3.2.2.3.6.5 Yohimbine overdose management

There is no question that yohimbine can “feel” dangerous. In psychiatric experiments (with animals and humans) it is used to induce panic attacks or as a challenge for Post-Traumatic Stress Disorder.

However, whether a drug feels dangerous, and whether it is dangerous, are two different matters, as is evident from the following abstract of a scientific article published in the American Journal of Psychiatry (2000 Aug;157(8):1236-1242):

Yohimbine challenge in children with anxiety disorders.

Sallee FR, Sethuraman G, Sine L, Liu H.

Department of Psychiatry, Medical University of South Carolina, USA.

OBJECTIVE: The authors evaluated the neurohormonal and subjective mood response of children with anxiety disorders who were challenged with yohimbine. METHOD: Seventeen children with DSM-IV diagnoses of anxiety disorders and 15 normal comparison children were given yohimbine orally (0.1 mg/kg). Neurohormonal measures and visual analog self-reports of tenseness were recorded over a 150-minute period. RESULTS: Yohimbine was uniformly well tolerated, and it behaviorally differentiated children with anxiety disorders from normal comparison children with higher maximum change (Deltamax) ratings of anxiety in the patients (mean=17.4 mm, SD=29.8) than in the comparison subjects (mean=0.3 mm, SD=4.4). Yohimbine-stimulated Deltamax growth hormone (GH) for children with anxiety disorders (mean=-1.5 ng/ml, SD=5.9) was significantly reduced compared to that of normal comparison children (mean=2.7 ng/ml, SD=4.5). CONCLUSIONS: Yohimbine selectively elevates self-rated anxiety in children with anxiety disorders and is associated with the blunting of GH in those children relative to that of comparison children. Presence of a blunted GH response to yohimbine in children with anxiety disorders is reminiscent of findings in adults with anxiety disorders, particularly panic disorder. These findings support enhanced central adrenergic sensitivity in children with anxiety disorders, as demonstrated by yohimbine-exacerbated

anxiety. The findings should be reconciled with the absence of clonidine-related GH blunting in the same cohort.

Please note that yohimbine elevated anxiety, even though it was well tolerated.

The following abstract of a scientific article, published in the Journal of Urology (1989 Jun;141(6):1360-1363) suggests that daily dosages of up to 42 milligram are no safety concern:

Effect of yohimbine hydrochloride on erectile impotence: a double-blind study.

Susset JG, Tessier CD, Wincze J, Bansal S, Malhotra C, Schwacha MG.

Department of Urology, Providence Veterans Administration Medical Center, Rhode Island.

A double-blind, partial crossover study on the therapeutic effect of yohimbine hydrochloride on erectile dysfunction was done in 82 sexually impotent patients. All patients underwent a multifactorial evaluation, including determination of penile brachial blood pressure index, cavernosography, sacral evoked response, testosterone and prolactin determination, Derogatis sexual dysfunction inventory and daytime arousal test. After 1 month of treatment with a maximum of 42.0 mg. oral yohimbine hydrochloride daily 14 per cent of the patients experienced restoration of full and sustained erections, 20 per cent reported a partial response to the therapy and 65 per cent reported no improvement. Three patients reported a positive placebo effect. Maximum effect takes 2 to 3 weeks to manifest itself. Yohimbine was active in some patients with arterial insufficiency and a unilateral sacral reflex arc lesion, and in 1 with low serum testosterone levels. The 34 per cent response is encouraging, particularly in a Veterans Administration population presenting with a high incidence of diabetes and vascular pathological conditions not found in regular office patients. Only few and benign side effects were recorded, which makes this medication worth an attempt, often as a first line of treatment even at a dose of 8 tablets.

The US packet inserts for yohimbine do not provide information on

overdoses of yohimbe, and problems that could be associated with such overdoses. However, we have found a number of scientific sources that deal with yohimbine toxicity.

The following has been written by Dr Wayne A. Temple, National Toxicology Group, University of Otago Medical School, and Dr Nerida A. Smith, Pharmacy School, University of Otago, PO Box 913, Dunedin, New Zealand. The information was reviewed in July 1992 by the Poisons Unit, New Cross Hospital, Avonley Road, London SE14 5ER, United Kingdom (Peer review by Drs Deng, Ferner, Landoni, Maramba, Shintani, Wickstrom.

