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PHYSIOLOGICAL ACTIVITY, TOXICITY, AND USES OF EPHEDRINE ALKALOID

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ABSTRACT

Ephedrine alkaloid (or ephedrine) can be derived from plant sources, but has been synthesized in 1927. The compound has various medicinal uses for treatment of broncho-spasms, for obesity, and for elevation of arterial blood pressure. Other clinical applications include the following uses: for allergies, hay fever, asthma, and bronchitis. However, adverse side effects include cardiovascular effects, and hypertension, myocardial infarction, seizures, and strokes that can be fatal. Various methodologies have been investigated for the detection and assay of ephedrine alkaloids and include: high performance liquid chromatography (HPLC), liquid chromatography, and titrimetry. One particular methodology utilizing HPLC showed a limit of detection (LOD) at 2.9833×10^{-5} molar and limit of quantitation (LOQ) to be 8.9500×10^{-5} molar. The standard curve showed coefficient of determination of $R^2 = 0.9857$, indicating that the model describes 98.57% variance in the dependent variable (peak area) that is predictable from the independent variable (molar concentration). The Pearson r correlation coefficient of the standard curve is 0.9928, a very high positive correlation. That particular methodology showed ephedrine alkaloid can be detected and assayed at very low concentrations, with applications for quality control, patient compliance, and environmental quantitation. Assay by gas chromatography and liquid chromatography are discussed. Ephedrine has been utilized to enhance athletic performance, but has adverse side effects. Further discussion of biological activity, toxicity, assay, and use and abuse are discussed.

KEYWORDS: Ephedrine, Ephedra, Ma Huang, alkaloids.

INTRODUCTION

The compound ephedrine (ephedrine alkaloid) does occur naturally in various plants, in addition, it has been prepared synthetically in 1927.[1] Ephedrine is among six compounds harvested from the plant *Ephedra sinica*.[1] It is a (sympathomimetic drug) stimulant compound that reproduces the effects of endogenous agonists of the sympathetic nervous system (sympathomimetic drug). It has been utilized for treatment of broncho-spasms, for obesity, and as an agent that will elevate arterial blood pressure.[1] This compound is able to be administered orally with a physiological action similar to adrenaline.[2] Ephedrine is known to assist in the short-term reduction of weight and for fat loss.[3] Clinical applications have included the following uses: for allergies, hay fever, asthma, and bronchitis associated with flu and swine flu.[4] Some side effects include significant safety hazards.[5] Side effects can involve cardiovascular effects, and hypertension, myocardial infarction, seizures, and strokes that can be fatal.[5]

Other side effects can result in cardiac effects intra-cerebral hemorrhage, mania, nephrolithiasis (crystalline stones within the urinary system including kidneys and ureter), and death.[6] Methods for assay of ephedrine alkaloids include high performance liquid chromatography.[7] Other methods evaluated include column-switching cation exchange high performance liquid chromatography (HPLC).[8] High performance liquid chromatography with ultra-violet detection can be used to identify ephedrine.[9] A titrimetric method utilizing methyl red indicator in solution that has been acidified, followed by titration with a standardized sodium hydroxide quantifying the amount of excess acid.[10] Other titrimetric methods for ephedrine hydrochloride was based on the formation of a copper complex formation.[11]

PROPERTIES

Ephedrine can be derived from plants or specifically such a plant as Ma Huang. This is an alkaloid that mimics the activity of epinephrine and the effects of the sympathetic nervous system, and so consequently this alkaloid will have various physiological effects that are pursued for medical purposes, but also inappropriate uses and abuse. The molecular structure of the compound in shown in Fig. 1.

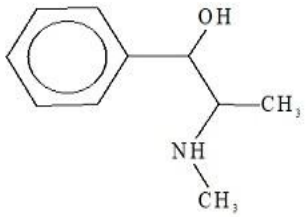

Figure 1: The molecular structure of ephedrine. There is present a single aromatic ring, along with a single hydroxyl group (-OH), a secondary amine group (-NHR2), and two methyl groups (-CH3).

As determined by EPISUITE[12], the formula is $C_{10}H_{15}NO$ and with a SMILES notation (Simplifies Molecular Input Line Entry System) of CC(C(c1ccccc1)O)NC. It has a Log Kow of 1.15 and molecular weight of 165.12 Daltons. The boiling point is estimated by EPISUITE to be 266.26°C and melting point at 39.20°C.[12] Measurement of solubility by Heuristic platforms showed value of 32653.48 milligram/Liter and Log S of -0.70 (Log(moles/L).[13] The following equation is used to calculate solubility:[12]

Log S (mole/Liter) = 0.796 - (0.854)(Log Kow) - (0.00728)(molecular weight) + 1.000

