Drug and Alcohol Dependence xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Review

Ibogaine for treating drug dependence. What is a safe dose?

L.J. Schep[a,*], R.J. Slaughter[a], S. Galea[b,c], D. Newcombe[c]

[a] National Poisons Centre, Department of Preventive and Social Medicine, University of Otago, Dunedin, New Zealand
[b] Community Alcohol and Drug Services, Waitemata DHB, New Zealand
[c] Social and Community Health and Centre for Addiction Research, University of Auckland, New Zealand

ARTICLE INFO

Article history:
Received 12 May 2016
Received in revised form 4 July 2016
Accepted 4 July 2016
Available online xxx

Keywords:
Ibogaine
Drug dependence
QT prolongation
Purkinje cells
Potassium voltage gated human
Ether-à-go-go-Related gene (hERG) channel

ABSTRACT

The indole alkaloid ibogaine, present in the root bark of the West African rain forest shrub *Tabernanthe iboga*, has been adopted in the West as a treatment for drug dependence. Treatment of patients requires large doses of the alkaloid to cause hallucinations, an alleged integral part of the patient's treatment regime. However, case reports and case series continue to describe evidences of ataxia, gastrointestinal distress, ventricular arrhythmias and sudden and unexplained deaths of patients undergoing treatment for drug dependence. High doses of ibogaine act on several classes of neurological receptors and transporters to achieve pharmacological responses associated with drug aversion; limited toxicology research suggests that intraperitoneal doses used to successfully treat rodents, for example, have also been shown to cause neuronal injury (purkinje cells) in the rat cerebellum. Limited research suggests lethality in rodents by the oral route can be achieved at approximately 263 mg/kg body weight. To consider an appropriate and safe initial dose for humans, necessary safety factors need to be applied to the animal data; these would include factors such as intra- and inter-species variability and for susceptible people in a population (such as drug users). A calculated initial dose to treat patients could be approximated at 0.87 mg/kg body weight, substantially lower than those presently being administered to treat drug users. Morbidities and mortalities will continue to occur unless practitioners reconsider doses being administered to their susceptible patients.

1. Introduction

The indole alkaloid ibogaine is the most abundant hallucinogenic constituent present in the root bark of the West African rain forest shrub *Tabernanthe iboga.* Extracts derived from this plant have a long history of traditional medicinal and ceremonial use by local Bwiti people (Alper et al., 2008). Since approximately 1962, ibogaine has been employed in Western jurisdictions, such as Europe and the United States (Alper et al., 2001), as a treatment for drug dependence particularly to treat the cravings and withdrawal that accompany opioid and cocaine dependence (Lotsof and Alexander, 2001).

Nevertheless, evidence of its efficacy has been restricted to case studies in patients withdrawing from drug dependence, suggesting apparent reduction in withdrawal severity (symptoms) and drug seeking for up to 72 h post-treatment (Alper, 2001; Alper et al., 2008; Galea et al., 2011). Ibogaine appears to have a dose-dependent effect with low doses reportedly acting as a stimulant and higher doses being hallucinogenic (Alper et al., 2008; Mash et al., 2000). Patients undergoing treatment report oneirophrenic effects that can endure for 4–8 h post-ingestion followed by an evaluation phase, during which patients report a high level of mental activity, terminating with a residual stimulation state that may last up to 72 h (Lotsof and Alexander, 2001).

However, in addition to ibogaine's hallucinogenic properties, which allegedly contribute to its efficacy in treating drug addiction, case reports consistently report evidences of ataxia, gastrointestinal distress, ventricular arrhythmias and sudden and unexplained deaths (Alper et al., 2012). Given the risks associated with its use, this paper seeks to explore the drug's toxicity and show that doses employed in recovery clinics to treat patients are within values that demonstrate mammalian toxicity.

2. Mechanism of action

Ibogaine has a complex pharmacology and the underlying mechanisms that mediate its physiological and psychological effects are not well elucidated. Investigations of the pharmacological activity of ibogaine and its putative anti-addictive properties suggest that its action involves mediation of several classes of neu-

* Corresponding author.
E-mail address: leo.schep@otago.ac.nz (L.J. Schep).

http://dx.doi.org/10.1016/j.drugalcdep.2016.07.005
0376-8716/

rological receptors and transporters, including the sigma-2, kappa- & mu-opioid, $5HT_2$ and $5HT_3$ receptors, $\alpha 3\beta 4$ nicotinic receptors, and the *N*-methyl-D-aspartic acid (NMDA) ion channel (Glick et al., 2002; Maciulaitis et al., 2008).

There is some suggestion that ibogaine is a Sigma-2 selective ligand (Bowen et al., 1995); the receptor itself has a putative role in modulating cytotoxicity and cell death (Bowen, 2001) and the neurotoxic effects of ibogaine may be due, in part, to agonist action at this receptor (Bowen, 2001; Glick et al., 2001). Radioligand binding assays have demonstrated ibogaine binding to kappa- and mu-opioid receptors at low concentrations (Sweetnam et al., 1995), and it is an antagonist at nicotinic receptors and the NMDA receptor coupled ion channel (Glick et al., 2002; Popik et al., 1994). Research has suggested the combination of these receptor site activities may have a role in promoting anti-addictive properties in animal models (Glick et al., 1997). Ibogaine also acts upon 5-HT_2 and 5-HT_3 receptors and binds to the serotonin transporters, thereby preventing serotinin reabsorption, similar to a serotonin-selective reabsorption inhibitor (such as fluoxetine; Baumann et al., 2001). Evidence suggests there is a dose-related increase of extracellular 5-HT in the nucleus accumbens (Baumann et al., 2001).

