Mika Kemppi

The implications of patient use of stimulants for perioperative care

Syventävien opintojen kirjallinen työ

Syyslukukausi 2020

Mika Kemppi

The implications of patient use of stimulants for perioperative care

Kliininen laitos

Syyslukukausi 2020

Vastuuhenkilö: Teijo Saari

TURUN YLIOPISTO

Lääketieteellinen tiedekunta

Kemppi, Mika: Stimulanttien käytön vaikutus potilaan perioperatiiviseen hoitoon (The implications of patient use of stimulants for perioperative care)

Syventävien opintojen kirjallinen työ

Anestesiologia
Joulukuu 2020

Stimulantit eli keskushermostoon stimuloivasti vaikuttavat aineet ovat yleisiä nykyään. Niitä käytetään lääketieteellisesti yleisimmin aktiivisuuden ja tarkkaavuuden häiriön (ADHD) hoitoon, joka on yleinen oireyhtymä. Sen esiintyvyys on viimeisempien meta-analyysien mukaan koululapsilla 3,6-7,2% ja aikuisilla 2,5-3,4%. Stimulanteilla on lisäksi indikaatioita esimerkiksi narkolepsian ja autismin hoidossa. Lisäksi monta yleistä huumausaineena käytettyä ainetta luokitellaan stimulanteiksi.

Liitteenä olevan alkuperäisartikkelin tarkoituksena on käydä läpi nykytiedon valossa se, millä tavalla stimulanttien käyttö vaikuttaa perioperatiiviseen hoitoon ja anestesiaan. Stimulanteista käytiin läpi amfetamiini ja sen johdokset, metyylifenidaatti, modafiniili, MDMA eli ekstaasi, kokaiini, MDPV eli metyleenidioksipyrovaleroni, kofeiini ja nikotiini.

Artikkelia varten tehtiin kirjallisuushaku, jossa haettiin tietoa eri stimulanteista ja niiden vaikutuksista perioperatiiviseen hoitoon. Lopullista artikkelia varten valittiin ne tutkimukset ja julkaisut, jotka oleellisesti valittuun aiheeseen liittyivät ja toivat lisäinformaatiota aiheeseen. Eläintutkimukset rajattiin artikkelin ulkopuolelle. Alkuvaiheessa artikkeleita valittiin 42, joista lopulliseen artikkeliin valikoitui 39.

Stimulanttilääkityksellä ei näytä olevan vaikutusta haittatapahtumien riskiin, myöskään käytettynä perioperatiivisesti. Tehdyissä tutkimuksissa ei ole todettu eroavaisuksia stimulanttien käyttäjille ja verrokeilla hemodynamiikan ja vaadittavien anesteettien määrän suhteen. Osalla narkolepsiapotilaista lääkityksen jatkaminen perioperatiivisesti voisi olla jopa hyödyllistä. Narkolepsia potilaille suositellaan käytettävän lyhytvaikutteisia anesteetteja. Tajunnantason seuranta BIS-menetelmällä suositellaan osassa tutkimuksissa.

Aiheeseen liittyen on hyvin vähän laadukkaita tutkimuksia ja näiden otoskoot ovat pieniä. Tietoa aiheesta on lähinnä kertynyt tapausselostusten pohjalta. Aikaisemmin stimulanttien käyttö perioperatiivisesti on pyritty välttämään, koska teoreettisesti stimulanttien farmakologiset ominaisuudet ovat vastakkaiset, kuin yleisimmillä anesteeteilla. Tämän vuoksi stimulanttien on pelätty aiheuttavan tahatonta valveilla oloa anestesian aikana. Vaikuttaa kuitenkin siltä, että stimulantit ja niiden käyttö eivät lisää perioperatiivisesti haittatapahtumien riskiä.

