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A Systematic Review of the Association between Individual Drugs Injected Intravenously and the Development of Infective Endocarditis

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Abstract

Issues: Infective endocarditis (IE) is a relatively rare disease that is associated with a significant amount of morbidity and mortality. Injection drug use associated IE is increasing in incidence, warranting a better understanding of how the drug of choice impacts the development of IE. Many studies have drawn connections between certain drugs injected intravenously and the development of IE but none have rigorously evaluated why a particular drug might predispose persons who inject drugs (PWID) to IE.

Approach: The PubMed database was thoroughly searched using combinations of various key words. Human studies with 20 cases or more of injection drug use associated IE that reported on the drugs injected were analyzed and included in this review.

Key findings: No specific drug convincingly showed a strong association between its intravenous use and the development of IE, with studies having contradictory findings. The array of findings reported in the reviewed studies are more likely to be due to the frequency of use of particular drugs and their availability in the respective regions of study than the actual physiologic or pharmacologic properties of the drug.

Implications: One trend that requires further investigation is the recent surge in opioid injection that has been linked to increased IE hospitalizations in several studies.

Conclusion: Future research should aim to better understand how the preparation and/or physical properties of specific drugs may play a role in the development of IE.

Keywords: Infective endocarditis; Intravenous drug abuse; Cocaine; Heroin; Opioids

Introduction

A recent study in California and New York State found that the overall standardized incidence of infective endocarditis (infection of heart valves) has remained stable from 1998 through 2013. However, injection drug use (IDU) associated IE (IDUaIE) steadily increased over this period of time [1]. This problem is particularly highlighted in North Carolina where IDUaIE admissions increased twelvefold from 0.2 to 2.7 per 100,000 persons per year from 2010 to 2015. These findings reflect the marked increased in abuse of opiates and other pain relievers in the United States and other regions [2]. Alarming statistics of this nature call for a better understanding of the relationship between IDU and the development of endocarditis. It is well known that persons who inject drugs (PWID) have manifestations of IE that can differ from non-IDU patients, particularly more frequent involvement of the tricuspid valve. Several hypotheses have been put forth to explain this phenomenon, some of which implicate the physiologic effects of the injected substances [3]. A wealth of data has been produced to study the risk factors of IE [4] but very few have examined what role the injected drug of choice plays in the development of IE. Granted, it is often difficult to determine whether the drug itself is the culprit or whether the manner in which it is prepared or injected predisposes PWID to IE. The purpose of this review is to paper and appraise the literature that has reported on the drug(s) used in PWID who developed IE. By doing so, we hope to shed light on whether individual drugs that are injected are more likely to cause IE than others. We believe this information to be critical in that it can inform regulatory bodies of risks, influence prescribing patterns of physicians and help better understand which patients may be at greater risk of developing IE based on which drug(s) they inject. It is our hope that the following systematic review will spark further basic science and clinical research that will examine how a drug's properties, physiologic effects or preparation can influence the development of IE.

Materials and Method

This systematic review was made following the principles of PRISMA. A literature search of the PubMed database with no date range was conducted to identify articles that reported on the drugs used in PWID that went on to develop IE. The search was conducted on 15 October 2017 with the search strategy found in the supporting information document. Searches were limited to the English language and a filter was applied to limit the search to human studies. A total of 35 articles were found in PubMed, and studies with less than 20 cases of IDUaIE were excluded as we were interested in larger sample sizes to

answer our research question. A total of 6 articles that were used to cite epidemiology and other supporting information were found via the references section of the 35 PubMed articles and were included in this paper. Twenty-four articles were then assessed for eligibility and those that did not specify the drug(s) injected in the patients that developed infective endocarditis were also excluded. The remaining 7 studies were analyzed and included in this review.