Radio-ligand binding of ibogaine to these various receptor sites suggests IC_{50} concentrations necessary to achieve pharmacological activity range from 1 to 10 μM (Baumann et al., 2001). In comparison, oral administration of 50 mg/kg to rats has, for example, achieved ibogaine concentrations in the brain ranging from 4 to 17 μM (Staley et al., 1996), suggesting doses of ibogaine that achieve drug aversions in animal models are within those values necessary to achieve micromolar-affinity binding *in vitro* (Baumann et al., 2001).

3. Toxicity

There is limited information available on the toxicity of ibogaine in mammalian species. A summary of the investigations involving acute toxicity to ibogaine are presented in Table 1. Investigations have been undertaken with rats and mice, and, depending on the route of exposure, lethal doses varied from 145 to 175 mg/kg and 263 to 327 mg/kg body weight by the intraperitoneal (IP) and oral routes, respectively. The no observable adverse effect level (NOAEL), defined as the highest dose of a chemical which does not cause an observable adverse effect on a test animal, was 25 mg/kg IP (Xu et al., 2000), where the measurable parameter of adverse effect was evidence of neuropathology (purkinje cells) in the rat cerebellum. The lowest observable dose to cause observable neuronal injury in this study was reported to be 50 mg/kg IP. Other research suggests elevated acute doses (100 mg/kg, IP, rat) of ibogaine can cause tremors with resultant degeneration of purkinje cells (O'Hearn and Molliver, 1993). Chronic administration of 10 mg/kg IP in the rat did not show evidence of neuropathology (Helsley et al., 1997).

Tremors are a common symptom following acute ibogaine administration in rodents, occurring as low as 12 mg/kg subcutaneous (SC; Zetler et al., 1972), though other authors have reported this phenomenon at 40 and 80 mg/kg doses (IP; Glick et al., 1992, 1991).

Mild cardiotoxicity has also been evident in animal models. Administration of 40 mg/kg IP in rats, showed no changes in resting heart rate or blood pressure whereas doses of 100 and 200 mg/kg demonstrated bradycardia without evidence of hypotension (Glick et al., 2000). Nevertheless, another investigation demonstrated hypotension and bradycardia in the same species at 50 mg/kg by the intraperitoneal route (Binienda et al., 1998). Unfortunately, the authors had not undertaken ECG profiles to identify any evidences of dysrhythmias.

4. Correlating animal toxicity to human clinical trials

Animal investigations can assist in assessing the toxicology of a drug in living systems. To establish the risk of toxicity to humans in clinical trials, for example, animal studies that establish a NOAEL can be applied to human investigations, following the application of an appropriate safety factor. This is determined by converting the animal NOAEL to a human equivalent dose (HED). Suggested values are derived by dividing the NOAEL by a safety factor that can range from 10 through to 50, depending on results from the preclinical investigations, such as the gradient of the dose response curve (FDA, 2005).

There is very limited information on the animal toxicity of ibogaine and less so by the route of ingestion. The only report that has established a NOAEL for ibogaine was determined following administration by the intraperitoneal route (see Table 1), which established a dose of 25 mg/kg. Some authors have suggested that on the basis of this experiment it is safe to administer 25 mg/kg orally for the treatment of drug dependency (Mash et al., 1998). However, there are flaws in this argument. Firstly, a dose administered by one route of exposure (IP) cannot be compared with another route (oral). Secondly, and more importantly, estimates of toxicity cannot solely depend on doses given to animals; there need to be, as described above, additional safety factors installed into the calculation. For example, if a safety factor of 30 was to be applied to this value (the approximate median value between values ranging from 10 to 50), then a theoretical dose of 0.83 mg/kg could be considered acceptable for a starting dose for human clinical trials, if administration of the drug was by the IP route.

However, a NOAEL for ibogaine has not been established for the oral route. The lowest reported oral dose of ibogaine that can cause lethality in animals is 263 mg/kg (Table 1). In the absence of any other data, this dose should be divided by several safety factors to estimate a considered dose by the oral route. Such factors would include dividing by 10 for intra-species variability, another 10 for inter-species variability (animal model to humans) and in some instances another value, such as 3, for susceptible people in a population (such as long-term drug users that have medical comorbidities; Alper et al., 2012) or to account for possible weaknesses in the design and application of the animal investigation (IPCS, 1994). Based on a 263 mg/kg oral investigation in mice, an initial starting dose, possibly acceptable for human exposure, could therefore be 0.87 mg/kg.

Although this suggested dose is theoretical, it is not surprising that the clinical trial approved by the U.S. Food and Drug Administration in 1995 recommended similar doses, to treat patients with a history of drug abuse; doses were initiated at 1–2 mg/kg body weight (Mash et al., 1998). Additionally, a recently completed controlled clinical trial employed a 20 mg dose of ibogaine (assuming an 80 kg weight, this would equate to 0.25 mg/kg), which was well tolerated without evidence of host toxicity (Glue et al., 2015). In contrast, doses used to treat patients in unregulated treatments have ranged from 6 to 30 mg/kg. (Alper, 2001), within doses that have shown evidence of toxicity in animal models.

5. Human toxicity

Doses necessary to achieve efficacy in rodents are within those that cause observable toxicity. A number of studies, such as summarised by Zubaran (2000), for example, suggest aversions to various drugs of abuse were achieved in animal models at 40 and 80 mg/kg IP; these are, however, within doses that have been shown to cause neuronal injury by the same route of exposure (Xu et al., 2000).

Please cite this article in press as: Schep, L.J., et al., Ibogaine for treating drug dependence. What is a safe dose? Drug Alcohol Depend. (2016), http://dx.doi.org/10.1016/j.drugalcdep.2016.07.005