Other molecular properties include polar surface area of 27.07 Angstroms^2, molecular volume of 167.54 Angstroms^3.[13] The molecular structure has 2 stereo centers and 3 rotatable bonds.[13]

The pKa of the most basic group is 9.40, with a pKa of the most acidic group to be 15.06.[13]

A Bioconcentration Factor (BCF) is an indicator of a compounds tendency to accumulate in a testing living organism. It is a parameter that can be estimated by calculation based on Log P and can be referred to as the bio-accumulation test.[12] Calculated BCF value ephedrine is 0.333 and Log BCF of -0.48.[12] BCF values greater than 1, indicate a compound is greater in the testing organism, as opposed to the medium (soil or water).[12] BCF value for this compound can be determined using the following equation:[12]

Log BCF = (0.77) (Log Kow) - 0.70 + (correction of -0.650)

Ephedrine would have a drug-likeness score of 0.54, whereas most drugs would fall within a score of -2 to approximate 2.2 (as measured by Heuristic platform Molinspiration).[13] In solid form it exists as colorless to white wax-like solid in the form of crystals or granules.[14,15] The solid is soluble in ethanol, ether, water, benzene, and chloroform.[16]

APPEARANCE IN ATHLETIC COMPETITION

The lack of regulation of industrial supplement production within North America has allowed the spread of products, some of which may have adverse effects in users.[17] Various products are officially prohibited in sports, include anabolic steroid precursors (common stimulants).

Examples of this problem are those products that contain ephedrine, and have been associated with significant morbidity and mortality.[17]

A product that contains ephedrine and is common in use is Ma Huang herb (ephedra), and is a sympathomimetric acting alkaloid mixture that is used for reducing fatigue, increasing strength, increasing power, increasing speed, and improving body composition.[18] However, the safety and efficacy of Ma Huang to be used in athletics as an ergogenic supplement is being examined.

[18]It is being examined, with the risks involved appearing to counter any associated ergogenic benefits.[18] It is considered important that athletic level trainers inform athletes of the risks so that educated choices can be made to enhance health and safety of the athlete.[18]

The use of ephedrine in combination with caffeine is known to enhance physical muscle strength, but this mixture is prohibited widely.[19] The alkaloids that are used actually demonstrate several physiological effects with no certainty that they are safe for individuals to use.[19] Some studies have shown that the use of ephedra or caffeine, actually does not enhance anaerobic exercise performance or muscle strength.[20] In addition, even with ephedra with caffeine use, there is no significant difference in peak anaerobic power, muscle endurance, or muscle strength, albeit users report increases in mood and alertness.[20]

It is commonly known that users of ephedrine and ephedra do so for enhancing weight loss.[21] Previously, it has been noted that ephedrine with caffeine has brought about incremental weight loss.[21] However, there have been multiple highly publicized deaths of athletes who had self- administered ephedrine and/or ephedra.[21] Ephedrine, with or without caffeine, resulted in incremental weight loss, however, the benefits of ephedrine for weight loss or for enhanced athletic performance are modest at best.[21] The occurring "minor" adverse events following self administration are common, and serious events are rare but are catastrophic.[21] Others have noticed that ephedrine use has been associated noticeably with gastrointestinal symptoms, palpitations, anxiety, and hypertension.[22]

PHYSIOLOGICAL AND TOXIC ACTION

A highly publicized death of a professional baseball pitcher occurred in 2003, following heat stroke, however, a large amount of ephedrine was found in the athletes blood stream.[22] When consumers purchase ephedra for miscellaneous uses, individuals will not realize that ephedra has actually six active alkaloids, which include varying amounts of: ephedrine (the predominant alkaloid), pseudoephedrine, norephedrine (or

phenylpropanolamine), methylephedrine, norpseudoephedrine, and methyl-pseudoephedrine.[22]

The notable action of ephedrine/ephedra are numerous and include notable effects, such as: increase in heart rate, increase in blood pressure, increase cardiac output, broncho-dilation, stimulation, diuretic action, urinary retention, and appetite suppressant.[22] To contrast with amphetamine, the effects of ephedrine beyond the central nervous system are stronger. Adverse effects of ephedra/ephedrine use are numerous and noticeable, varying in seriousness of appearance, but includes: asphyxia, flushing, tachycardia, heart palpitations, heart failure, cardiac arrest, dizziness, anxiety, insomnia, anorexia, nephrolithiasis (which can be calcium oxalate stones, calcium phosphate stones, uric acid stones, or cystine stones), nausea, vomiting, seizure, and difficulty urinating.[22] Ephedrine can cause death through myocardial necrosis.[22] Ephedrine may also predispose individuals to both hemorrhagic and ischemic stroke.[22] It is also notable that cardiovascular toxic effects from ephedra are not limited to massive doses.[22]

