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Mini review

5-Iodo-2-aminoindan (5-IAI): Chemistry, pharmacology, and toxicology of a research chemical producing MDMA-like effects

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HIGHLIGHTS

- 5-Iodo-2-aminoindan (5-IAI) is a new designer drug of abuse.
- This substance is marketed via online research chemicals stores.
- 5-IAI is used as alternative to other illicit club drugs.
- 5-IAI can produce MDMA-like effects.
- Preliminary evidence suggest a low risk of long term neurotoxicity.

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ABSTRACT

In 2010, an internet snapshot of EMCDDA anticipated the presence of 5-iodo-2-aminoindan (5-IAI) within the recreational drug market. In 2011, this compound, a psychoactive derivative of 2-aminoindane, was identified in recreational products sold in the United Kingdom. 5-IAI is a rigid analogue of p-iodoamphetamine producing MDMA-like effects. The aim of this paper is to summarize the clinical, pharmacological, and toxicological information about this new potential drug of abuse.

Contents

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1. Introduction

Legal highs are both synthetic derivatives and vegetable compounds mimicking the psychotropic effects of traditional and illicit drugs (Zawilska, 2011). In the last years the spread of these substances has been continuously on the rise among young people becoming a public health concern (Gibbons, 2012). A flash Eurobarometer Survey (a cross-national longitudinal study) conducted in 2011 has shown that about 5% of the interviewed European population between 15 and 24 years reported had used new recreational drugs at least once (europa.eu, 2011). In the United Kingdom (UK), Latvia, and Poland the percentage was about 10%, while in Ireland was 16% (ec.europa.eu, 2011). Conversely, the study highlighted that Finland, Italy, and Greece were the countries in which the use of legal highs was less widespread (europa.eu, 2011). Over the months, the scientific literature has been enriched by clinical reports describing cases of severe acute intoxication and deaths related to the consumption of products containing new recreational substances (McQuade et al., 2012; Dargan et al., 2012; Shields et al., 2012; Wood et al., 2009, 2012a,b; Wood and Dargan, 2012; Schifano et al., 2012; Gallagher et al., 2012; Harris and Brown, 2012; Seetohul et al., 2012; Kronstrand et al., 2011; Murray et al., 2012; Pant et al., 2012; Pearson et al., 2012; Sauer et al., 2011; Nielsen et al., 2010; Andreasen et al., 2009). Between 1997 and 2012 more than 200 new substances have been officially notified in the European Union (EU) via the Early Warning System (EWS) showing an increasing trend from year by year (emcdda, 2012). In 2011 have been notified 49 new drugs that represent the largest number ever reported in a single year (emcdda, 2012). All the new compounds reported in 2011 were synthetic and for two thirds were constituted by two groups of substances: synthetic cannabinoids (23 substances), and synthetic cathinones (8 substances) (emcdda, 2012). These new compounds are principally sold via web shops or in specialized street shops known as "smart or head shops" (emcdda/new-drugs-and-trends, 2011). In particular, the number of online stores is constantly on the rise suggesting that this market is one of the most used by legal highs users. The number of online shops offering at least one psychoactive substance or product rose from 314 in January 2011 to 693 in January 2012 (emcdda, 2012). 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) (Fig. 1) within the recreational drug market. In 2011, this compound, a psychoactive derivative of 2-aminoindane (Fig. 2), was identified in recreational products sold in the UK (emcdda, 2012; emcdda/snapshot, 2011). There is a paucity of information about the pharmacology and toxicology of this substance and there are no data about its acute and chronic effects in human. Because of its 3,4-methylenedioxymethamphetamine (MDMA)-like effects (Nichols et al., 1991), club drug users report that 5-IAI is used in substitution of illicit methamphetamine derivatives (researchchemicalsguid, 2012; bluelugt, 2010; partyvibe, 2010; drugs-forum/126295, 2010; hipforums, 2010). The consumption of club drugs is a public health concern worldwide (drugabuse.gov, 2012; Castro et al., 2012; Guerreiro et al., 2011; Karila and Reynaud, 2011). It is estimated that around 12 million Europeans aged 15–64 have tried amphetamines at least once in their lives (emcdda/amphetamines, 2011). United Nations Office on Drugs and Crime (UNODC) has estimated that in 2010, the number of MDMA group users among people aged 15–64 ranges between 10.5 and 25.8 million worldwide (unodc, 2010). Czech Republic and Denmark have reported a prevalence of 3% while Estonia, Bulgaria, and UK have reported a prevalence of 2% (emcdda/amphetamines, 2011). Furthermore, club drugs are frequently used by people infected with human immunodeficiency virus (HIV) (Zuckerman and Boyer, 2012; Yamamoto et al., 2010). In addition, in recent years various new designer drugs such as synthetic cathinones (Coppola and Mondola, 2012a; Winstock et al., 2011), pyrrolidinophenones (Meyer and Peters, 2012), and pipradrol derivatives (Coppola and Mondola, 2012b) have gained in popularity among youth as MDMA substitute. Considering this worrying scenario, the legal status of 5-IAI meets the growing demand for legal club drugs and represents a risk factor for the spread of this MDMA-like compound. The aim of this paper is to summarize the clinical, pharmacological, and toxicological information about this new potential drug of abuse.

