METHYLPHENIDATE (RITALIN) USE AND ABUSE

Anthony Crutchley, James A Temlett

ISSUES OF CONCERN

There are a number of issues that need careful evaluation with regard to the use of methylphenidate (Ritalin) and other psychostimulants in childhood and adolescence. Despite a large body of literature showing overall safety for the use of methylphenidate in children[1] with attention deficit disorder (ADD), with or without hyperactivity, as well as in a number of other neurological disorders (narcolepsy, co-morbid behaviour disorders and adults with attention deficit/hyperactivity disorder (AD/HD)), there remains uncertainty about long-term use,[2] addiction rates,[3] abuse,[4-6] and excessive use consequent on incorrect diagnosis. Is the use of methylphenidate to stimulate performance undesirable? Furthermore, we do not fully understand the cause or the neurophysiology of AD/HD.

OVERUSE OF METHYLPHENIDATE

The overdiagnosis of AD/HD is difficult to quantify.[7] The impression exists that more and more children are being referred for medication for poor school performance, the problem being one of inattention or restlessness. The problem in South Africa is compounded by changes occurring in the regional political and education systems. What, for instance, is the prevalence of AD/HD in children who were disadvantaged both nutritionally and academically? A large number of children who have moved into the more advantaged school system are considered by their teachers to have AD/HD, and are referred for therapy. These children are having to adapt to language changes, causing frustration, lack of understanding and inattention. They may require extra time to adapt.

The diagnosis of AD/HD varies in different countries and in varying localities. In the USA as many as 6% of schoolchildren are taking psychostimulants.[1] Despite a popular misconception among the lay population, methylphenidate is freely available in the UK; however, in 1991 there were only 50 children receiving methylphenidate in the UK (Godman R, Institute of Child Health, University of London — personal communication, 1991). The number of children in South Africa receiving methylphenidate is unknown. However, the sales figures indicate that there has been a steady increase in use from 1994 to 1997 (A K Aucamp, Ciba (Pty) Ltd — personal communication, 1997). (See Table I.)

Table I. Methylphenidate sales

Year	Packs of 30
1994	145 569
1995	171 228
1996	175 511
1997	179 548

A survey conducted in the Pinetown municipal area of KwaZulu-Natal in 1991 indicated that 1.65% of all pupils were on methylphenidate. The ratio of boys to girls on methylphenidate was 9:1, and the age at which treatment was begun ranged from 2.11 to 11.0 years, with a mean of 7.6 years. No Afrikaans pupils were reported to be on methylphenidate (Weekes D. Ritalin questionnaire, Pinetown municipal area, 1991 — personal communication). The breakdown by grade is shown in Table II.

Table II. Percentages of schoolchildren using methylphenidate in Pinetown, KwaZulu-Natal, 1991

Primary school		High school	
Grade	On methylphenidate (%)	Grade	On methylphenidate (%)
1	6	8	1
2	20	9	0
3	31	10	3
4	16	11	0
5	17	12	0
6	4		
7	1		

PHARMACOLOGY OF METHYLPHENIDATE

Methylphenidate is a piperidine derivative related to amphetamines, with central nervous system effects more prominent on mental but also motor activities.

Methylphenidate has been marketed by a reputable pharmaceutical company, Ciba Geigy (now known as Novartis), since the 1960s for AD/HD and for other conditions since 1944. It is readily absorbed from the bowel, reaches peak concentration after 2 hours, has a half-life of 1 - 2 hours, and is de-esterified into the urine as ritalinic acid within 48 hours. Brain concentrations of methylphenidate exceed that of the plasma, since it is concentrated in catecholaminergic systems with free passage across the blood-brain barrier.

Methylphenidate has a rapid uptake in the brain, similar to cocaine, but differs in having a much slower rate of clearance from the brain. This pharmacokinetic action limits repeated administration and addiction.[3]

Chelmsford Medical Centre, 107 Chelmsford Road, Durban
Anthony Crutchley, MB ChB, DCH (SA), FCP (SA) Paed

University of the Witwatersrand Medical School and Johannesburg Hospital
James A Temlett, MB BCh, DA (SA), FCP (SA), MMed (Neurol), PhD

Methylphenidate tablets are available in 10 mg oral strength. Usually adults are given 10 mg by mouth two or three times daily. Children should receive 0.3 - 0.6 mg/kg/day.[2,8-12] Although up to 3 mg/kg/day has been utilised with apparent safety, psychosis, addiction and convulsions may be encountered at higher doses. Ingestion with meals does not affect absorption, hence the drug is most commonly given just before leaving for school in the morning in order to maximise benefit at school.[11] A slow-release preparation is available overseas to allow benefit throughout the morning, avoiding the need to ingest another tablet at mid-morning, but it is not available in South Africa. Interestingly, the slow-release preparation contains water-insoluble incipient constituents. The latter have been found to cause accelerated peripheral vascular sclerosis and pulmonary fibrosis when injected intravenously, so South Africa is possibly better off without this drug being locally available. Intravenous methylphenidate has a higher mortality rate than cocaine and amphetamines.[4]