Avainsanat: stimulantit, perioperatiivinen hoito, anestesia

Kemppi, Mika; Ahlmén-Laiho, Ulla; Koskinen, Joel; Saari, Teijo; The Implications of Patient use of Stimulants For Perioperative Care

Abstract

Background: Stimulants are a group of substances that have a stimulating effect on the central nervous system. Their usage is common, both for medical indications and for illegal recreational usages. However their implication for perioperative care has been based mostly on case reports and theoretical interactions.
Methods: A comprehensive review of all publications on the topic accessible through PubMed was done, including case reports. 42 articles were initially found, of which 39 were considered relevant enough to be included.
Results: Chronic stimulant use appears to not have that great impact on perioperative care and discontinuing stimulant medication preoperatively may not be necessary. Chronic stimulant usage doesn't alter the need for anaesthetic agents for general anaesthesia.
Conclusions: There is still a lack of large scale studies regarding chronic stimulant medication and its effect on perioperative care. Already published data seems to indicate that interactions between anaesthesia drugs and these substances may not pose as great a risk as previously suspected.

Keywords
Stimulants, perioperative care, anaesthesia, amphetamine, methylphenidate, MDMA, MDPV, cocaine, modafinil

Introduction

Stimulants have medical uses in several neurological or neuropsychological disorders, such as attention deficit hyperactivity disorder (ADHD) and narcolepsy [1]. They have excitatory effects on the central nervous system and sympathomimetic properties [1,2]. The most commonly used substances belonging to this group are methylphenidate and the amphetamine derivative lisdexamphetamine. Amphetamine itself is also still used as a medication though modern derivatives have decreased its usage [3,4].

ADHD patients are the biggest group of legal stimulant users, stimulant medication being the basis of the treatment for the disorder in most cases requiring pharmacological intervention. The incidence of ADHD in latest meta-analyses is between 3.6–7.2% in schoolchildren [5,6,7] and 2.5–3.4% in adults [8,9], making it likely for anaesthesiologists working with children and young adults to encounter these patients. Chronic amphetamine exposure has been suggested to cause depletion of catecholamine receptor storages, which is suspected to cause a blunted physiological response to hypotension [10].

Stimulants, especially amphetamine, its derivatives and cocaine, have a long history of recreational use [11]. The peripheral actions of amphetamines include increased blood pressure and a weak bronchodilator and respiratory stimulant action [10]. Besides naturally occurring substances, there are also synthetic stimulants which are used as recreational drugs, such as methylenedioxypyrovalerone (MDPV)[12]. People using recreational drugs have a higher risk of developing severe infections and getting into accidents [13,14] and thus needing emergency surgery or reliable intravenous access as inserted by anaesthetists.

Notable substances

Amphetamine exists as two enantiomers: dextro- and levoamphetamine. The active substance in amphetamine is called dextroamphetamine, to which several different amphetamines metabolise. Amphetamine blocks the uptake of adrenergics and dopamine, stimulates the release of monoamines and inhibits monoamine oxidases. It is prescribed commonly for ADHD and narcolepsy, although — due to its abuse potential — its use has been in decline. In treating ADHD, amphetamine is used both in racemic and enantiopure forms. Recreationally amphetamine is used both orally and intravenously, as a cognitive enhancer and for its euphoric effect. Adverse effects — both in medicinal and recreational use — include increased heart rate and blood pressure, vomiting, and insomnia. Lisdexamphetamine is a prodrug that is converted into dextroamphetamine in the body and therefore is similar to amphetamine, although with a lower abuse potential. [15]

Methylphenidate is a central nervous stimulant which inhibits the reuptake of dopamine and norepinephrine (noradrenaline) [16]. It is commonly prescribed for treating ADHD [16]. Since its creation, methylphenidate has also been used recreationally, both orally and intravenously, for an amphetamine-like effect [17]. There have been animal studies in which methylphenidate has been studied as a means to facilitate faster emergence from general anesthesia. Although animal studies support this finding, there are no human studies or anecdotal case reports to support this [18].