Results

We identified 7 eligible studies out of the 30 that were assessed which are summarized and discussed in this section, beginning with a pioneering study with regards to IDUaIE. Chambers et al. [5] were the first to report on the association between the type of drug used and development of IE. In 1981, they used San Francisco General Hospital's admission logbook to identify 152 PWID. Of the 143 patients for whom records were available, 102 patients met their criteria of having a febrile illness as the reason for hospitalization and being a PWID. Of the 23 patients determined to have IE, seven were reported as having definite IE, 13 as probable IE and 3 as possible IE. The criteria used were mainly in accordance with the current modified Duke Criteria. Logistic regression analysis showed that of: heroin (n=19), cocaine (n=18), amphetamine (n=2), Ritalin (n=6), and other drugs (n=4), only cocaine had a statistically significant ($P<0.001$) and independent effect in predicting endocarditis with an odds ratio of 138 (95% CI 8, 2318) when compared to PWID that did not have IE (Table 1). The tricuspid valve was the suspected site in 15 of the cases. It is worth noting that of the 18 cocaine users, 17 used heroin in combination (often mixed together as a "speedball") but heroin alone was only borderline significant ($p=0.051$) upon univariate analysis and not statistically significant after logistic regression analysis whether it was used alone or in combination with cocaine or other drugs. It is unclear what criteria were used to classify PWID as cocaine or a heroin user with there being so much overlap. It can be assumed that patients were included in each drug category that they have injected but there is no comment on the frequency of injection of the drugs. Hypothetically, if a patient only injected cocaine once and primarily injected heroin, false classification may have occurred. Furthermore, the complex procedure to co-formulate heroin with cocaine (and thus a greater risk of contamination) may have led to the higher risk rather than the individual contents of the injectate.

Author (Year of Publication)	Geographic Location	Total Number of Patients in Study	Number of Patients with IE	Number of Patients with IDUaIE	Drug(s) injected in those that developed IE
Chambers et al. (1987) [5]	San Francisco, U.S.	102	23	23	Heroin (n=19)
					Cocaine (n=18)
					Heroin+Cocaine (n=17)
					Amphetamines (n=2)
					Ritalin (n=6)
Williams et al. (1997) [10]	Johannesburg, South Africa	86	21	21	Wellconal (n=21)
Jain et al. (2008) [13]	San Francisco, U.S.	247	247	184	Heroin (n=67)
					Heroin+Cocaine (n=62)
					Amphetamines (n=15)
					Heroin+Amphetamines+Cocaine (n=11)
					Cocaine (n=7)
					Heroin+Amphetamines (n=5)
					Amphetamines+Cocaine (n=2)
					Drug use data not available (n=15)
Hartman et al. (2016) [9]	North Carolina, U.S.	127	127	48	Oxymorphone (n=20)
					Specific drug not identified (n=13)
					Oxycodone (n=8)
					Heroin (n=6)
					Morphine extended release (n=1)
					Methadone (n=1)

					Cocaine (n=1)
Østerdal et al. (2016) [12]	Norway	29	29	29	Opioidsa (n=20)
					Amphetamines (n=15)
					Benzodiazepines (n=7)
					Other (n=5)
					Unknown (n=4)
					Mixed abuse (n=19)
Suzuki (2016) [14]	Boston, U.S.	29	29	29	Heroin (n=27)
					Prescription Opioid (n=5)
					Buprenorphine (n=4)

Table 1: Type of drug(s) injected in those that developed infective endocarditis, [a]Reported in paper as: "Common illicit drugs were opioids (69%; i.e. heroin, buprenorphine and methadone hydrochloride)"; IE: infective endocarditis; IDUaIE: injection drug use associated infective endocarditis.

The authors suspect that usage patterns, differences in bacterial flora, or a more direct effect of cocaine itself could be responsible for the reported association. Of these possibilities, it is unlikely that cocaine's stimulant effects would be the sole reason for the association because amphetamine showed no association, with only two of the 23 (9%) IVDUs with endocarditis having used amphetamines and 35 of 92 (38%) of those without endocarditis used amphetamines [5]. Usage patterns could certainly be a contributing factor since cocaine injection generally occurs more frequently than heroin injection; cocaine's short duration of effect, local anesthetic and psychomotor stimulant properties result in it being injected more frequently and frenetically [6]. Another study conducted in Sydney, Australia found that the period prevalence of cocaine use in PWID was 67% in the previous 6 months and that cocaine use was associated with higher levels of heroin use, polydrug use/injection, and injection frequency [7]. Therefore, it is possible that the sheer number of injections that cocaine users subject themselves puts them at a greater risk of developing IE when compared to other drugs.