2.1 Main risks and target organs

Yohimbine is a centrally acting alpha-2-adrenoceptor blocking agent. It may also interact with alpha-1-adrenoceptors and, in high concentrations, serotonin and dopamine receptors. Yohimbine is a monoamine oxidase inhibitor, and has the potential to interact with tyramine-containing foods and stimulants such as phenylephrine and phenylpropanolamine.

Yohimbine affects the gastrointestinal, genito-urinary, respiratory, cardiovascular and central nervous systems.

2.2 Summary of clinical effects

Yohimbine produces cardiovascular effects, including increases in heart rate and blood pressure. Bronchospasm and increased mucous secretion has been reported.

CNS effects include anxiety, hallucinations and manic reactions.

Gastrointestinal effects include nausea, anorexia and diarrhoea.

Dysuria, and back and genital pain have occurred. 2.4 First aid measures and management principles Support respiratory and cardiovascular function. Emesis may be indicated for substantial ingestions, especially if initiated within 30 minutes of ingestion. Activated charcoal may also be administered. Diazepam may be useful in reducing anxiety.

7.1 Mode of action

Yohimbine is a competitive antagonist selective for alpha 2-andrenoceptors, which are thought to be located on nerve terminals and receptors and to mediate inhibition of transmitter release. The presynaptic release of noradrenaline is increased by an alpha-2-antagonist resulting in increased sympathetic outflow. Yohimbine may also interact with alpha- 1-adrenoceptors and, in high concentrations, serotonin and dopamine receptors (Dukes, 1988). Yohimbine has monoamine oxidase inhibitory effects (Bhattacharya et al., 1991).

7.1.1 Toxicodynamics

It has been suggested that a central beta-origin toxicity exists, since only beta blockers which cross the blood-brain barrier are capable of antagonizing this activity (Bourin et al., 1988).

7.1.2 Pharmacodynamics

Yohimbine is an alpha-2-adrenergic antagonist. It increases the heart rate and blood pressure and causes CNS stimulation and anti-diuresis (Reynolds et al., 1989).

7.2 Toxicity

An ingested dose of 1.8 g (100 times the average daily dose) resulted in unconsciousness for some hours, with priapism. The patient recovered fully within a few days (Roth et al., 1984; as cited in Dukes, 1988).

9.1 Acute poisoning

Fatalities resulting from acute overdosage of yohimbine have not been reported. Signs of overdosage include CNS depression, ranging from drowsiness to coma. Respiratory depression, hypothermia, diarrhoea, vomiting, mental depression, flushing of the skin, hypertension, cardiac arrhythmias, tachycardia and short-term reversible paraesthesias of the legs and feet may occur.

10.3 Life supportive procedures and symptomatic/specific treatment

Support respiratory and cardiovascular function.

Diazepam has been shown to be useful in treating yohimbine-induced anxiety. Dose is given either orally or by slow intravenous injection:

Adult 5 to 10 mg

Child 0.1 – 0.3 mg/kg bodyweight

If priapism is prolonged (more than 4 hours) then specific treatment may be required, e.g. aspiration of the corpus may be required.

10.7 Management discussions Clonidine 5 micrograms/kg bodyweight was found to eliminate not only yohimbine-induced anxiety but also the increases in blood pressure, plasma MHPG, and other autonomic symptoms in a study using normal volunteers who ingested 30 mg yohimbine. However, before clonidine can be recommended as a routine antidote for yohimbine toxicity, further clinical evaluation is required (Charney et al., 1983).

11.1 Case reports from literature

Case 1

An ingested dose of 1.8 g yohimbine (100 times the average daily rate) resulted in unconsciousness for some hours with priapism. The patient recovered fully within a few days (Roth et al., 1984; as cited in Dukes, 1988).

Case 2

A 38-year-old man with insulin dependent diabetes was admitted two hours after taking 350 mg yohimbine. The drug had been prescribed by a consultant psychiatrist for erectile impotence complicated by depression.

