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Genders and the concurrent use of cocaine and alcohol: Pharmacological aspects

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ABSTRACT

Aims: Gender-related differences in the pharmacological effects of addictive drug are an emerging issue. This review examines gender differences in both pharmacokinetic and pharmacodynamic aspects of alcohol and cocaine intake since they cause complex pharmacological interactions, not least the formation of the active metabolite cocaethylene.
Methods: The MEDLINE database was searched from 1990 to 2014 in order to find articles related to gender differences in alcohol, cocaine and cocaethylene pharmacokinetics and pharmacodynamics.
Results: Besides the well known gender differences in alcohol pharmacokinetics, women appear more susceptible to alcohol-mediated brain damage and seem to suffer more than men the acute effects of alcohol on hepatic and gonadal hormones. No significant gender differences have been found in the pharmacokinetics of cocaine taken alone; yet, in women pharmacological sensitivity to the drug seems to vary in relation to menstrual cycle; moreover, progesterone attenuates subjective effects of cocaine in women. Higher ratings at a subjective measure of mental/physical well-being have been observed in women when given cocaine and alcohol, alone or in combination. Finally, among subjects dependent on both alcohol and cocaine, men only benefit from naltrexone, whereas women used more cocaine during the trial and were less compliant to therapy than men.
Conclusions: The observed subtle gender differences in the pharmacokinetics and pharmacodynamics of both alcohol and cocaine may have no subtle influence on the natural history of the co-abuse of the two drugs by women.

Introduction

It has been estimated that 1% of the United States population suffers from both alcohol and drug use disorders [1,2]. In particular, concurrent intake of cocaine and alcohol in both sexes is a well documented, increasing type of multiple drug use [3–5]. A recent report about prevalence of cocaine use among adolescents in Europe indicates that about 70% of them reported that the first use of cocaine was under the effects of alcohol [6]. In turn, there is evidence that cocaine use in heavy drinkers increases the risk of developing alcohol dependence by 3.8 times [7], whereas co-abuse of cocaine and alcohol is associated with more severe psychological problems [8] and in particular with an increment of suicidal and homicidal behaviour [9] with respect to the use of cocaine or alcohol alone.

Currently, few epidemiological data about gender prevalence of the concurrent use of cocaine and alcohol are available [8]. A recent study by Martinotti et al. [10] aiming to examine the clinical correlates of poly-substance dependence showed no difference in sex prevalence between mono- vs. poly-substance abusers, while another aimed to explore possible gender differences among cocaine-dependent patients show a higher frequency of alcohol intake in male subjects [11]. Another report [5] examining substance use and dependence among cocaine dependent subjects ($N = 459$, 52.9% female) recruited for treatment, reported that poly-substance dependence was the rule: among this population 56% of women reported a lifetime dependence on alcohol.

A study aimed to analyze the quantity and frequency of alcohol use among Afro-Americans reported that female heavy drinkers used more crack cocaine than light and moderate drinkers [12]. Interestingly, among women entering the criminal justice circuit, co-abuse of alcohol and cocaine was related to high levels of

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psychiatric distress [13]. Considering that epidemiological survey converge in detecting an increase in the use of cocaine [14] in the prevalence of heavy drinking [15,16] and in a progressively higher percentage of women abusing psychotropic drugs [17–19], it is conceivable that the concurrent use of cocaine and alcohol is spreading among women.

Yet, few studies have addressed gender differences in the pharmacological effects of combined cocaine–alcohol abuse, in spite of the fact that growing literature is dealing with the biological and molecular basis of gender-related differences in response to drugs [20–24] and more generally with gender perspective in clinical research [25]. This is not surprising because little information is available about gender differences in the pharmacokinetic and pharmacodynamic aspects of drug addiction [26–28]. The purpose of this review is to provide an overview of gender differences in pharmacokinetic and pharmacodynamic aspects of the concurrent abuse of alcohol and cocaine. We choose to use the term gender according to the definition of National Research Council in USA [29]: "Gender refers to a person's self-representation as male or female and how the individual is responded to by social institutions, based on the individual's gender presentation. This definition includes self-representation, which also includes biological aspects".

In order to pursue our aim, we first reviewed gender differences in the pharmacological aspects of alcohol and cocaine separately and then we focused our attention on the effects of their combined use. Although experimental findings are not the primary focus of the present review, we have occasionally included animal or in vitro studies, particularly when male and female differences found in animals may suggest further studies in humans.