Modafinil is a wakefulness-promoting drug. Not all of it’s exact mechanisms of action are known, but it appears to differ from other central nervous stimulants which have a direct effect on dopaminergic activity. Modafinil enhances glutamatergic neurotransmission in several regions of brains, acting directly on the hypothalamus. Modanifil also causes an increase in dopaminergic neurotransmission by blocking activity of dopamine transporter increasing dopamine. Modanifil also modulates norepinephrine and serotonin transporter activity. It is used for treating narcolepsy, and there is also military interest regarding potential use for maintaining alertness in prolonged combat situations. [19, 20]

MDMA (3,4-methylenedioxymethamphetamine), also known as ecstasy, has pharmacological features similar to amphetamine, though it also increases the release of serotonin and causes psychedelic sensations in addition to euphoria. Risk of adverse events with MDMA may be lower than with other recreational substances. However, a tablet or powder consumed as ecstasy can frequently contain other substances or it may not contain MDMA at all. The adverse effects of MDMA use include hyponatraemia, hyperthermia, rhabdomyolysis, metabolic acidosis, and dehydration, and a large overdose may lead to a comatose state. [14,21]

Cocaine, also known as benzoylmethylecgonine, is a stimulant which effects on many different receptor families. It blocks the reuptake of catecholamines in sympathetic presynaptic receptors causing sympathetic stimulation. This results in an increase of dopamine, adrenergic transmitters and serotonin production in a manner similar to amphetamine. Cocaine can also be used as local anesthetic as it reversibly blocks sodium channels in neurons. Topically used, it also causes local vasoconstriction. While once commonly used as a local anesthetic, today cocaine is mainly used as such only in ENT operations. Recreational use of cocaine is common. Hypertension, tachyarrhythmias and myocardial ischemia are common adverse events in patients admitted to hospital due cocaine intoxications. [14,22]

MDPV— 3.4-methylenedioxypyrovalerone— is one of the new synthetic stimulants used recreationally being one of so called “Designer drugs”. MDPV and other synthetic substances are mainly called collectively as “bath salts”, other street names include “Hurricane Charlie”, “Ivory wave” and “Cloud 9”, though there are more. [23] MDPV and other synthetics stimulants are structurally related to pyrovalerone and to cathinone. They act as stimulants inhibiting dopamine and noradrenaline reuptake. Adverse events are like those of other stimulants, thought hyperthermia, agitation and psychosis are often remarked.[24]

Of legal stimulants sold without prescription, caffeine and nicotine are particularly noteworthy. Caffeine is a mild stimulant trought it’s antagonism of adenosine receptors. This results in increased dopaminergic activity. There are rodent studies in which data suggest that caffeine may increase recovery speed from general anaesthesia, and there are some preliminary studies in human patients, though more studies are needed. [25] Nicotine is a cholinergic receptor agonist and it is classified as a stimulant of autonomic ganglia. It has two effects, stimulating effect and reward effect in the limbic system. It is found in tobacco and is used in tobacco withdrawal medications. [26]

The purpose of this study

While stimulant use — whether that be legally prescribed or recreational — is not uncommon among patients coming in for surgery, there is no consensus regarding the management of these patients in terms of peri- and intraoperative care or postoperative pain management. To create a synthesis of the scattered reports

and background information available in prior publications, a systematic survey of previously published data was done in order to see if practical advice for clinical anaesthesiologists could be formulated.

Methods

A systematic search was performed on PubMed in December 2018. Search parameters are presented in attachment. We analyzed titles and abstracts and chose the articles that might be related to our topic or give insight to related topics. Animal studies were excluded as were studies not available electronically. In the end, 42 articles were selected for more detailed examination. Finally, 39 articles from searches were deemed relevant to the subject and giving relevant information to our study.