HERBS AND EPHEDRINE

The herb *Ephedrae Herba (*or Ephedra) is known in China and referred to a "Ma Huang", which is a straw stem that is dried.[23] Thus far, over 60 species of *Ephedra* plants are recognized, that contain many compounds, over 100, that include flavonoids, alkaloids, sugars, organic phenolic acids, and tannins.[23] The alkaloids are the major portion of the compounds contained therein, that cause toxicity.[23] However, the herb has been used for some time to treat liver disease, asthma, skin diseases, and various other disease.[23] The ephedrine component can precipitate in the urine to form crystals, followed by kidney stones. The excessive use of ephedrine or prolonged use is shown to increase the appearance of adverse consequences. Some investigators contend that the non-alkaloid components of Ephedra can be used to acquire the beneficial activities associated with Ephedra administration.[23]

Various case reports of patients that have been self administering Ma Huang extract, that contain ephedrine, show alpha and beta catecholamine effects, and have developed nephrolithiases.[24] Ma Huang is considered to be a "natural product" and is often embraced by the "alternative medicine genre".[24] It is the "alternative medicine" genre that has promoted the use of ephedrine and it's metabolites for asthma, energy enhancement, sexual enhancement, and weight loss.[24]

Ephedrine is a sympathomimetic amine, that is a plant alkaloid and has been utilized for various pathologies, such as asthma, colds, narcolepsy treatment, in sports medicine, athletic enhancement, obesity management, etc.[25] Some investigations have indicated that its principal action mechanism is a direct adrenergic activity and an indirect action of releasing norepinephrine and epinephrine.[25] Again, other investigators have recognized the potential serious side effects of drug abuse (and drug interactions), stroke, and heart attack.[25]

DETECTION AND ASSAY BY GAS CHROMATOGRAPHY

For analysis of dietary supplements, a methodology utilizing gas chromatography-mass spectrometry and that determines multiple components with ephedrine alkaloids, is shown to detect: ephedrine, pseudoephedrine, norpseudoephedrine, norephedrine, and methylpseudoephedrine.[26] The investigator utilized a liquid-liquid extraction in alkaline conditions with chloroform/isopropanol (9:1, v/v), with 3,4-methlenedioxylpropyl amphetamine as internal standard.[26] The chromatography was performed with fused capillary column and with the analytes derivatized with pentafluoropropionic anhydride, were then targeted using selected-ion-monitoring (SIM) mode.[26] Mean recovery ranged between 65.7% and 81.3% for the different analytes in the dietary supplements with the quantification limits at 0.3 microgram/mg for ephedrine, 0.06 microgram/mg for pseudoephedrine, 0.04 microg/mg for norpseudoephedrine, as well as norephedrine, and methylpseudoephedrine.[26] This method was shown to be efficacious for analysis of Ma Huang and *Sida Cordifolia*.[26]

Another methodology using gas-chromatography-mass spectrometry analysis following extraction with ammoniacal chloroform solvent and two-stage derivatisation.[27] Consequently there is a production of the O-trimethylsilyl, N-trifluoracetyl derivatives (O-TMS, N-TFA) for the primary and secondary amine alkaloids, and the O-TMS derivatives for the tertiary amine alkaloids.[27] The methodology is shown to provide quantitative outcomes for ephedrine and pseudoephedrine, and good estimates for the four minor alkaloids.[27] This methodology can be applied for rapid screening of the ephedrine alkaloids in whole Ephedra plants, liquid plant extracts, dried powder plant extracts and various Ephedra containing dietary supplements.[27]

DETECTION AND ASSAY BY HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

A method for assay by high performance liquid chromatography (HPLC), included the elution of the analyte and detection by ultraviolet light detector, at 255 nm.[28] It was necessary to prepare the stock solution of this ephedrine alkaloid in solvent conditions of 10% ethanol (v/v) and 90% water (v/v), and at a concentration of 7.1568×10^{-2} molar. The test samples of ephedrine hemihydrate that were injected into HPLC instrument were in a solvent that consisting of 90% (v/v) water and 10% ethanol (v/v).[28] However, the solvent utilized for column of the HPLC instrument was 5% ethanol, 1% glacial acetic acid (v/v), and 94% water (v/v). The limit of detection (LOD) was found to be 2.9833×10^{-5} molar and the limit of quantitation (LOQ) was found to be 8.9500×10^{-5} molar.[28] A standard curve presented showed a coefficient of determination of $R^2 = 0.9857$,

which indicates that the model describes 98.57% variance in the dependent variable (peak area) that is predictable from the independent variable (molar concentration).[28] The Pearson r correlation coefficient of this standard curve is 0.9928, indicating very high positive correlation. With the (LOD) determined to be 2.9833×10^{-5} molar, then the limit of quantitation (LOQ) is determined to be 10 times the baseline.[28,29] The average percent recovery is 100% with standard deviation of 3.7%.[28]

