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Pemoline-Associated Hepatic Failure: A Critical Analysis of the Literature

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Pemoline is a central nervous system (CNS) stimulant approved for use as part of the comprehensive medical management of attention deficit hyperactivity disorder (ADHD). An increased risk of acute hepatic failure is believed to be associated with pemoline usage, raising concerns about its prescription. A descriptive meta-analysis of the existing scientific literature and drug reporting databases was undertaken to provide more accurate understanding of this possible risk. The analysis appears to indicate that current assumptions of the risk of acute hepatic failure posed by pemoline usage alone are overestimates. Several recommendations regarding hepatic monitoring in the setting of pemoline prescription are provided.

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Introduction

The diagnosis of attention deficit hyperactivity disorder (ADHD) is increasingly made recently as the result of heightened public, educational, and physician awareness of this entity [1]. With increasing recognition of ADHD, the prescription of pharmacologic agents as part of the comprehensive management of this disorder, specifically central nervous system (CNS) stimulants such as methylphenidate (Ritalin-Ciba Geigy) and pemoline (Cylert-Abbott Laboratories), has increased substantially in the past few years [2]. Many concerns regarding the widespread prescription of these agents have been expressed, and one of the concerns focuses on the possible increased risk of fulminant hepatic failure (FHF) associated with pemoline usage [3]. By critically evaluating the published literature on the hepatotoxic effects of pemoline (descriptive meta-analysis), we wish to put this concern in proper perspective and provide broad recommendations regarding the prescription of pemoline in the context of possible hepatic injury.

Review of Literature

Extensive search of online computerized medical databases (Medline, Peruse) reveals four reported cases of fatal FHF associated with pemoline use [3-5]. The first two cases, summarized in a letter by Jaffe [4] were taken from FDA-1639 forms provided to him by Abbott Laboratories. The first case was that of a 10-year-old boy who had been hospitalized previously for 2 weeks at age 6 years for biliary cirrhosis. This child developed jaundice at age 10 years, 3 weeks after having been prescribed pemoline, prompting initial hospitalization. Seven months later, the child was rehospitalized for jaundice, ascites, and splenomegaly. A diagnosis of "biliary cirrhosis and hypoplasia of extrahepatic ducts" was made, and death occurred as a result of "cardiac arrest and hepatic dysfunction" 2 months later. The second case summarized by Jaffe [4] was that of 12-year-old who had been treated with pemoline for 3 years. Fatal toxic hepatitis developed in this child soon after a deliberate pemoline overdose.

The third case was reported by Nehra et al. [5]. At 12 years of age, the boy began receiving pemoline and for a period of 5 years was prescribed pemoline alternating with methylphenidate. This protocol was discontinued, and for 1 year he received pemoline alone until he developed symptoms of malaise, fatigue, and jaundice. Liver enzymes and bilirubin levels were markedly increased, gastrointestinal bleeding developed, and death resulted. Postmortem examination revealed massive hepatocellular necrosis.

The fourth case was recently reported by Berkovitch et al. [3]. A 14-year-old boy had been prescribed pemoline

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for 14 months without incident. Two months after methylphenidate was added to his treatment regimen, he developed nausea, vomiting, anorexia, and fatigue. Two and a half weeks after developing these symptoms, jaundice became evident. Rash and hepatomegaly was observed at hospitalization, and liver enzymes, bilirubin levels, and prothrombin/activated partial thromboplastin times were all markedly increased. A liver biopsy revealed massive multilobar necrosis, inflammatory changes, cholestasis, and some giant cells. Despite two orthotopic liver transplants, the child died. Enterovirus was cultured from the brain at postmortem examination, but not from the original liver biopsy.

In addition to assessing published cases, we contacted the Adverse Drug Reaction Monitoring Division of the Bureau of Drug Surveillance of Health Canada (the Canadian Federal Ministry of Health). A search of their computerized database (inclusive to November 1995) [6] revealed only one case of acute hepatic failure associated with pemoline usage, which was the case reported by Berkovitch [3]. Medwatch, the medical products reporting program of the U.S. Food and Drug Administration, was also contacted. Lack of any independent verification of any reports in their possession, together with the restraints of the Freedom of Information Act effectively precluded ascertainment of any further definite reports of acute hepatic failure that could withstand scientific scrutiny. This was acknowledged by an agency representative [7].