Results

Some studies regarding whether chronic stimulant use should be stopped preoperatively have been performed. For pediatric ADHD patients, a study found that the use of stimulant medication on the day of surgery doesn't alter patients bispectral index (BIS) compared to control subjects [27]. Another study on pediatric ADHD patients found no difference in the hemodynamic profiles of patients who continued usage of amphetamine or methylphenidate medication preoperatively and those who did not take their usual dose [3]. Study prospectively evaluating eight patients on stimulant medication undergoing general anesthesia, reported no adverse events in the study population suggesting stable anesthesia management in patients receiving chronic stimulant medication [10]. Additionally few case reports describe stimulants using patients undergoing general anesthesia without adverse events [28, 29].
In none of these studies, no higher risk was found in patients who continue stimulant use throughout the perioperative period [27,3,28,29].There appears to not be a need for increased dosage of anaesthetics for patients with chronic stimulant usage [27,30,31]. Study of sedative and analgesic requirements of trauma victims in ICU setting didn't find increased need for stimulants user's [30]. This study didn't differentiate stimulant users in different groups between recreational use and chronic medical users [30]. Also this study didn't address initial requirements of anaesthesia substances for induction of general anesthesia and tracheal intubation [30]. There might be an increased need for anesthetics in patients with acute usage of stimulants who are in hyper-adrenergic state [11].

For narcolepsy patients, data suggests that continuing stimulant usage perioperatively may be beneficial, although this is a result from only a few small scale studies and one systematic review on the topic [4,32,2]. BIS or other such monitoring is recommended by these reports due to a theoretically increased risk of intraoperative awareness [2]. A small, retrospective study supported the perioperative continuation of stimulant medication in narcolepsy patients as they

found no difference in postoperative morbidity and mortality as compared with the general population [4]. For obstetric patients regional anesthesia may be beneficial over general anesthesia for cesarean deliveries [4, 33]. Preferring TIVA and shorter acting anesthetics is also recommended because of the possibility of fewer adverse events [4].

A retrospective review of perioperative care of the children with autism spectrum disorder (ASD) noted that the heterogeneous nature of children with autism as a patient group poses challenges to drawing conclusions about their perioperative care. ASD patients may have comorbid ADHD, for which stimulant medication may be prescribed to help with hyperactivity or inattention. [34,35]

During recreational drug use, on significant acute intoxication of MDMA, hyperpyrexia is a major side effect, which can lead to rhabdomyolysis [14,10]. Other adverse effects may also occur, such as hyponatremia which can lead to comatose state [14]. Metabolic acidosis, hypertension, arrhythmias, and disseminated intravascular coagulopathy [14]. Monitoring temperature is important [14]. In acute amphetamine use, hemodynamic instability has been reported [14]. General supportive measures were recommended for controlling hemodynamic instability [14]. One study retrospectively analyzed ecstasy intoxication patients in the emergency department. Most were discharged after several hours of surveillance. However, of the 32 total patients in the study, 3 were transferred to ICU after being in a comatose state in the emergency department. Each of them developed multiple clinical manifestations, such as convulsion, requiring mechanical ventilation, aspiration, rhabdomyolysis, lactic or metabolic acidosis, requiring ICU care [36].

Discussion

Amphetamines are a group of powerful central nervous system stimulants and sympathomimetics. They and other stimulants are common enough that every anesthesiologist will occasionally encounter patients taking them. However, there are few systematic or blind-controlled studies on their potential implications on managing the anesthesia process. Most studies on the topic are small-scale retrospective works or case reports.

Chronic amphetamine exposure causes depletion of catecholamine receptor storages, which is suspected to cause a blunted physiological response to hypotension. This can result in severe bradycardia and refractory hypotension during induction of general anesthesia. Direct vasopressors, such as adrenaline or phenylephrine, have been recommended to be used during such events because there have been reports of a blunted response with a commonly used first-line vasopressor, ephedrine. [11]

The stimulant effect of stimulating the central nervous system through various mechanisms has been traditionally thought to be increased risk for general

anaesthesia, and intraoperative accidental wakefulness has been a particular concern. That is why caution seemed to be used with patients taking stimulant medications and why such medications have been discontinued before operation. However, this practice has been based mostly on theoretical risk and few case reports indicating possible interactions between these substances and anaesthetic drugs. As noted before, there is an increasing number of case reports and small retrospective studies supporting the idea that it may not be necessary to cease stimulant medication on operation day and it may even be beneficial in certain patient groups to continue them throughout the operative treatment process.