Method

We reviewed the literature related to gender differences in alcohol, cocaine and cocaethylene pharmacokinetics (PK) and pharmacodynamics (PD). The MEDLINE database was searched from 1990 to 2014, using PubMed. Keywords used were: alcohol, cocaine, cocaethylene, ethanol, pharmacology, pharmacokinetics, pharmacodynamics, sex/gender difference; individually or variously paired. Importantly, search results were restricted to English language with particular attention to human studies. Manual searches of reference lists of pertinent reviews and studies, as well as abstracts from relevant conferences were also conducted.

Aspects of gender differences in alcohol pharmacology

Epidemiological studies show that alcohol use starts at an early age in both genders. The recent SAMSHA survey (2014) reports that during 2012 56.5% of males and 47.9% of females aged 12 or older were current drinkers; however, among youths aged 12–17, the percentage of males who were current drinkers (13.3%) was similar to the rate for females. Among young adults aged 18–25, an estimated 57.5% of females and 62.9% of males reported current drinking; in this age group, 45.8% of males and 33.2% of females reported binge drinking. Among pregnant women aged 15–44, 8.5% reported current alcohol use, 2.7% binge drinking, and 0.3% heavy drinking; nevertheless, these rates were lower than those for non pregnant women in the same age group.

Attitudes concerning drinking clearly differ between genders [30], women perceiving greater social disapproval for drinking although they tend to consume less quantity of alcohol [31–33]. Yet, recent findings confute the notion of gender differences in the attribution to types I and II of alcoholism [34] showing that type II alcoholism is not limited to male alcoholics, but also exists in women, confirming that female alcoholics are represented in both Cloninger's Type I and Type II of alcoholism [35,36]. In addition, Lesch type III category [37] that includes subjects that use alcohol to cope with their signs of depression, is dominated by women [38], and in a recent study [39] genetic markers of alcoholism and comorbid depression were identified in alcohol dependent females. Finally, a study conducted on a multisite sample of college students shows that female students were more likely to exceed weekly alcohol intake limits than men [40]. In a review examining factors associated with the risk of developing alcoholism, Schulte et al. [16] found that among teenagers physiological and also psychosocial factors differently interact with the gender in eliciting progression into problematic drinking when adults.

However, the consequence of heavy alcohol use as well as alcoholic complications may be heavier in women than in men: women tend to be more vulnerable to alcohol-induced physical illnesses [31,41] and display more severe cognitive and motor impairment with significantly lower alcohol exposure compared with men [42]. Both pharmacokinetic and pharmacodynamic factors may contribute to gender difference in the pattern of alcohol abuse and response to alcohol intake.

Gender differences in alcohol pharmacokinetic/pharmacodynamics

Several studies have demonstrated gender differences in alcohol pharmacokinetic (PK) in different animal species [43–46] and in humans. Table 1 shows a summary of the results of clinical studies addressed to gender differences in PK parameters of alcohol.

For a given oral dose of alcohol (but not for intravenous administration), women exhibit higher and more prolonged blood alcohol levels [47–50] indicating that women own greater oral bioavailability, as shown by an increased area under the curve (AUC) with respect to men. As known, systemic bioavailability upon oral administration of drugs is subject to a wide array of variables, such as speed of gastric emptying, gastric enzyme activity, and first-pass metabolism (pre-absorption metabolism, both in stomach and liver), which differ between the two genders. Accordingly, in a study aimed to explore factors underlying gender differences in the bioavailability of alcohol, Baraona et al. [48] found a significant delayed gastric emptying in women with respect to men: the slower gastric emptying time may explain the gender-difference in the shape of the curve, but not the difference in the peak alcohol levels. Moreover, it could not explain gender differences in the AUC of alcohol, since the slower gastric emptying time observed in women [22,24] is expected to reduce it. In fact, gastric alcohol dehydrogenase (ADH) activity seems to contribute to the observed gender differences in oral bioavailability of alcohol, as far as most of the studies (see Table 2), although with some exceptions [54,56] agree that gastric total ADH activity is significantly lower in women than in men when the enzyme activity is measured at high alcohol concentrations (such as it happens in the stomach after alcohol binge intake) [47,52,53,59] in young [52,53,58,60] and healthy subjects [47,48,52]. Importantly, since alcoholism is associated with a decrease in gastric alcohol dehydrogenase activity in both genders, alcoholic women display a particularly low first-pass metabolism of alcohol up to the point of showing little differences in blood alcohol concentrations upon oral or iv administrations [47]. Moreover, many authors [52,53,58,60] found in men, but not in women, an inverse correlation between gastric ADH activity and age. Furthermore, significant lower enzymatic activities in total ADH and class I and II ADH isoenzymes were also showed in women human liver [61].

When alcohol reaches the circulation, other physiological differences between men and women emerge affecting alcohol distribution [62]. On average, women have total body water (both extracellular than intracellular water), blood and plasma volume, and red blood cell volume smaller than men, while they have