

Cardiovascular effects of ADHD medications in children

1. Gary Stiefel, Specialist registrar, Southampton General Hospital
garystiefel@doctors.org.uk
2. Professor Frank M.C. Besag, Consultant Neuropsychiatrist
SEPT: South Essex Partnership University NHS Foundation Trust

Abstract

While methylphenidate, amphetamines and atomoxetine play a significant role in the pharmacological management of ADHD, there have been some safety concerns raised over the last few years with respect to cardiovascular morbidity. The literature has been reviewed, exploring the effects of ADHD medications with respect to sudden death and alterations of heart rate (HR), blood pressure and QT interval. There is some evidence of increased HR and BP using these medications but there is no evidence of a clinically-significant impact. However, most of the published data is on average results and might mask individual cases in which there is a clinically significant change. Regular monitoring of BP and pulse, using the same procedure on each occasion, is recommended. There is no convincing evidence of an association with QT interval prolongation or sudden death. Routine ECGs before starting these medications are not considered to be necessary. However, for each child a careful personal and family history of cardiovascular problems should be taken and a cardiovascular examination should be performed before medication is commenced.

Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the commonest neurobehavioural conditions in children with a worldwide mean prevalence of approximately 5% (1). The figures for prevalence depend on the criteria used. In the UK, a survey of 5-15 year old children revealed that 3.62% of boys and 0.85% of girls had ADHD (2).

The management of ADHD is predominantly a combination of behavioural strategies and pharmacological agents, commonly methylphenidate, amphetamines and atomoxetine. There is good evidence that these measures have a beneficial effect. As these drugs are so widely used it is important to ensure that they are safe. In recent years concerns about the cardiovascular safety of drugs used in the treatment of ADHD have been raised and this culminated in the suspension of a mixed amphetamine salt in Canada (2005) and a "black box" warning by the US FDA Drug Safety and Risk Management Advisory Committee (2006) about possible cardiovascular risks associated with stimulant medication (3).

This article will explore the cardiovascular effects of the main ADHD medications, namely methylphenidate, amphetamines and atomoxetine in relation to sudden death and, alterations in heart rate, blood pressure and QT interval.

Sudden Death

In the general paediatric population, sudden death is a very rare event with a rate ranging from 0.8 to 8.5/100000 patient-years (4). In comparison, the reported rates were 0.2 to 0.5 per 100000 patient-years associated with methylphenidate, amphetamine products and atomoxetine (5). The risk of methylphenidate causing sudden death to patients has been estimated to be 0.22 deaths per 1 million prescriptions (6). The USA the Food and Drugs Administration (FDA) combined with Health Canada, have identified 12 cases of children aged 1 to 18 years taking ADHD medications between 1999-2003 who fulfilled the criteria for sudden death (4). This data must be interpreted with caution as only an estimated 1-10% of serious adverse effects are actually reported and an association does not necessarily imply causation. In the UK a similar system is led by the Medicines and Healthcare Products Regulatory Agency (MHRA). With respect to methylphenidate only 12 reports of fatalities have been reported for all ages from 1964 to 2010 (7). Many of these deaths were placed in categories unrelated

to sudden death. Finally the analysis of 10 year adverse event reporting in Denmark revealed no sudden deaths in children taking ADHD medications (8).

A recent matched case-control study compared stimulant use in 564 children who had sudden unexplained death in one group and passengers dying in motor vehicle accidents in the other group (9). There were ten (1.8%) children in the former group compared to 2 (0.4%) children who in the latter were on stimulant medications. The authors stated that this provided support for the association of stimulant use and sudden unexplained death. The FDA expressed reservations about this study: a retrospective cohort study of over 1.2 million children and young adults (2-24 years old) has not shown an increased risk of serious cardiovascular events (sudden cardiac death, acute myocardial infarction, and stroke). However, the authors stated that the upper limit of the 95% confidence interval indicated that a doubling of the risk of a serious cardiovascular event could not be ruled out.

Although it is difficult to interpret and compare data directly, it would appear that sudden death remains an extremely rare event. At present there is no convincing data suggesting that ADHD medications increase the risk of sudden death.

Heart rate & blood pressure

Both heart rate (HR) and blood pressure (BP) are dynamic variables influenced by several factors. Studies assessing the effects of ADHD medications on HR and BP need to take these factors into account and should attempt to standardise these measurements as much as possible (39). There should be a clear protocol for measuring BP and HR and this should include serial measurements. Because there are various formulations of methylphenidate, including immediate-release and extended-release varieties, comparing BP and HR at a set time after the drug dose may not be appropriate in view of the different pharmacodynamics. Further confounding factors for long-term studies (over several months to years) attempting to assess the impact of ADHD medications on HR and BP are the normal decrease in HR and increase in BP which occur with increasing age (39). It should also be noted that average data are presented in most publications; such data may conceal individual cases in which large, clinically important, changes might occur.