There aren't many reports of dangerous adverse events during normal perioperative care. One case report detailing cardiac arrest of 4 year old patient with long-term methylphenidate medication after induction of general anaesthesia. The patient was given propofol and alfentanil, after which a severe bradycardia developed, followed by asystole. I.v. atropine was given and chest compressions performed and a normal cardiac rhythm returned monitored after 30 seconds. The subsequent operation and emergence from anaesthesia were uneventful, and the patient was discharged the same day. Catecholamine receptor storage depletion was thought to be contributed for cardiac arrest with combinated with propofol and alfentanil, both of which have been associated with bradycardia and asystole. [37] Lesser adverse event was reported in another case report. It concluded that midazolam may have reduced sedative effect on patients taking methylphenidate. The patient in question also developed a severe postoperative nausea, vomiting and dehydration. It was thought to be caused by the administration of ketamine as a part of anaesthetic cocktail and it's interaction with chronic methylphenidate usage. The mechanism of this interaction is unknown, but it was speculated that it may have been caused by methylphenidate's dopaminergic agonist action potentiating the emetic effect of ketamine. [38]

There are a few case reports detailing the perioperative management of patients who have recently used new synthetic stimulants recreationally. A report detailing the case of a pregnant patient near term who was in an acute psychotic state after taking methamphetamine and bath salts. She behaved aggressively, and was successfully sedated first with midazolam and then incremental doses of dexmedetomidine. Afterwards, general anesthesia was induced with succinylcholine and a higher-than-usual dose of propofol (5,5mg/kg). The patient was hemodynamically stable even with this significant large propofol dose, and subsequent operation and it's anaesthetic management were uneventful. [39] Another case report detailed a patient who had taken bath salts (MDPV); after being delivered to the emergency department due to unusual behavior, the patient was found to be hyperthermic, tachycardic and aggressive. He was successfully intubated with relatively normal doses of midazolam, ethomidate and succinylcholine. However, the patient was transferred to ICU afterwards, where he

developed renal failure, fulminant hepatic failure, disseminated intravascular coagulation and rhabdomyolysis. The patient recovered after ICU care. [24]

Acute and chronic stimulant usage must be differentiated for their effect on perioperative care. Acute stimulant usage is encountered in patients who use stimulating substances recreationally. These patients may require medical care for a number of reasons: intoxications and injuries above all. These patients are usually adults. They may require general anaesthesia due to injuries or severe intoxications. Generally, there may be an increased need of anaesthetic agents if the patient has acutely used stimulants, especially if they are acting aggressively or appear psychotic. The hemodynamics of acute users should be carefully monitored due to the possibility of increased instability.

Chronic, stable use is encountered in patients who have stimulant medication. These patients range from young children to young adults generally, though there are older users as well. These patients usually need general anesthesia for scheduled non-emergency operations. These patients are susceptible for suggested catecholamine receptor depletion and blunted physiological response for hypotension, however impact of this in practice has yet to be proven. Direct vasopressors have been recommended for these patients.

In conclusion, there is a lack of larger, blind-controlled studies regarding stimulants and their effect on general anaesthesia, particularly on the hemodynamic interactions of hypnotic and analgesic drugs and these substances. Most of the practices exercised in perioperative care of stimulant-using patients are based mainly on case studies and other small-scale studies. Further studies in a larger scale are needed in order to develop more comprehensive guidelines for the perioperative care of stimulant-using patients.