In another study for assay of alkaloids by high-performance liquid chromatography-UV, the assay from commercial products for the following components in the products was accomplished: ephedrine and pseudoephedrine, norephedrine, norpseudoephedrine, methylephedrine, and methylpseudoephedrine.[9] Extracts obtained from samples were treated with a solid phase extraction under a strong-cation exchange column for removal of interfering components.[9] Using a polar-embedded phenyl column with UV detection at 210 nm, the reproducibility relative standard deviation ranged from 0.64% to 3.0.% for ephedrine, of a high protein drink mix.[9] Recoveries ranged from 84.7% to 87.2% for ephedrine.[9] The assay of ephedrine alkaloids from Ephedra plant material with derivatives was done using pentafluorophenylpropyl stationary phase.[30] HPLC assay was carried out utilizing Discovery HS F5 column (150 mmx4.6 mm i.d., 5 microm), with an isocratic mobile phase of ammonium acetate (7mM) in acetonitrile-water (90:10, v/v), and at a flow rate of 1.0 ml/min. The column temperature was pre-set at 45 degrees C. and with UV detection at 215 nm and 225 nm. This gave a total analysis time of 16 min.[30]

Another assay methodology, from *Ephedrae Herba,* for a total of five alkaloids; norephedrine, norpseudoephedrine, ephedrine, pseudoephedrine, and methylephedrine, was developed applying a perfluorooctyl column.[31] A mobile phase was comprised of acetonitrile and 15 mM ammonium trifluoroacetate eluting the targets in isocratic elution mode. This method was validated for linearity ($R > 0.999$), repeatability, intraday and interday precision, recoveries with trueness (93.87%-110.99%), limits of detection (5.35-5.76 µg/mL), and limits of quantification (20 µg/mL).[31] Another method was effective in determination of ephedrine alkaloids and synephrine from dietary supplements by column-switching cation exchange high performance liquid chromatography.[8] This methodology used scanning wavelength UV and fluorescence detection.[8]

DETECTION OF ALKALOIDS BY LIQUID CHROMATOGRAPHY

A study was accomplished that evaluated the accuracy and precision of a methodology for ephedrine-type alkaloids: norephedrine, norpseudoephedrine, ephedrine, pseudoephedrine, methylephedrine, and methylpseudoephedrine in dietary supplements as well as various botanicals.[32] Quantitation of the amount of ephedrine-type alkaloids present was determined by utilizing liquid chromatography and a tandem mass selective detection.[32] Dilution of the samples were effectuated too reflect a concentration of 0.0200 microgram/mL to 1.00 microgram/mL for each alkaloid.[32] Using an internal standard the alkaloids were separated using a 5 microm phenyl LC column having an ammonium acetate, glacial acetic acid, acetonitrile, and water mobile phase.[32] The amount of ephedrine-type alkaloids present was determined using liquid chromatography with tandem mass selective detection.[32]

In another study using liquid chromatography with tandem mass selective detection, the method assayed for ephedrine-type alkaloids: norephedrine, norpseudoephedrine, ephedrine, pseudoephedrine, methylephedrine, and methylpseudoephedrine.[33] However, this methodology assayed from human urine and plasma.[33] Here the test samples were diluted to obtain a concentration of 5.00-100 ng/mL for every alkaloid.[33] Application of an internal standard was done and the alkaloids were separated using a 5 micromphenyl LC column having an ammonium acetate, glacial acetic acid, acetonitrile, and water mobile phase.[33]

CONCLUSION

Ephedrine is among six compounds that can be harvested from the plant *Ephedra sinica.* There are clinical uses for the alkaloids that have included the following uses: for allergies, hay fever, asthma, and bronchitis associated with flu and swine flu. However, there exists significant side effects which do encompass significant safety hazards such as: cardiovascular effects, hypertension, myocardial infarction, seizures, and strokes that can be fatal. Some studies have concluded that athletes who utilize ephedrine for the physiological advantages, risk potential significant harm for little actual benefits. Various other physiological effects of ephedrine/ephedra include: increase in heart rate, increase in blood pressure, increase cardiac output, broncho-dilation, stimulation, diuretic, urinary retention, and appetite suppressant.

Various methodologies for assay of these alkaloids have been shown to be accurate and sensitive. Types of assay methods include high performance liquid chromatography, liquid chromatography, and gas chromatography. This compound has been shown to express beneficial physiological activity, but in addition, adverse, dangerous, and life threatening side effects.

Further study is desired to ascertain the potential medicinal benefits of this alkaloid, in addition to limitations of dosage and usage.

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