METHYLPHENIDATE

Methylphenidate (Ritalin®) is one of a class of sympathomimetic amine stimulants, all of which are structurally related to amphetamine. The other members of the class include amphetamine, methamphetamine, and pemoline. Amphetamine, and the related compounds, have been in use since the early 1930’s at which time they were used as bronchodilators and respiratory stimulants as well as in the treatment of depression. More efficacious antidepressants largely supplanted stimulant use in the treatment of depression in the 1950’s. Currently the sympathomimetic amines, including methylphenidate, are FDA approved only for the treatment of attention deficit disorders with hyperactivity (ADHD) and narcolepsy. Off label, however, methylphenidate is also used to treat apathy and withdrawal in the medically ill, to potentiate the effects of narcotic analgesics, and to treat residual attention deficit disorder in adults.

Throughout their clinical use, issues of abuse have plagued the sympathomimetic amines, though it was initially hoped that the abuse potential of methylphenidate would be significantly lower than the others within the class. Currently, pemoline, methylphenidate and amphetamine are Schedule 2 drugs. While there is no data regarding the death rate due to methylphenidate, the number of methamphetamine related deaths reported nationwide by medical examiners nearly tripled from 151 to 435 in the period of 1991 to 1994. (9) The majority of these additional deaths occurred in the western states, with California, Washington, Nevada and Hawaii leading the way. There was a concurrent increase of 240-300% in the rate of emergency department encounters and hospital admissions. There is no reason to suspect any difference in the increase in abuse rates of methylphenidate compared with methamphetamine, as both are cheaper and have a more sustained effect than cocaine.

Clinical Pharmacology

Amphetamine is a racemic beta-phenylisopropanolamine, of which the D-isomer is 3-4 times more biologically active than the L-isomer. Methylphenidate is a piperidine derivative of amphetamine and is structurally quite similar, whereas pemoline is structurally very different. As a result, the clinical consequences of a toxic ingestion of methylphenidate closely mimic those of amphetamine.

Currently methylphenidate is available in an immediate release or sustained release tablet, as well as an intravenous preparation. It is readily absorbed after oral administration with peak absorption 1-3 hours after ingestion. The peak effect is within 2 hours in the immediate release preparation or within 4-7 hours in the sustained release preparation. The half-life of intravenous methylphenidate is 1-2 hours, compared with 2-4 hours in the oral preparations; however, the concentration in the brain exceeds that of the plasma producing an effective clinical duration of 6-8 hours. After absorption, methylphenidate is 15% protein bound, with a volume of distribution ranging 12-33 L/kg. Methylphenidate is hydroxylated in the liver to ritalinic acid. It is then excreted in the urine as both ritalinic acid (80%) and unmetabolized methylphenidate (20%); however, in animal models, as much as 45-50% of the drug is excreted unchanged in the feces bound to bile salts.

Both methylphenidate and amphetamine promote the release of norepinephrine, dopamine and serotonin from presynaptic neuronal membranes; however, unlike amphetamine, methylphenidate does not appear to block the reuptake of norepinephrine and dopamine. Peripherally, at clinical doses, the increase in norepinephrine and dopamine produce a slight elevation in systolic and diastolic pressure as well as a slight increase in heart rate. The central effects of methylphenidate are more difficult to explain beyond the direct neuronal effects. It is generally thought that methylphenidate increases alertness by stimulating the ascending reticular activating system. The relative increase in dopaminergic neurotransmission in the forebrain probably generates euphoria and hyperactivity, while the hypothalamic actions are thought to produce appetite suppression. There is no good explanation for the clinical improvement seen in children with ADHD. The previously held theory that there is a paradoxical sedating effect of facilitated neurotransmission in patients with ADHD does not explain why a similar clinical effect is seen to a lesser degree in children without ADHD. Furthermore, in ADHD, unlike narcolepsy, tolerance does not seem to develop with respect to the therapeutic clinical effects.

The standard dose of methylphenidate in children with ADHD starts at 0.3 mg/kg/day. In narcoleptic adults, the usual dose starts at 10mg given 2-3 times a day and advances slowly up to a maximum dose of 200 mg/day. Tolerance develops in narcoleptics to the stimulatory effects of methylphenidate, necessitating intermittent “drug holidays”.

Methylphenidate has a number of side effects ranging from appetite suppression or slight elevations in heart rate and blood pressure to insomnia, headaches and abdominal pain. In a randomized double-blind placebo-controlled crossover trial, Ahmann et al (10) found that the incidence of insomnia, appetite suppression, stomachache, headache and dizziness all significantly increased in 206 children on methylphenidate therapy for ADHD. As these authors and Efron et al (11) suggest, only the appetite suppression and insomnia can be reliably attributed to methylphenidate in these children.