Methylphenidate is thought to improve school performance through increased concentration, improved problem-solving ability, mental alertness and less distracting motor events.[2,13] In fact the initial development of methylphenidate was in pursuit of a drug that would improve memory in elderly people. Thereafter doctors extended the thesis of improved alertness to children with emotional, behavioural and learning difficulties.[2]

THERAPEUTIC INDICATIONS

Despite extensive clinical trials there does not appear to be any convincing double-blind review or study to show that use of methylphenidate improves academic achievement in the long term.[1] In our experience improved academic performance is the major reason for parents requesting the medication. Academic achievement is probably a secondary reason for teachers, since teachers want a decrease in disruptive behaviour, impulsivity and the need for constant attention. Conducted trials recognise these effects, hence the importance of double-blind trials with placebo comparisons. Behavioural and family therapy should include assessment of individual variability and performance, both during intense counselling and periods thereafter.

Recent literature searches on Ritalin and methylphenidate yielded very few double-blind trials that eliminate any bias and statistically demonstrate methylphenidate to be better than placebo.

While advances in understanding are being made with regard to AD/HD, researchers do not claim to understand the neurological mechanisms behind either AD/HD or learning disorders. How and whether psychostimulants work to correct these problems remains a mystery. At the end of the day clinicians are required to inform patients, parents and educators and should be in a position to point out the potential benefits and possible harm of these drugs. Double-blind studies suggest that 50 - 75% of AD/HD children will improve on psychostimulants. Millichap[14,15] and more recently Efron *et al.*[16] concluded that methylphenidate is superior to the amphetamines. Before we examine harmful effects, we will look at the behaviours that clinicians anticipate will improve on psychostimulants.

MECHANISMS OF BEHAVIOURAL CHANGE

Attention

Children need to develop skills in order to evaluate environmental sensory stimuli, make sense of the information and remember it for future use. If one has a block to this integration of sensory input, one cannot learn from experience. Children who cannot execute these learning mechanisms will not benefit from adequate teaching. Hence focusing concentration on the task at hand is crucial to learning. Children with AD/HD are recognised to be impulsive, impatient and easily distracted. They blurt out answers, talk excessively and do not appear to listen. In addition, they may not be able to sit still, and are restless, fidgety and squirm in their seats.[17]

A theory exists that these children are under-aroused,[18] do not respond to normal endogenous brain noradrenalin and hence when given methylphenidate are catecholamine-stimulated to best cortical functioning. However there is no evidence, either neurochemically or with imaging studies, that this is the case. Examination of AD/HD children shows that their reticular activating systems and catecholaminergic cortexes are normal compared with those of control children.[19] However, teachers have observed improved attention, better behaviour and improved grades. Since the mechanisms are only partially understood, speculation abounds.

Impulsivity

Without question, teachers have found that AD/HD children on methylphenidate exhibit less disruptive behaviour and are more settled, which then allows for undisturbed learning.[11]

Academic progress

Here methylphenidate should produce dramatic results. Objective measures of school performance should be statistically easy to document. Do these children actually perform better academically than they would have done off psychostimulants? This should be the final proof; however, the evidence is not at all persuasive. It is estimated, using objective academic tests, that 60% of AD/HD children will benefit from methylphenidate. However, that leaves at least 40% who have met the *Diagnostic and Statistical Manual* (*DSM-IV*)[17] criteria for AD/HD but who do not improve.[2] The concept of AD/HD has received such widespread acceptance that people are beginning to think that it is a 'disease', reflecting a true entity, rather than a syndrome, meaning a collection of neurobehavioural or

developmental attributes.[20] This may be one of those situations in medicine where we make a hypothesis and then attempt to fit the symptoms and signs, rather than taking the signs and symptoms to create homogeneous and more easily identifiable groups. Of course if one day a genetic defect is identified,[21] the diagnostic criterion may be defined more accurately. Methylphenidate has been found to be useful in some children with AD/HD who are mentally handicapped or who have other neurological abnormalities.[22]

As there is no evidence that methylphenidate improves school grades in the long term, what should we advise with regard to starting or stopping therapy? Important reported benefits include improved confidence, better self esteem, completing work on schedule and improved fine motor control. School grades are not the only factor in deciding on treatment — overall well-being, inclusive of mood and self esteem, should be considered. With methylphenidate therapy, improved mood and performance may lead to an improvement in school grades. The effects of counselling, encouragement and support at school should be separated from the observed benefit derived from methylphenidate. Clearly this is difficult to evaluate statistically.