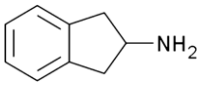

Fig. 1. 5-Iodo-2-aminoindan.

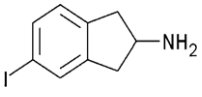

Fig. 2. 2-Aminoindane.

2. Methods

Literature searches were performed using the following electronic databases: PubMed, Embase, PsycINFO, Cochrane database. The keywords used were: 5-iodo-2-aminoindan, 2-amino-5-iodoindane, 5-IAI, 3-dihydro-5-iodo-1H-inden-2-amine, p-iodoamphetamine analogues, aminoindanes, 2-aminoindane derivatives, MDMA analogues. The titles and abstracts of the resulting articles were examined to exclude irrelevant studies. The full texts of selected articles were read to extract information on the topic of interest. Bibliographies and citation sections of retrieved articles were also reviewed for additional pertinent studies. Furthermore, in order to conduct a research of data as extensively as possible, adjunctive information were carried out from websites of unconventional references such as drug forum, chemical databases, and web-journals. No restriction in language was used in our research.

3. Aminoindanes

Aminoindanes are a group of synthetic compounds characterized by the presence of the phenethylamine skeleton. These substances may be also considered as indane analogues of the phenylisopropylamines (ewsd, 1944). 2-Aminoindane, IUPAC name 2,3-dihydro-1H-inden-2-amine, is the indane analogue corresponding to amphetamine (ewsd, 1944). Furthermore, this compound shows a structural correlation with the 2-amine-1-indanol [IUPAC name (1R, 2S)-1-amine-2,3-dihydro-1H-inden-2-ol] and phenylpropanolamine [IUPAC name (1S, 2R)-2-amino-1-phenylpropan-1-ol] (ewsd, 1944). 2-Aminoindane is a mild central nervous system (CNS) stimulant exhibiting both a slight bronchodilator activity and a strong analgesic action not antagonized by nalorphine (Salomons and Sam, 1973; Witkin et al., 1961; Levin et al., 1944). In addition, it is used as a starting point for the synthesis of other aminoindanes (Cannon et al., 1980). Aminoindanes are a class of substances producing a relatively selective potent effect on serotonin release and re-uptake (Sainsbury et al., 2011). Furthermore, unlike the corresponding amphetamines, some studies in animal models have shown that these substances do not produce any long term neurotoxicity (Johnson et al., 1991a; Monte et al., 1993; Marona-Lewika et al., 1996). Some aminoindanes have been investigated as bronchodilator and analgesic agents (Salomons and Sam, 1973), and most recently, as neuroprotective (Bar-Am et al., 2010), and antipsychotic medicines (Graham et al., 2007). Aminoindanes have been synthesized using indanone, indene or after intramolecular cyclization of dihydrocinnamic acid. Using dihydrocinnamic acid, the first step requires the conversion of the carboxylic acid to an acid chloride through a chlorinating reagent such as phosphorus