Clinical Toxicology

Toxicity due to methylphenidate abuse/overdose relates directly to its sympathomimetic effects with cardiovascular and neurologic symptomatology predominating. In general, these patients present with tachycardia, hypertension, dry mouth and pupillary dilatation, often with an accompanying toxic psychosis or delirium. These patients are generally agitated, and may be paranoid or violent. Death can occur due to the sequelae of hypertension, cardiovascular dysrythmias or uncontrollable seizures.

There is a wide range of cardiac effects associated with toxic ingestions of methylphenidate ranging from dysrythmias to myocardial ischemia or infarction. Henderson and Fischer (12) found that rats and mice given varying doses of methylphenidate all had evidence of changes in myocardial cell ultrastructure, regardless of the duration.
of exposure. Moreover, these changes persisted up to 12 weeks after the methylphenidate was withdrawn. These changes may provide a cellular explanation for the observed clinical changes in cardiac conduction at toxic levels. Indeed, Lucas et al. report a case of cardiac dysrhythmias occurring in a patient with no known history of cardiovascular disease following intravenous methylphenidate administration. A case report described myocardial ischemia, with ischemic ECG changes, in a 16 year old patient on high doses of methylphenidate within an hour of his last dose. The paucity of case reports and case series may represent physician and patient underreporting, especially in cases of drug abuse, rather than a lack of significant cardiovascular toxicity.

A wide range of CNS side effects is reported following clinical and recreational ingestions of methylphenidate. Methylphenidate has been implicated in the emergence of "motor tics" (7), mania (8), akinesia and mutism, (9) hallucinosis, (10) chorea (11) and paroxysmal dystonia (12). In all of these case reports, however, it is unclear whether the observed disorder represents a side-effect of methylphenidate, or if methylphenidate triggered the onset of a genetically determined disorder.

The role of methylphenidate in inducing seizures is relatively controversial. While it is thought to be a side-effect of methylphenidate, a retrospective study of 30 patients with seizure disorders on methylphenidate found a trend toward seizure reduction.

Other toxicities are reported following the initiation of methylphenidate for therapeutic or recreational reasons, though they seem to be much less common. Mehta et al. and Steckyk et al. each report individual cases of hepatic dysfunction following high dose of intravenous methylphenidate, with the case reported by Steckyk et al. going on to have persistent liver and renal dysfunction. Cohen et al. reported 2 cases of a fixed drug eruption involving the scrotum, which resolved after cessation of methylphenidate. There are also multiple case reports, including one by Elengas et al. of patients developing local skin abscesses or cellulitis following parenteral self-administration of methylphenidate.

There are no case reports giving a minimal lethal dose associated with methylphenidate ingestion, though in children Kim et al. found that 1 of 2 patients that accidentally ingested 204 mg/kg became symptomatic. On the other hand, chronic amphetamine abusers have been reported using as much as 15 grams per day. Thus, the clinical observation of toxic effects is more relevant than an estimate of the total ingested/administered dose.

As methylphenidate is heptatically metabolized, it will competitively bind to hepatic enzymes. As a result, co-administration of the drug will increase serum concentrations of tricyclic antidepressants, warfarin, phenytoin, phenobarbital and primidone, amongst others. Similarly, based on its mechanism of action, methylphenidate can increase the relative effects of MAO inhibitors, as well as guanethidine and bryceylium. All of these should be taken into consideration in the appropriate patient.

Management

Management of methylphenidate overdose is primarily supportive. All patients, if possible, should be decontaminated with activated charcoal. Ipsac is contraindicated due to the risk of neurotoxicity. The hypertensive side effects can be managed with a direct-acting vasodilating agent such as nitroprusside if needed. Patients with hyperthermia should be aggressively managed with fluids, antipyretics and possibly cooling blankets. Diazepam (5-10 mg) or lorazepam (1-2 mg) can be used for the agitation and restlessness, while haloperidol (5 mg) can help control any associated psychosis or hallucinations. Patients with seizures should receive aggressive airway management, and rapidly acting anti-convulsants, as historically seizures associated with stimulant abuse have been very difficult to control.

In terms of laboratory data, these patients should all have a serum and urine toxicologic screen sent. In the last survey of methamphetamine related deaths within the United States, 92% of all deaths associated with methamphetamine involved at least one other drug, suggesting a proclivity for polysubstance abuse at least amongst recreational stimulant abusers. Similarly, given that liver dysfunction and rhabdomyolysis have been associated with methylphenidate and amphetamine abuse respectively, liver function tests and CPK levels are reasonable in the right clinical situation. All of these patients should have a 12 lead ECG and continuous cardiac monitoring if the clinical evidence of methylphenidate toxicity clears.

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References