References

1. David J Heal et all Amphetamine, past and present – a pharmacological and clinical perspective Journal of Psychopharmacology27(6) 479 –496

2. Sally Hu, M Singh et all Anesthetic Management of Narcolepsy Patients During Surgery: A Systematic Review Anesth Analg 2018;126:233–46

3. Richard S. Cartabuke et all Hemodynamic profile and behavioral characteristics during induction of anesthesia in pediatric patients with attention deficit hyperactivity disorder Pediatric Anesthesia 27 (2017) 417–424

4. Alexandre N. Cavalcante et all Perioperative risks of narcolepsy in patients undergoing general anesthesia: A case-control study Journal of Clinical Anesthesia 41 (2017) 120-125

5. Polanczyk GV, Willcutt EG, Salum GA et all ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. Int J Epidemiol 2014;43:434-42

6. Polanczyk GV, Salum GA, Sugaya LS ym. Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. J Child Psychol Psychiatry 2015;56:345-65

7. Thomas R, Sanders S, Doust J et all Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. Pediatrics 2015;135:e994-1001

8. Simon V, Czobor P, Bálint S et all Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. Br J Psychiatry 2009;194:204-11

9. Fayyad J, De Graaf R, Kessler R et all Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. Br J Psychiatry 2007;190:402-9

10. Stephen P. Fischer et all General Anesthesia and Chronic Amphetamine Use: Should the Drug Be Stopped Preoperatively? Anesth Analg 2006;103:203–6

11. G. T. C. Wong and M. G. Irwin Poisoning with illicit substances: toxicology for the anaesthetist Anaesthesia 2013, 68 (Suppl. 1), 117–124

12. Travis M. Lajoie and Anne Rich “Bath Salts”: A New Drug Epidemic—A Case Report *The American Journal on Addictions*, 21: 572–573, 2012

13. Marcelle Hernandez et all Anesthetic management of the illicit-substance-using patient Curr Opin Anaesthesiol 18:315–324. _ 2005 Lippincott Williams & Wilkins.

14. Pierre Beaulieu, Anesthetic implications of recreational drug use Can J Anesth/J Can Anesth (2017) 64:1236–1264

15. David J Heal et all Amphetamine, past and present – a pharmacological and clinical perspective Journal of Psychopharmacology27(6) 479 –496

16. Hui C. Kimko et all Pharmacokinetics and ClinicalEffectiveness of Methylphenidate Clin Pharmacokinet 1999 Dec; 37 (6): 457-470

17. Elisabeth Frauger et all Patterns of Methylphenidate Use and Assessment of Its Abuse among the General Population and Individuals with Drug Dependence Eur Addict Res 2016;22:119–126

18. Jessica J. Chemali et all Active Emergence from Propofol General Anesthesia Is Induced by Methylphenidate *Williams & Wilkins.* Anesthesiology 2012; 116:998–1005

19. Eric Murillo-Rodríguez et all An Overview of the Clinical Uses, Pharmacology, and Safety of Modafinil *ACS Chemical Neuroscience* 2018 *9* (2), 151-158

20. A. Doyle and D. Wilkinson2 Day case general anaesthesia in a patient with narcolepsy Anaesthesia, 2008, 63, pages 880–882

21. Harold Kalant The pharmacology and toxicology of"ecstasy" (MDMA) and related drugs CMAJ2001;165(7):917-28

22. Ana Luft; Florentino Fernandes Mendes Anesthesia in cocaine users Rev. Bras. Anestesiol. vol.57 no.3 Campinas May/June 2007

23. Travis M et all “Bath Salts”: A New Drug Epidemic—A Case Report *The American Journal on Addictions*, 21: 572–573, 2012

24. Heather A. Borek and Christopher P. Holstege Hyperthermia and Multiorgan Failure After Abuse of “Bath Salts” Containing 3,4-Methylenedioxypyrovalerone Ann Emerg Med. 2012;60:103-105