In contrast to the findings of Chambers et al. who found no significant association between IV amphetamine use and IE, Cooper et al. [8] proposed that a nationwide increase in the United States in the number of hospitalizations for injection drug use associated IE (IDUaIE) was due to increasing methamphetamine use during the study period. To identify cases of IDUaIE occurring from 1996 to 2003, they used the Centers for Disease Control and Prevention National Hospital Discharge Survey database (NHDS). The NHDS produces nationally representative annual data on hospitalizations in non-Federal, short-term care facilities. NHDS uses International Classification of Disease, Ninth Revision, Clinical Modification system, which does not specify whether cases of IE are IDU related and as such the authors developed two algorithms to identify patients who had IDUaIE. One algorithm was specific; the other was sensitive and contained many more cases. Using both algorithms, a nationwide increase in the number of hospital discharges for IDUaIE between period 3 (2000-2001) and period 4 (2002-2003) was seen.

By analyzing several temporal trends, the authors ruled out various causes of the spike between period 3 and 4 and proposed that methamphetamine use could be the main culprit because users of methamphetamine increased nationwide from 1996-2003, with the steepest increase occurring in 2001-2002. Cooper et al. argue that methamphetamine injection would increase IE risk through pathophysiologic mechanisms similar to those of cocaine. However, cocaine's mechanism of action was never reliably shown to cause IDUaIE and the only observational data at the time of publication that supported this hypothesis was that of Chambers et al. As Chambers noted, it was unlikely that cocaine's pathophysiologic mechanisms were linked to the development of IE because amphetamine use did not show a similar association. Thus, to our knowledge, there is no reliable evidence that methamphetamine use is disproportionately related to the development of IE compared to other drugs and although it is possible that its use caused the spike in hospitalizations, other factors that were not examined should also be considered.

With the benefit of hindsight, the rise in opiate pain reliever (OPR) overdoses and injection drug use in the United States began in the early 2000s [9]. This data has been corroborated by several studies that found opioids to be the main drug abused by PWID. Hartman et al. [9], reported high rates of oxymorphone IDUaIE in their study conducted in North Carolina. The investigators used ICD-9 codes to identify cases of IE from 2009 to 2014; cases were then verified by individual chart review and had to have met the modified Duke Criteria for definite IE. Of 128 IE cases, 48 were found to have IDUaIE. Of interest is that the fraction of IDUaIE cases increased from 14% of hospitalizations for IE in 2009 to 56% in 2014. The temporal increase in IDU-IE rates was mainly attributed to increased OPR injection use. Injecting drug users in their study mainly reported using oxymorphone and oxycodone with oxymorphone being the most frequently reported drug in IDU-IE patients. The oral formulation of oxymorphone, Opana® (Purdue), which came to market in 2006, was modified to an abuse deterrent form in 2012, which coincides with when the increase in OPR injection was reported. These findings mirror those found by Toyoda et al. [1] who found that IDUaIE increased from 1998 through 2013. The sharpest increase was found between the periods of 2006-2009 (2289 cases of IDUaIE) and 2010-2013 (2849 cases of IDUaIE). Hartman et al. report that it is unclear if the higher rates of oxymorphone IDU related IE in the study are exclusively due to availability of oxymorphone or if it is the

characteristics of the formulation that increases the risk of developing IE. This is a common theme in studies regarding IDUaIE and similar questions were left unanswered in the study by Chambers et al [5].