On admission to hospital he was alert and oriented. His blood pressure was 130/80 mmHg and his pulse was regular at 88

beats/minute. Six hours after admission he discharged himself, but was readmitted 17 hours later in a drowsy and confused state. He was having rigors and complained of retrosternal pain. He did not appear to have taken any other drug. His rectal temperature as 35.5degree celsius and his blood pressure was 135/85 mmHg. His hands and feet were warm and well-perfused. Blood urea was 12.8 mmol/L, serum creatine 175 umol/L, and blood glucose 16.7 mmol/L. An electro- cardiogram showed atrial fibrillation with a ventricular rate of 150 beats/minute. The day after admission an electrocardiogram showed sinus rhythm, and retrograde amnesia for the preceding 24 hours persisted for four days.

Case 3

A 16-year-old female took an estimated 250 mg of a white powder alleged to be yohimbine. Within 20 minutes she was weak, had generalized paraesthesia, loss of coordination, and was disassociative. She had a severe headache, was dizzy, and had no tremors. A severe pressure-like substernal chest pain was noted 4 hours post-ingestion, and remained for 2 hours before subsiding spontaneously. The next day, the patient remained weak and dizzy, with nausea, sweating, severe headache and intermittent palpitations. On examination more than 30 hours after ingestion, she had a blood pressure of 150/80, pulse of 116 and respiration rate of 24. She was anxious, with a blotchy erythematous rash on her back and submucosal haemorrhage in the right tympanic membrane. Symptoms resolved spontaneously but had lasted 36 hours (Linden et al., 1985).

In addition to the above information, another source that I have seen dealing with yohimbine overdose questions is the web site of Slovakofarma, a Slovakian manufacturer of yohimbine tablets:

Contraindications

Yohimbine is contraindicated in hypotension, in patients with the risk of rapid blood pressure decrease or development of tachycardia. It is not suitable for children, pregnant and breast-feeding women and for individuals with allergy to any compound of the preparation.

Dosage is strictly individual in patients with low blood pressure and ischaemic heart disease. Close monitoring is needed.

If conditions mentioned in this paragraph occur during the treatment, consult your doctor.

Adverse drug reactions

After intake of therapeutical dose adverse reactions are rare: excitations, flash, tremor of hands, muscle cramps, increase of motor activity and insomnia, exceptionally skin flush.

In case of adverse drug reactions or other unusual effects consult your physician about further administration of this preparation.

Interactions

Therapeutic effect of yohimbine after including pentoxifylline into the therapy is enhanced in patients with erectile dysfunction. There were reported exceptional cases of priapism in co-administration of yohimbine with trazodone (however, it is potentially dangerous combination and patients should be carefully monitored). More important seems to be the fact, that most of antidepressants provoke erectile dysfunction and that co-administration of yohimbine in the treatment markedly supports the therapy of depressions. Triggered desire for sexual activity has indubitably positive influence on a patient's mood. In general (due to pharmacodynamic properties of yohimbine) interactions can be assumed (an increased or decreased effect) in co-administration of yohimbine with other agents acting on a -adrenoreceptors.

Overdosage

Overdose may take place when daily dose was exceeded 5-6 times what results in increase of noradrenaline level. Symptoms of overdose include weakness, generalised paraesthesia, loss of coordination, memory disorders, severe headache, dizziness, tremor, palpitations, anxiety, chest pain, nausea, vomiting. Antidote clonidine is recommended in overdosage which inhibits sympathetic as well as psychic symptoms (0.1-0.2 mg of clonidine orally, then 0.1 mg in one-hour intervals untill a patient?s state is improved). Hypertensive

crisis is recommended to be treated with b -blockers which can be combined with a -blockers (phentolaminum) or vasodilators (nitropruside). Benzodiazepines can be applicated in anxiety only in condition when sympathomimetic reactions are absent.

