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Review Aminorex poisoning in cocaine abusers

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ABSTRACT

Levamisole is found in more than 80% of illicit cocaine seized within United States borders. Percentages are somewhat lower in Europe. In 2009, controlled in vivo studies demonstrated that horses metabolize levamisole to aminorex. Earlier this year our laboratory demonstrated that the same conversion occurs in man. Levamisole itself causes aplastic anemia and numerous reports have begun to appear in the literature, but the conversion of levamisole to aminorex is of much more concern. Aminorex ingestion was responsible for a five-year epidemic (1967–1972) of idiopathic pulmonary hypertension (IPH) confined to Switzerland, Austria, and Germany, the only countries where aminorex had been marketed as an anorectic. The incidence of IPH reverted to normal levels as soon as aminorex was withdrawn. In most cases onset of symptoms in IPH began after six to nine months of aminorex use, with average dosage ranges of 10 to 40 mg per day. The outcome was almost uniformly fatal. The conversion rate of levamisole to aminorex has not been established, but given the high daily intake of cocaine by many abusers, it seems likely that many of them will have ingested enough contaminated cocaine to ultimately cause IPH. Until the disease is well established, the symptoms of IHP are vague, and existing drug registries specifically exclude drug abusers, making it difficult to track these cases. This review is intended to draw attention to what may be a slowly emerging new epidemic.

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1. Introduction

Levamisole made its first appearances as a cocaine adulterant in 2004 [1]. Three years later Italian authorities seized 28 kg of cocaine hydrochloride adulterated with nearly 10 percent levamisole [2]. Levamisole was not mentioned in a 2009 report from the Netherlands, where only common adulterants, such as phenacetin, hydroxyzine and diltiazem were detected. However, the authors of the Dutch report also observed that cardiac and hallucinatory effects in that region's cocaine abusers were, for no apparent reason, being reported more frequently. They suggested that the adverse effects might have been due to some unrecognized adulterant [3]. These speculations were followed five years later by controlled studies demonstrating the equine conversion of levamisole to aminorex [4]. Our laboratory demonstrated that the same conversion of levamisole to aminorex occurs in humans [5]. We have just completed a retrospective study of stored forensic urine specimens that had previously been found to contain cocaine. Of 154 samples tested nearly one half (n = 62) were positive for both levamisole and aminorex [6].

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2. Levamisole-adulterated cocaine

The US Food and Drug Administration (FDA) approved levamisole for use as adjuvant therapy with fluorouracil for the treatment of colorectal cancer (under the brand name of ErgamisolTM) in 1991. In spite of the limited FDA approval, levamisole was used "off label" as an immuno-modulator in the treatment of numerous, unrelated disorders. Levamisole proved to be a very effective antihelmintic [7], but results when it was used with other disorders were unimpressive [8,7]. Levamisole was withdrawn from the U.S. market in 1999 after clear associations with the occurrence of agranulocytosis become apparent [9]. Frequent cases of agranulocytosis are now being reported in patients who used levamisole-adulterated cocaine [10,11,9,12-16].

Data from the DEA's Signature Program (a federal program that tracks the composition of cocaine seizures within the United States) showed less than 1% of the samples tested in 2001 contained levamisole. By July 2009, that number had risen to approximately 69%[17]. In Florence, Italy, from November 2009 to November 2010, 34% of cocaine seizures analyzed in our laboratory were found to contain levamisole. Similar results have been observed elsewhere in Italy [18], and the rest of Europe [19], though the true percentage is not known. Levamisole now permeates the U.S. cocaine supply [3,7,9,11,12,20-25], and there may well be a medical price to pay.

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3. Levamisole induced agranulocytosis

Two complications of levamisole-adulterated cocaine have been reported with increasing frequency since late 2009: agranulocytosis and necrotizing vasculitis [12,11,26]. Neither condition is very common, but their diagnosis is fairly straightforward. Granulocytopenia is defined as a reduced number of blood granulocytes, namely neutrophils, eosinophils, and basophils. If there is merely a decrease in the absolute neutrophil count (less than 1500 per μ L is the accepted definition), the condition is referred to as neutropenia. An absolute neutrophil count of less than 100 is diagnostic for agranulocytosis. Neutropenia may, under some circumstances be benign as the absolute number of neutrophils determines susceptibility to bacterial infection [27]. Agranulocytosis is potentially fatal. Both conditions are easily diagnosed, but not so easily treated. Neutropenia or agranulocytosis in a drug user should now be considered strong evidence for the chronic ingestion of levamisolecontaminated cocaine.