Studies examining the effects of methylphenidate treatment over a few weeks either reported that methylphenidate did not result in a statistically significant increase in HR and BP or, in circumstances where there was a statistically significant increase, that the effects were not considered to be clinically significant (10-17). One long-term study over several months indicated that methylphenidate might increase HR and systolic BP by up to 3.9 beats per minute (bpm) and 3.3mmHg respectively, although another study demonstrated no effect on HR and a 3.4mmHg rise in systolic BP (18, 19).

Amphetamines in the short-term (within 12 weeks of commencing treatment) caused statistically significant increased HR of up to 5 bpm in some studies compared to placebo, (3,20) whereas others showed no significant difference in HR (21-23). None of these studies showed significant changes in BP. Long-term treatment with amphetamines did cause statistically significant increases in HR (up to 4.4 bpm) and BP (up to 1.7mmHg for systolic BP) but these were judged by the authors of the studies not to be clinically significant (20, 22, 24-26).

Atomoxetine does appear to cause statistically significant increases in HR in the short-term and long-term (27-32). The mean increase in HR was up to 9 bpm in these studies. Diastolic BP increased by up to 3mmHg while systolic BP was not affected in some studies and in others it rose by up to 9mmHg. These figures did not take into account the changes that occur to HR and BP with increasing age (up to 4 years in some studies) and the authors did not consider that these changes were clinically significant. It should also be noted that these measurements were not the primary outcome of the studies.

Although there are significant methodological limitations, some studies demonstrate statistically significant effects on BP and HR, while others demonstrate no effect. Therefore, it is very important to consider whether these have clinically significant effects on children and more important whether any associated morbidity arises from these effects. At present there is no strong evidence demonstrating

a clinically significant effect of increased HR and BP or cardiovascular morbidity associated with ADHD medications (39).

QT interval prolongation

A prolonged QT interval may be associated with fatal cardiac arrhythmia and has therefore become a surrogate marker for a potential increased risk of sudden cardiac death (45). Data on ECG changes with methylphenidate is lacking, although there is no evidence supporting prolonged QTc interval with this drug. Methylphenidate may cause other ECG changes but these appear to be very rare. Furthermore, current National Institute for Health and Clinical Excellence (NICE) and American Academy of Pediatrics (AAP) guidelines state that children commencing methylphenidate do not routinely require an ECG (33, 34).

Amphetamines and atomoxetine have been studied in more detail. The majority of evidence suggests that amphetamines do not cause a statistically significant increase in QTc interval; in a couple of studies there was a significant change in QTc, but this was considered to be clinically insignificant by the authors (40-44). Case reports to the MHRA have suggested that atomoxetine might increase the QTc interval (46). The published literature indicates that atomoxetine does not appear to prolong the QTc interval when used at the correct doses in the majority of studies (27, 35-37). However, in a recent long-term study, although there was no overall significant change in QTc interval, as many as 30% of children had an increase in QTc ≥ 30 msecs. This depended on the formula used to measure the QTc but suggests that in individual cases atomoxetine may indeed increase the QTc (31). The authors regarded the increases seen as clinically insignificant.

Conclusions

Methylphenidate, amphetamines and atomoxetine are the commonest medications used to treat ADHD. Although there is some evidence of increased HR and BP with these medications, there is no evidence of any clinically significant impact. Similarly, there is no convincing evidence of QT interval prolongation or sudden death and therefore, a routine ECG in children with ADHD is not recommended (34). The recent European guidelines on managing the adverse effects of ADHD medications suggest the checking of BP and HR prior to treatment with monitoring every 3 to 6 months, although it states this may vary with individual cases (4). Further research and continued reporting of suspected cardiovascular adverse effects are recommended, to identify potential rare adverse effects. However, at present, these ADHD medications appear safe and they play an important role in the comprehensive management of ADHD in children.

GP Comment.

What have I learned from this paper?

1. Provided there is no personal or family history of cardiovascular problems and if the cardiovascular examination is normal, I can reassure families that there is no evidence showing an increased rate of heart problems or sudden death associated with methylphenidate, dexamfetamine or atomoxetine.
2. There is some evidence for increased heart rate and blood pressure with ADHD medication; regular monitoring of heart rate and blood pressure is recommended.
3. Despite the reassuring lack of strong evidence that these drugs have a significant impact on cardiovascular health, the paper still acknowledges potential risks; it cautions clinicians to monitor HR and BP prior to treatment and at 3-6 monthly intervals, even if there is no personal or family history of cardiovascular problems and if cardiovascular examination is normal.
4. I would suggest there is a need to investigate the long-term health outcome of these drugs, arguably over many years into adulthood.

5. In contrast psychological help to re-inforce the natural support system of family plus educational support has no adverse effects or risks to health- to my knowledge! In addition these simple measures support independence rather than encouraging reliance on drugs and professionals.

6. Without doubt, drug therapy is needed for some children and this article offers some reassurance.

7. As a GP with no expert knowledge of these drugs, I have witnessed the benefits of early psycho-social support.

8. I wonder in times of limited resources, if targeting vulnerable children and families to improve coping skills before crises develop might prevent escalation to ill-health and be more beneficial for long term health outcome and for the public purse?

Dr Anthea Robinson

GP, Moakes Medical Centre and Whipperley Medical Centre, Luton.

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