It has to be noted that the antidote to yohimbine, clonidine, is potentially much more dangerous than yohimbine. A clonidine overdose definitely carries the risk of death, as evident from the following source:

Authored by David Riley, MD, Director of Resident Education & Ultrasound Training, Department of Emergency Medicine, St. Luke's-Roosevelt Hospital Center, Columbia University College of P&S

Symptoms [of a clonidine overdose] develop rapidly (usually within 30-60 min) postingestion and may resemble a narcotic overdose with miosis, bradycardia, respiratory depression, and coma. From a differential standpoint, comatose-appearing children with clonidine toxicity may awaken and be intermittently lucid when subjected to vigorous stimuli (eg, physical, verbal), whereas patients with narcotic overdoses subjected to the same stimuli may awaken but are obtunded. Symptoms tend to be relatively more severe in pediatric patients. Toxic presentations also may include hypotension, hypertension, mydriasis, hypothermia, ileus, hypotonia, hyporeflexia, intermittent apnea, atrioventricular (AV) nodal heart block, and seizures.

With significant ingestions, patients usually present with bradycardia.

Associated hypotension may be severe and last up to 24 hours.

Hypertension is less common and usually more transient.

Hypothermia has been reported but is usually mild.

Patients may present with CNS depression, which may range from mild drowsiness (common) to coma.

Baseline mental status usually returns within 24-48 hours of ingestion.

Hyporeflexia may develop.

Seizures may occur.

Dysrhythmias may occur and include AV nodal block, Wenckebach, and tachycardia.

Respiratory depression is common, especially in children, and may require endotracheal intubation.

Respiratory failure usually occurs within 1-2 hours of ingestion.

Ataxic breathing may be observed.

Patient may experience periods of apnea.

Pallor and cool extremities have been reported.

Emergency Department Care

Focus initial treatment on ABCs. Clonidine toxicity can cause serious respiratory depression and apnea requiring immediate endotracheal intubation and mechanical ventilation. Once the airway is secure, place the patient on continuous ECG, blood pressure, and oxygen saturation monitoring. Place at least one large-bore IV line. Consider central venous pressure (CVP) monitoring in patients who are markedly hypotensive.

Clonidine toxicity can cause serious respiratory depression and apnea requiring immediate endotracheal intubation and mechanical ventilation.

Hypotension is very common with clonidine toxicity; initially treat patient with aggressive crystalloid infusion. If aggressive volume resuscitation fails to raise blood pressure, consider pressors such as dopamine and epinephrine. Maintain good urine output because clonidine is excreted at least 50% unchanged in the urine.

Bradycardia, either sinoatrial (SA) nodal or AV nodal, has been reported with clonidine toxicity.

Atropine is the first-rate drug of choice. Consider dopamine if atropine fails with SA nodal, first-degree, or Mobitz I AV nodal block; however, in Mobitz II and third-degree AV nodal block, atropine is only temporizing until definitive pacing is initiated.

Transcutaneous pacing is quicker to initiate, yet it causes patient more discomfort than transvenous pacing. Consider transvenous pacing in patients with massive ingestions who have third-degree AV nodal block.

Hypertension may occur initially from peripheral alpha1-agonist activity and vasoconstriction. This hypertension is usually transient and does not require treatment; however, in patients with sustained diastolic pressures above 130 mm Hg, consider a short acting, easily titratable intravenous agent such as sodium nitroprusside.

Administer activated charcoal by mouth or nasogastric tube for clonidine toxicity in a 1-g/kg dose (standard for toxic ingestions). If significant CNS depression exists, intubate before administering activated charcoal to prevent aspiration. Lavage is controversial; yet consider if ingestion is significant and occurred less than an hour before arrival.

Naloxone (Narcan) may treat clonidine toxicity. It improves the mental status of adults and children who have ingested toxic amounts of clonidine; this, however, has not been universal and naloxone can cause hypotensive and hypertensive responses. Narcan also has been reported to cause severe hypertension.

American Academy of Pediatrics recommends a dose of 0.1 mg/kg for infants and children up to age 5 years or weighing 20 kg. Children older than 5 years or weighing more than 20 kg may be given 2 mg of Narcan. Adults may be given 2 mg doses of Narcan, titrated to effect.

Provide symptomatic and supportive care, the main therapy for clonidine toxicity. Passively warm patients with hypothermia. Most comas resolve with supportive measures.

Two case reports document yohimbine reversal of clonidine toxic states. Yohimbine is a central alpha2-adrenergic antagonist with effects that directly oppose clonidine, making it theoretically a useful antidotal agent. The dosage has been a single 5.4 mg tablet administered orally or via nasogastric tube; a parenteral form is not clinically available.