Clusters of cocaine-levamisole related agranulocytosis were reported in the U.S. at the end of 2009 [17] and in the spring of 2010 [9]. Levamisole contaminated cocaine seems to result in a distinctive clinical syndrome, including the presence of circulating plasmacytoid lymphocytes, increased bone marrow plasma cells, with mild megakaryocytic hyperplasia. More than half of those who become ill will have antineutrophil and HLA-B27+ antibodies [9]. Vasculitis induced by levamisole has been recognized for more than a quarter of a century and also appears to be the result of circulating immune complexes [28].

4. Levamisole, aminorex, and pulmonary hypertension

With the discovery that humans metabolize levamisole to aminorex, a whole new set of concerns now confronts us, because chronic ingestion of aminorex is definitely linked with the occurrence of idiopathic pulmonary hypertension. In January of 1971 a brief report in the British Medical Journal described a sudden increase in the incidence of a particularly virulent form of pulmonary hypertension of undetermined cause, in 40 young Swiss women. The only common feature shared by all of these patients was the prolonged use of a new anorectic drug called aminorex fumarate, sold in Switzerland, Austria, and German as an anorectic beginning 1965. The first cases were not reported until six to 12 months after aminorex fumarate (sold by McNeil Laboratories as Menocil[™] or Apiquel[™]) had come to market [29]. The average dose per day ingested by the affected women ranged from 14 to 42 mg/day; the average patient had been taking the drug for more than one year [30]. A Swiss researcher reported that in 1968 alone, the number of patients presenting with pulmonary hypertension had increased 10- to 20-fold [31].

There followed a flurry of similar reports published in the European literature [32-34]. Aminorex was never sold in the United States or United Kingdom and that may explain why awareness of the problem was slow to emerge [35,36]. Still, a relationship between anorectics, cocaine abuse, and pulmonary hypertension has been suspected for some time [37-39], as has a relationship between tIPH and deranged serotonin metabolism. The existence of such a relationship was first suggested more than 40 years ago [40], though the actual mechanism was not really understood. Even those who did write about a possible relationship between cocaine and IPH had no idea how, or even if, the cocaine abused by the patients had been adulterated.

Now it is understood that aminorex is a substrate for serotonin (5HT) transporters (SERT) and is, therefore, an indirect 5HT agonist. 5HT is synthesized in pulmonary artery endothelial cells by the enzyme tryptophan hydroxylase 1 (TPH1). 5HT then acts at the 5-HT (1B) receptor and SERT to mediate vasoconstriction constriction together with proliferation of pulmonary artery smooth muscle cells. Downstream signaling molecules that play a role in serotonin-

induced constriction and proliferation include reactive oxygen species (ROS), Rho-kinase (ROCK) p38 and extracellular signal-regulated kinase (ERK). There is also evidence to suggest that serotonin may interact with the bone morphogenetic receptor type II (BMPRII) to provide a 'second hit' risk factor for PAH [41].

5. Conclusion

The key issue to be addressed now is not whether humans convert levamisole to aminorex (we know they can), or whether aminorex can cause IPH (it does). The question that urgently requires answering is whether chronic users of levamisole-tainted cocaine actually convert enough levamisole into aminorex to cause IPH. This is not a trivial question.

According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 3.3% of all European adults used cocaine in 2009; 2.5 million were classified as lifetime users. The most recent U.S. estimates indicate 0.7% of the population (roughly 1.9 million people) are chronic cocaine users [42]. IPH is a profoundly debilitating disease. Even if only a small fraction of cocaine users suffered aminorex toxicity, the medical community would be left with a problem of enormous magnitude.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology[43].

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