To our knowledge, the first suggested association between opioid injection and IE was in a retrospective analysis from 1991 to 1992 of 86 patients who were current intravenous abusers of dipianone hydrochloride/cyclizine hydrochloride (Wellconal) [10]. Twenty-four of the 121 admissions were for tricuspid valve endocarditis. The tablets of Wellconal were dissolved in tap water and then injected intravenously. No further reports of Wellconal in relation to endocarditis have been published as this drug was not widely used and was subsequently removed from the market, but this study offers good insight as only 1 patient of the 86 admitted to concomitant use of heroin with the remainder reporting that they solely used Wellconal. This finding is of significance as American drug users are rarely drug purists [11], and as such, it is more difficult to draw an association between an individual drug and the development of IE. The median age of the patients was 24 years and only two of 72 study patients were HIV positive. Thus, the authors hypothesized that the drug itself or the manner in which it was injected can be a major contributor to the development of IE [10]. Further making the case for the association between opioid injection and IE was a retrospective study of 29 PWID who underwent surgical treatment for IE at a hospital in Norway between 2001-2013 [12]. The two main drugs injected were opioids (n=20) and amphetamines (n=15); however, 19 of the 29 PWID abused more than one drug.

Jain et al. [13] noted that the theories explaining why a large proportion of right-sided cases of IE occur in PWID had not been supported by significant data. As such, they sought to utilize a retrospective cohort study to examine whether any specific drugs predisposed patients to right-sided endocarditis. Records from San Francisco General hospital from 1996 to 2003 were searched to identify cases of IE; 247 episodes of IE occurring in 238 adult patients were evaluated. 184 of these patients were PWID and of them, the type of drug injected was available in 169 patients. While this study has a large sample size relative to others, it is difficult to ascertain whether heroin does in fact contribute heavily to IE or whether the majority of PWID in that region and time period mainly used heroin. The authors report that "IDUs using heroin were significantly more likely to have tricuspid disease compared to IDUs not using heroin (OR 4.03, p=0.033)… in addition, users of cocaine and/or amphetamines were not more likely to have tricuspid valve involvement than non-IDUs." However, with regard to the aforementioned argument, those with any heroin use (n=145) were a much larger sample size than non-heroin use (n=24) and therefore the power to detect a pattern in the non-heroin users was very limited. No confidence intervals were reported in the study and there were only 63 patients with IE that were not IDU making it difficult to find a statistical difference in cocaine/amphetamine use with the valve involved (compared to non-IDU patients) if there was one. Nevertheless, heroin is commonly one of several drugs injected in those that develop IE and should be further studied in this context. In a retrospective study conducted in Boston, MA, 29 patients admitted for IDUaIE treatment had a history of intravenous heroin use (93.1%), with a minority using intravenous prescription opioids and/or buprenorphine [14].

Discussion

The aim of this review was to gain a better understanding of how the drug that is injected may play a role in the development of IE. Unfortunately, there is a deficit in the amount of research conducted that pertains to this particular question. We thus hoped to report on the current evidence to fuel further investigation into certain drugs that pose a greater risk than others. Although several studies claimed to demonstrate this phenomenon, the results between studies were contradictory, and the strength of evidence in any particular study was poor. The use of additives and adulterants by the patients in the injected drugs were not inquired about in the studies covered, thus producing further confounding factors. The research question itself is difficult to address due to the multiple factors that play a role in IDU: frequency of use, diluent used, unsterile practices during preparation, opioid or other drug of choice in the region, prescribing practices and injection technique. It is not possible to conduct a randomized control trial to answer such a question and as such, we must rely on observational data, which come with their set of limitations. It is also very difficult for researchers to collect all of the relevant data from participants particularly as there may be hesitance for PWID to provide full disclosure about their drug use. However, our goal was to report on all such studies and highlight temporal trends that would draw attention to certain drugs. Although increases in the incidence of IDUaIE has been associated with increases in injection drug use, there is insufficient data to suggest that any specific drug or drug class is more likely to lead to the complication of IE.

Conclusion

Further studies to clarify this issue would be helpful particularly in light of increased usage of IDU in the face of the present opioid epidemic. Going forward, it would be of great importance to study the pharmacologic and physiologic properties of various drugs in a model to see if certain drugs cause more endothelial damage or are more prone to bacterial contamination than others. Furthermore, data regarding the differences in the frequency of injection associated with the various drugs used would certainly aid in elucidating some of the questions posed in this review.

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