Discussion

Several articles have described the occurrence of transient hepatitis during treatment with pemoline [5,8-11]. These cases have almost always been mild, with transient increases in hepatic enzymes occurring at variable times after initiation of pemoline treatment, and fully reversible on discontinuation of use of the medication. Clinical manifestations such as nausea, vomiting, fatigue, malaise, and anorexia or physical manifestations such as jaundice or hepatomegaly may occur. Fever, rash, or eosinophilia has not been observed. Rechallenge with pemoline has been attempted rarely [5,8], with mixed results. The high values of serum aminotransferases suggest a hepatocellular mechanism of injury [5]. The timing of the hepatic dysfunction, together with the absence of the hallmarks of hypersensitivity and the low frequency of occurrence (2%) [12], suggests an idiosyncratic metabolic phenomenon, perhaps the production of a hepatotoxic metabolite [5]. Thus far, progression from a mild increase in liver enzymes to a fulminant, potentially fatal, hepatitis has not been demonstrated.

FHF is a clinical syndrome resulting from a sudden, rapidly progressive, and severe impairment of hepatic function [12]. FHF is defined presently by the development of hepatic encephalopathy within 8 weeks of onset of manifestations of liver disease in persons without preexisting liver disease [13]. Although its exact incidence is unknown, FHF is a relatively infrequent occurrence in the pediatric population but was found to be responsible for 6.6% of hospital-based deaths in a pediatric tertiary care facility in an 8 year period [14]. This syndrome results from infectious, metabolic, toxic, and immunologic etiologies that vary according to age [15]. In a review of 31 pediatric cases of FHF, the cause could not be identified in 26 cases [15].

The four cases of pemoline-associated fulminant hepatic failure thus far reported deserve careful scrutiny. One case was the result of a deliberate pemoline overdose [4]. Although it is important to advise physicians and patients of the potentially fatal risks associated with an excess dose of pemoline, one cannot infer from this report that the therapeutic use of pemoline is a risk factor for FHF. In another report of liver-related death [4], the patient had preexisting cirrhosis. By definition, this is not FHF. One can only conclude from this report that caution should be used with respect to the prescription of pemoline to patients with underlying chronic liver disease. In the third reported fatality [3], pemoline had been well tolerated for 14 months without incident. Hepatic necrosis developed 8 weeks after the addition of methylphenidate to pemoline. In this instance, it is difficult to attribute the subsequent observed liver failure to pemoline use alone. At best, one can speculate that combination therapy (pemoline and methylphenidate simultaneously) may be especially hepatotoxic. The final case report [5] attributing massive hepatocellular necrosis to pemoline is plausible. However, a thorough evaluation (infectious and autoimmune serology) to exclude other causes of FHF was not documented in this report. Therefore, of the four reported cases of FHF secondary to pemoline, detailed review indicates that only one appears to be justified.

In their article, Berkovitch et al. calculated a relative risk of 45.3 (95% confidence interval 4.1-510) of a child developing FHF while receiving pemoline [3]. The calculation of this rather alarming figure was based on three reported cases of pemoline-associated hepatic failure, when only one possible bona-fide case of a child without prior liver disease prescribed pemoline alone developing fatal FHF exists. The calculation is further flawed by their relative underestimation of pemoline usage (0.06% of the school age population) based on assumptions that 3% of school age children are prescribed CNS stimulants and that only 2% of such children are prescribed pemoline. Although most ADHD children prescribed medication are prescribed methylphenidate, 6%-10% in some samples are prescribed pemoline [16,17]. The calculation is even further flawed by the estimation of Berkovitch et al. [3] of an only 11% "idiopathic" rate for FHF in the pediatric population based on the report of Devictor et al. [18]. Careful review of that series of 35 children with FHF [18] reveals that the etiology was "unknown" in four cases and that five other cases had a presumed, but not proved, viral cause. Therefore, a truer estimate of indeterminate cause

from this series [18] is 25%. With only a single definite case reported thus far available to scrutiny, accurate quantification of the relative risk of pemoline-associated hepatic failure with any degree of statistical confidence is simply not possible at present, but appears to be substantially less than the figure quoted by Berkovitch et al. [3].

Pemoline's chemical structure (2-imino-5-phenyl-4-oxazlidinone) places it in the hydantoin group (specifically phenylisophydantoin). The idiosyncratic nature of pemoline-associated hepatotoxicity and the response to rechallenge suggests the possibility of a "toxic threshold" mechanism [3,5,9]. This may be dependent on a genetically based metabolic deficiency that allows production or incomplete elimination of a hepatotoxic metabolite resembling that which occurs with diphenylhydantoin [3,19].

Our recommendations based on a review of the existing literature for the prescription of pemoline are as follows. First, pemoline is potentially hepatotoxic. Physicians prescribing pemoline and parents of children receiving pemoline should be aware of this. Baseline liver function testing before prescription may be advised. Physicians should use a low threshold for testing liver enzymes (AST/ALT) in circumstances in which a patient treated with pemoline develops manifestations suggestive of possible hepatic injury, such as unexplained nausea or vomiting, lethargy, malaise, jaundice, or hepatomegaly. Increase in liver enzymes in such circumstances should result in prompt discontinuation of pemoline.