25.Nafisseh S Warner et all Effects of caffeine administration on sedation and respiratory parameters in patients recovering from anesthesia *Bosn J Basic Med Sci. 2018;18(1):101-104. © 2018*

26. SHOSHANA ZEVIN et all Clinical Pharmacology of Nicotine Clinics in DermatologyY1998;16:557–564

27. Neil A. Chambers et all Ingestion of stimulant medications does not alter bispectral index or clinical depth of anesthesia at 1 MAC sevoflurane in children Pediatric Anesthesia 22 (2012) 341–344

28. Stephen P. Fischer et all General Anesthesia in a Patient on Long-Term Amphetamine Therapy: Is There Cause for Concern? Anesth Analg 2000;91:758–9

29. Cheng-Hsi Chang et all General Anesthesia in a Juvenile With Attentiondeficit Hyperactivity Disorder Accompanied by Long-term Use of Methylphenidate (Concerta®) *Acta Anaesthesiol Taiwan* 2009;47(4):208−211

30. Bridgette Kram et all Analgesia and Sedation Requirements in Mechanically-Ventilated Trauma Patients with Acute, Pre-Injury Use of Cocaine and/or Amphetamines Anesth Analg. 2017 March ; 124(3): 782–788.

31. Georges Mion Chronic Amphetamine Users Do Not Need More Drugs During General Anesthesia DOI: 10.1213/ANE.0000000000002078

32. Bethanie Burrow et all Postoperative outcome of patients with narcolepsy. A retrospective analysis Journal of Clinical Anesthesia (2005) 17, 21–25

33. S. Soltanifar, R. Russell Neuraxial anaesthesia for caesarean section in a patient with narcolepsy and cataplexy doi:10.1016/j.ijoa.2010.07.015

34. Brook Arnold et all Autistic children and anesthesia: is their perioperative experience different? Pediatric Anesthesia 25 (2015) 1103–1110

35. Bistra G. Vlassakovaa and Dimitris E. Emmanouil Perioperative considerations in children with autism spectrum disorder Curr Opin Anesthesiol 2016, 29:359–366

36. Ron Ben-Abraham et all 'Ecstasy' intoxication: life-threatening manifestations and resuscitative measures in the intensive care setting European Journal of Emergency Medicine 2003, 10:309–313

37. C. Perruchoud M. Chollet-Rivier Cardiac arrest during induction of anaesthesia in a child on long-term amphetamine therapy doi:10.1093/bja/aen012

38. Douglas g. ririe et all Case report Unexpected interaction of methylphenidate (Ritalin) with anaesthetic agents Pediatric anaesthesia 1997 7: 69-72

39. Nina Schloemerkemper Psychotic due to bath salts and methamphetamines: emergency cesarean section under general anesthesia The Journal of Biomedical Research, 2018 32(4): 311–313

Table 1

Substance	Medical use/recreational use	Mechanism of action	Main uses	Side effects
Amphetamine	Both	Blocks the uptake of adrenergics and dopamine, stimulates the release monoamines and inhibits monoamine oxidases	Different derivatives are used as treatment of ADHD and narcolepsy. Recreational use is common, both intravenously and orally.	Increased heart rate and blood pressure, vomiting, insomnia
Methylphenidate	Mainly medical but there is also recreational use	Inhibits the reuptake dopamine and norepinephrine	Commonly used as treatment of ADHD and other neuropsychological disorders. It is alsu used recreationally for amphetamine like effect, thought this effect is milder.	Similar to amphetamine
Modanifil	Medical	Enhances glutamatergic neurotransmission in several regions of brain , acting directly on hypothalamus. Increases dopaminergic neurotransmission by blocking activity of dopamine transporter. Modulates norepinephrine and serotin transporter activity.	Treatment of narcolepsy	Possibly addictive
MDMA (3,4-methylenodioxymethamphetamine, ecstacy)	Recreational	Similar to amphetamine. Additionally it increases the release of serotin	Recreational	Hyponatraemia, hyperthermia, rhabdomyolysis, metabolic acidosis and dehydration.
Cocaine (Benzoylmethylecgonine)	Mainly recreational	Blocks the reuptake of catecholamines in sympathetic presynaptic receptors causing sympathetic stimulation. This results in an increase of dopamine, adrenergic transmitters and serotin production. Reversibly blocks sodium channels in neurons.	Recreational use. In past it has been used as local anesthetic	Hypertension, tachyarrhythmias, and myocardial ischemia
MDPV (3,4-methylenedioxypyrovalerone)	Recreational	Inhibites dopamine and noradrenaline reuptake.	Recrational	Similar to other stimulants, thought hyperthermia, agitation and psychosis are often remarked
Caffeine	Both	Antagonism of adenosine receptors which leads to increased dopaminergic activity	Recreational mainly. There are few medical indications for use of caffeine.	Stimulation of diuresis. Addiction
Nicotine	Both	Cholinergic receptor agonist and stimulant if autonomic ganglia	Recreational. Medically used in tobacco withdrawal medications.	Addiction

