decreased or stopped. Depressive states and anorexia are considered as contra-indications.

2- Long term:

Numerous contradictory studies have focused on the possible psychostimulant induced break of the growth. The most recent study of Vincent et al. (20) proves once more, that methylphenidate has no effect on growth. Moreover, neither addiction nor dependence to drug has developed in psychostimulants treated children (16).

We can conclude that most of the fears underlying the very weak use of psychostimulants in children in Europe are not justified. It is interesting to note that some parents who use to live with a hyperactive child complain about the stillness of the psychostimulant treated child, although, in this case, it is not an adverse effect but a therapeutic one. In some particular cases, a decrease of the dose can be considered.

Although stimulants have been the most studied compounds, there is huge body of literature indicating an important role for other psychopharmacological agents.

Other Possible Treatments for Adhd in The Future

Serotonergic, noradrenergic and dopaminergic modulation appears to be necessary for effective anti-ADHD treatment as regard as multiple biochemical and molecular biological proofs of the linkage between various dopaminergic (21-24) and serotonergic genes (25), and even catechol-O-methyltransferase (26).

These medications include antidepressants, some neuroleptics and clonidine. In addition, promising evidence of new cholinergic agents may provide other useful alternatives. Therapeutic combinations of these drugs with psychostimulants have also been efficacious not only to treat comorbidity, but also to achieve an effective response (12).

Moreover, the association of psychotherapy (behavioral or cognitive therapies or training parents for a behavioural approach) with psychostimulant drugs does not improve the treatment (27).

Conclusions

Disorders of the hyperactive children are more heterogeneous than described in the DSM IV. These psychiatric problems may influence the development of the child and must consequently be taken into account and pharmacologically treated if necessary.

Methylphenidate is a major and safe drug when used carefully (28). Such a process illustrates the necessary promotion of the developmental psychopharmacology and research in the field of new treatments implying biochemical and genetic studies in improving the treatment of ADHD.

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