Is the 5-iodo-2-aminoindan (5-IAI) the New MDMA?

Coppola M* and Mondola R

*Department of Addiction, ASL CN2, Viale Coppino 46, 12051, Alba (CN), Italy
1Department of Mental Health, ASL CN1, Via Torino 70/B, 12037, Saluzzo (CN), Italy

Abstract

Between 1997 and 2011, more than 200 new substances have been officially notified in European Union via the Early Warning System with the largest number of compounds ever reported in a single year in 2011 (49 substances). In 2010, an internet snapshot anticipated the presence of 5-iodo-2-aminoindan (5-IAI) within the recreational drug market. In 2011, this compound, a psychoactive analog of p-iodoamphetamine, was identified in United Kingdom. The aim of this paper is to summarize the clinical, pharmacological and toxicological information currently available about this new potential recreational drug.

Keywords: 5-iodo-2-aminoindan; 5-IAI; MDMA analogues; Research chemicals; Legal highs

Introduction

Council Decision 2005/387/JHA defines a new psychoactive substance as a new narcotic drug or a new psychotropic drug in pure form or in a preparation, that has not been scheduled under the 1961 United Nations Single Convention on Narcotic Drugs, and that may pose a threat to public health comparable to the substances listed in Schedule I, II or IV (new narcotic drug) or under the 1971 United Nations Convention on Psychotropic Substances, and that may pose a threat to public health comparable to the substances listed in Schedule I, II, III or IV (new psychotropic drug). A preparation is defined as a mixture containing a new psychoactive substance (Article 3) [1]. In the last years, the spread of new psychoactive drugs sold as legal substances producing the same effects of traditional and illicit drugs, has been continually on the rise. Between 1997 and 2011, more than 200 new substances have been officially notified in European Union (EU) via the Early Warning System (EWS) with the largest number of compounds ever reported in a single year in 2011 (49 substances) [2]. These compounds are frequently classified as research chemicals and labelled as "not for human consumption". As demonstrated by several evidences, research chemicals are generally sold via web-shops or in specialized street shops known as "smart or head shops". In particular, online market is able to respond rapidly to changes in the legal status of the psychoactive drugs offering for sale new legal alternatives [1-4]. In 2010, an internet snapshot, a multilingual internet monitoring used by the European Monitoring Centre for Drugs and Drug Abuse (EMCDDA) for rapid assessments of the online availability of psychoactive substances undertaken during a limited time window, anticipated the presence of 5-iodo-2-aminoindan (5-IAI) (Figure 1) within the recreational drug market [5]. In 2011, this compound, a psychoactive analog of p-iodoamphetamine (PIA) (Figure 2), was identified in United Kingdom (UK) [1]. To date, there is very little information about the pharmacological and toxicological properties of this substance. Furthermore, there are no data on acute and chronic effects of 5-IAI in humans. As suggested by users, 5-IAI can produce 3,4-methylenedioxymethamphetamine (MDMA)-like effects, and is used as a club drug in substitution of other amphetamine and methamphetamine derivatives [6-8]. The legal status of this compound meets the growing demand for legal amphetamines and is a risk factor for the spread of this MDMA-like compound among young people [9,10]. The use of amphetamine and methamphetamine derivatives is a public health concern in many countries [11,12]. It is estimated that around 12 million European adults aged 15-64 have tried amphetamines at last once in their lives [11]. Prevalence levels of more than 3% have been reported by the Czech Republic and Denmark while UK, Estonia and Bulgaria have reported a prevalence of more than 2% [11]. United Office on Drugs and Crime has estimated that in 2010, the number of MDMA-group users ranges between 10.5 and 25.8 million people worldwide (people aged 15-64) [13]. Overall, these substances are considered club drugs and are used by young people in so called "rave or party scenes". Furthermore, their use is also high among person infected with human immunodeficiency virus (HIV) [12]. The aim of this paper is to summarize the clinical, pharmacological and toxicological information currently available about this new potential MDMA substitute.

Methods

Literature searches were performed using the following electronic databases: PubMed, Embase, Psychnfo, Cochrane database. The keywords used were: 5-iodo-2-aminoindan, 5-IAI, 3-dihydro-5-iodo-1H-inden-2-amine 2-Amino-5-iodoindane, 5-Iodo-2-aminoindane, 5-IAI, PIA, MDMA substitute.
and p-iodoamphetamine analogues. Furthermore, in order to conduct a research of data as extensively as possible, we also explored the information present within the unconventional references such as drug forum, web-journals and chemical databases. No restriction in language was used in our research.

Chemistry

5-IAI, IUPAC name 2,3-dihydro-5-ido-1H-inden-2-amine, is a rigid analogue of PIA belonging to the phenylethylamine family [14]. This substance, molecular formula C9H10I1N, was synthesized by Nichols et al. at Purdue University in 1990s as a non-neurotoxic analogue of PIA useful to visualize serotonin binding sites in brain with autoradiography techniques [15]. 5-IAI is generally supplied as a crystalline solid with a molecular weight of 259.087 g/mol, a boiling point of 299.224°C at 760 mmHg, a density of 1.749 g/cm³, a flash point of 134.766°C, and a molar volume of 148.16 cm³ [14,16,17]. The drug is sold as a hydrochloride salt soluble in organic solvents such as dimethyl sulfoxide and dimethyl formamide with a solubility of approximately 0.5 mg/ml and 0.3 mg/ml, respectively [14].