Table 2

Author and year of publication	N	Study population	Study parameter	Result	Control group
Neil A. Chambers et all (2011)	34	Children aged between 5-16 coming for elective surgery and who had been diagnosed with adhd and had stimulation medication.	Anaesthesia were inducted for patients with sevoflurane. After 10 minutes at 1 MAC et several parameters were monitored.	There were no significant difference in BIS or other clinical markers of anaesthesia depth.	Children without ADHD and no stimulation medication.
Richard S. Cartabuke et all (2017)	50	Patients from 2-18 year olds with diagnosed ADHD and stimulation medication (amphetamine or methylphenidate)	Hemodynamic parameters were monitored (heart rate, systolic and diastolic BP and mean arterial pressure) before and during anesthetic induction.	There was no difference in hemodynamic profile between groups. No intraoperative gypotension in either group.	Patients with adhd, who did not take their usual medication on operation day
Stephen P. Fischer et all (2006)	8	Adult patients with amphetamine medication aged between 22 to 77.	General anesthesia was performed to patients using normal perioperative procedures. Patients took their stimulant medication normally.	No hemodynamic instability during or after anesthesia. There was no adverse events.	No control
Bridgette Kram et all (2017)	150	Trauma patients admitted to ICU, with UDS positive for cocaine and/or amphetamine	Primary endpoint was daily opioid dose. Secondary endpoints was sedative requirement (benzodiazepine, propofol and dexmetomidite), duration of mechanical ventilation, ICU and hospital lenght of stay and mortality.	Stimulant use was not associated with increased need for analgesic or sedatives during ICU care.	Trauma patients in ICU with negative UDS for stimulants
Alexandre N. Cavalcante et all (2017)	76	Narcolepsy patient and their matched controls	Perioperative care was closely monitored and documented.	Narcolepsy patients did not have inreased rate of hemodynamic complications or respiratory events intraoperatively or immediately after. There was increased risk for respiratory adverse events on hospital wards. There was no difference between narcolepsy patients whom used stimulant medication to those who did not.	Matched controls without narcolepsy.
Sally Hu et all (2017)	19 studies (16 case reports, 3 case series)	Systematic review regarding narcolepsy patients and general anesthesia	Different studies were analyzed .	Continuation of preoperative medication, TIVA anesthesia, regional anesthesia and depth of anesthesia monitoring were associated with favorable outcome. Obstetric patients were associated with worsening symptoms of narcolepsy.	
Bethanie Burrow et all (2003)	37	Retrospectivly analyzed narcolepsy patients who had undergone general anesthesia.	Anesthesia charts were retrospectivly analyzed for certain events: time of extubation, duration of stay in the postanesthesia care unit and duration of the stay at hospital.	No increase risk was found for pharmacologically treated patients undergoing general anesthesia.	10 of patients had stimulant medication.