Side-effects

Although substance abuse is infrequently reported in the methylphenidate literature, it would seem appropriate to sound a warning. This is a very real issue, since there is literature documenting abuse and its inherent dangers. In other words, patients are not going to acknowledge willingly that they are abusing methylphenidate. One study showed that patients abusing methylphenidate had little difficulty getting it from doctors, hospitals and even specialised clinics for children or patients with AD/HD.[4] Other dangers include addiction to other substances such as heroin, cocaine, LSD or cannabis. Intravenous substance abuse with right-sided endocarditis and pulmonary granuloma and even neck infections have been reported.[4] Dyskinesias and especially tics may get worse on methylphenidate. There does not appear to be any link between the use of methylphenidate and the development of Tourette's syndrome.[23,24] However, tics are commonly aggravated and even precipitated on methylphenidate therapy. Methylphenidate appears to be safe and effective in children with well-controlled epilepsy and AD/HD, provided that anticonvulsants are taken concurrently.[25,26] Higher doses of methylphenidate than recommended may exacerbate epilepsy. Methylphenidate causes a diminished seizure threshold and an increase in seizures. There are other less severe adverse effects such as anorexia, abdominal pains, insomnia and weight loss, which seem to be tolerated better with time. The issue of stunted growth remains controversial, although adult dimensions and height attained are normal. Nevertheless growth in the longer term should be monitored.

Long-term side-effects

The long-term effect on the neurochemistry of the brain is cause for concern. Acute hallucinations are seen in both the spontaneously hypertensive rat model (a model of AD/HD) and man. Long-term problems may emerge relating to the dopamine and noradrenergic systems. The catecholamines of the brainstem function in an ascending pathway that connects the locus caerulus with the frontal, prefrontal and limbic brain. This comprises a cortex for memory, planning, thought, integration of the senses and deeper basal ganglia that control movement.

This ascending meso-limbic-cortical basal ganglia system is similarly innervated by dopaminergic tracts, originating from the substantia nigra. This limbic system originates from the medial substantia nigra (ventral tegmental area) and controls the emotional tone of thought and movement. All these systems interconnect in complex chemical pathways to allow the brain to function as a useful organ, able to think, plan, execute and remember. When one sleeps, the automatic nuclei of the brainstem keep active electrically and neurochemically, like the pilot light of a gas geyser. The main ascending input rests with sleep and upon awakening the cortex is activated by the noradrenergic, but also by the dopaminergic, systems.

For some reason, this dopaminergic pathway is excessively activated in AD/HD children. This results in motor hyperactivity and concentration difficulties. What is paradoxical, yet may have beneficial effect, is that stimulation of this noradrenergic system with methylphenidate can reverse this abnormality. There is also no information as to what happens to those children on long-term methylphenidate who leave school. What is of concern is the chemical imbalance of limbic catecholamines, with observable and well-documented potential addiction not only to methylphenidate, but also to other substances.[4] Dopaminergic systems are influenced by this mechanism, explaining the exacerbation of tics and dyskinesias.

Conclusion

There seems to be little doubt that methylphenidate is effective and on balance a safe medication, provided that it is used in the correct circumstances. In addition, many children appear to have other problems unlikely to improve on methylphenidate, a possibility that may not be appreciated by teachers, parents and therapists. This medication, and others like pemoline and the amphetamines, should be withdrawn if they do not achieve the expected result or if adverse effects are encountered.[27] If there is dubious improvement or the occurrence of tics, then medication should be withdrawn.

In South Africa, additional problems are emerging in that children who were previously socially, nutritionally and academically disadvantaged are now moving into more advantaged school systems, with all the associated pressures.

This raises difficult practical issues, as an increasing number of these children are attending paediatric neurology clinics, developmental assessment clinics and educational and psychological support services for the management of poor concentration and hyperactivity.

Psychostimulants may also be useful in providing relief from intractable cancer pain. Attempts to get addicted patients off cocaine have met with some success where methylphenidate is used as a temporary weaning agent. One should distinguish between an agent that is abused (where all agree that the drug should be regulated by the State) and use of the same drug where the intention is to correct concentration problems and AD/HD. In the latter instance the parent will often be required to make an informed decision with the help of understanding medical practitioners. Countries such as the USA and South Africa urgently need to re-evaluate the indications for and closely regulate the use of methylphenidate. Uncontrolled use could lead to a drug control problem as well as to an iatrogenic neurochemical tardive syndrome, especially tics.

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