Pharmacology and toxicology

There are no published data on pharmacological and toxicological effects of 5-IAI in humans. In vitro studies performed on rat brain cortical synaptosomes have demonstrated that 5-IAI is a selective serotonin (5-HT) uptake inhibitor, with a potency compared to 75% of that displayed by p-chloroamphetamine (PCA), and a potent releaser of non-vesicular 5-HT. On the other hand, 5-IAI was a weak inhibitor of dopamine and noradrenaline uptake [15,18]. In drug discrimination paradigm in rats trained to discriminate saline solution from (MDMA) or saline solution from methylbenzodioxolylbutanamine (MBDB), 5-IAI was behaviorally active and fully substituted in both groups of animals. However, it was significantly less potent than other amphetamine derivatives such as PIA and PCA [15]. In another study, one week after subcutaneous administration dose of 5-IAI (40 mg/kg) to rats a small but significant reduction in 5-hydroxyindoleacetic acid (5-HIAA; the main 5-HT metabolite) levels in the cerebral cortex, and the number of 5-HT uptake sites in the hippocampus was observed [15]. In the evaluation of these results, it must be considered that the dose of 40 mg/kg is 20-40 fold higher than a behaviorally active dose, and many amphetamine derivatives are lethal at this dosage [15,18,19].

Clinical effects

Considering the absence of formal studies about the clinical effects of 5-IAI in humans, we explored the users reports present within the drugs forum in order to reconstruct the pattern of acute toxicity, desirable, and undesirable effects induced by this substance. 5-IAI is generally considered a less potent MDMA substitute producing pleasant stimulant effects. Desirable effects include: mild euphoria, sociability, increased self-confidence, increased desire to dance, increased intensity of the perceptions and colors, slight distortion of time and space. Users report a rapid onset of action even after ten minutes with a peak effect that lasts about one hour. The comedown is normally not so unpleasant, and it is similar to a standard hangover [6-8,20]. In contrast, some users reported that effects are not satisfactory, and cannot compete with those exerted by MDMA. Furthermore, users also described negative effects of 5-IAI, such as: anxiety, psychomotor agitation, panic attacks, tachycardia, headache, insomnia, prolonged hallucinations, and derealization [8,21].

Modality of use

5-IAI is generally sold via research chemicals suppliers as a powder and administered orally or via insufflation. There are no reports of injecting use of this substance. The most common dosage range is between 20-200 mg in a single session, however a re-dosing is also possible. Sometimes 5-IAI is taken together with other drugs of abuse, such as MDMA and others stimulants (to enhance the psychotropic effects), benzodiazepines, cannabis, alcohol (to reduce the side effects) [6-8,20].

Epidemiology

Despite it was synthesized in 1990s, the popularity of 5-IAI as drug of abuse increased since 2010 as demonstrated by the online discussion within the drugs forum [6-8,20,21]. The use of Google Insights for Search, a google application for compare search volume patterns across specific regions, categories, time frames and properties, has shown that numbers of searches increased since 2010 [22].

Medical use

Although some aminoindans have been investigated for their important bronchodilating and analgesic effects [23], to date, there are no approved indications for 5-IAI use in humans.

Discussion

To the best of our knowledge, this is the first article in the literature summarizing the clinical, pharmacological and toxicological information currently available about 5-IAI. Despite being marketed as research chemical and labelled as “not for human consumption”, this substance is used by club drug users as MDMA or mephedrone substitute. In vitro and animal model studies have demonstrated that 5-IAI acts as both a non-vesicular monoamines releaser, and a monoamines uptake inhibitor. It is considered less potent and neurotoxic than MDMA, however, pharmacological and toxicological studies have not assessed many parameters that are essential for determining its neurotoxicity in human. First, the studies have not completely investigated the activity of 5-IAI on dopaminergic, serotonergic, and noradrenergic systems. Second, no study has investigated its pharmacokinetic properties in vivo. Third, there is no information about the effects of this substance in combination with other recreational drugs. Fourth, no study has investigated the effects of 5-IAI on oxidative system, neuroinflammation, apoptosis, and glutamatergic transmission. Several data have evidenced that oxidative system, neuroinflammation, apoptosis, and glutamatergic transmission play a key role in the neurotoxicity induced by amphetamine derivatives [24-35]. In addition, the legal status of this substance and the presence of studies showing its low serotonergic neurotoxicity could be wrongly considered by users as a guarantee of safety and could encourage people to experience the substance. Finally, considering that 5-IAI is principally sold via-internet, there is a high risk of a rapid spread of this product among drug users.

Conclusion

5-IAI is a research chemical recently appeared within the recreational drug market. Clinical information emerged by users reports suggest that it can produce MDMA-like effects. Although some studies have highlighted that 5-IAI is less neurotoxic than MDMA, there are no evidences demonstrating its safety in human. Thus, drug users must be discouraged from taking this substance because it could be dangerous to health. A better international cooperation is of great importance in order to monitoring and preventing the spread of this new potential recreational drug.
Limitation

Most of the works describing new recreational drugs show significant limitations mainly related to the absence of a substantial formal literature. Pharmacological and toxicological information are generally derived from similar drugs while clinical effects are derived from users reports present within the drugs forum. Drugs forum are rich in information, but it is difficult to separate the clinical data from gossip. In addition, the substances declared by users can not be analytically identified, so the effects reported could be related with the consumption of other drugs or mixtures of drugs. Thus, preliminary reports about new drugs of abuse must be considered a starting point and a stimulus for the realization of formal studies.

Conflict of Interest

The authors declare that there are no conflicts of interest.

References

16. 5-ido-2-aminoindan.
17. 5-idoindan-2-amine.