Second, routine liver enzyme testing in children prescribed pemoline is presently recommended [20]. The precise frequency of such monitoring is not specified. The value of such screening, while reassuring, remains unproved with regard to the actual prevention of significant hepatic injury, as is currently the situation with some antiepileptic drugs [21].

Third, prescription of pemoline in cases of preexisting liver disease must be very carefully considered, as must its prescription together with methylphenidate. Caution regarding the setting of preexisting liver disease is warranted owing to pemoline's metabolism in the liver and the report of hepatic failure in a child with prior biliary cirrhosis [4]. In the absence of further data, preexisting hepatic disease may be considered a relative contraindication to pemoline usage. In such circumstances, caution with respect to hepatic injury must be used, with the patient closely monitored and liver function tests performed frequently. Caution regrading prescription together with methylphenidate is warranted because of the single report of hepatic failure occurring in a child soon after methylphenidate was added to pemoline treatment [3]. Any significant increase in liver enzymes over baseline values should prompt discontinuation of pemoline. In such settings, insufficient reports simply do not allow a precise risk-benefit analysis presently.

To quantify the relative risk of pemoline-associated hepatic failure accurately, physicians should be strongly encouraged to report any cases of significant hepatic injury occurring during treatment with pemoline. The establishment of a central registry for such cases, similar to the valproate adverse reactions registry would be beneficial [22].

References

[1] **Swanson** JM, Lerner M, Williams L. More frequent diagnosis of ADHD disorder (Letter). N Engl J Med 1995;333:944.

[2] **Simeon** JG, Wiggins DM, Williams E. World wide use of psychotropic drugs in child and adolescent psychiatric disorders. Prog Neuro Psychopharmacol Biol Psychiatry 1995;19:455-65.

[3] **Berkovitch** M, Pope E, Phillips J, Koren G. Pemoline-associated fulminant liver failure: Testing the evidence for causation. Clin Pharmacol Ther 1995;57:696-8.

[4] **Jaffe** SL. Pemoline and liver function (Letter). J Am Acad Child Adolesc Psychiatry 1989;28:45.

[5] **Nehra** A, Mullick F, Ishak KG, Zimmerman HJ. Pemoline-associated hepatic injury. Gastroenterology 1990;99:1517-9.

[6] **Helal** A. Personal communication, June 18, 1996.

[7] **White** GG. Personal communication, July 8, 1996.

[8] **Tolman** KG, Freston JW, Berenson MM, Sanella JJ. Hepatotoxicity due to pemoline. Report of two cases. Digestion 1973;9:532-9.

[9] **Patterson** JF. Hepatitis associated with pemoline (Letter). South Med J 1984;77:938.

[10] **Pratt** DS, Dubois RS. Hepatotoxicity due to pemoline (Cylert): A report of two cases. J Pediatr Gastroenterol Nutr 1990;10:239-41.

[11] **Elitsur** Y. Pemoline (Cylert)-induced hepatotoxicity (Letter). J Pediatr Gastroenterol Nutr 1990;11:143-4.

[12] **Sallee** F, Stiller R, Paree J, Bates T. Oral pemoline kinetics in hyperactive children. Clin Pharmacol Ther 1985;37:606-09.

[13] **Bernuau** J, Rueff B, Benhamou JP. Fulminant and subfulminant liver failure: Definitions and causes. Semin Liver Dis 1986;6:97-106.

[14] **Lloyd-Still** JD. Mortality from liver disease in children: Implications for hepatic transplantation programs. Am J Dis Child 1985;139:381-4.

[15] **Psarcharopoulos** HT, Mowat A, Davies M, Portmann B, Silk DBA, Williams R. Fulminant hepatic failure in childhood. Arch Dis Child 1980;55:252-8.

[16] **DuPaul** GJ, Barkley RA. Medication therapy. In: Barkley RA, ed. Attention deficit hyperactivity disorder: A handbook for diagnosis and treatment. New York: Guilford Press, 1990:573-612.

[17] **Safer** DJ, Krager JM. A survey of medication treatment for hyperactive/inattentive students. JAMA 1988;260:2256-58.

[18] **Devictor** D, Deplanques L, Debray D, et al. Emergency liver transplantation for fulminant hepatic failure in infants and children. Hepatology 1992;16:1156-62.

[19] **Spielberg** SP, Gordon GB, Blake DA. Predisposition to phenytoin hepatotoxicity assessed in vitro. Engl J Med 1981;305:722-7.

[20] **Cylert.** In: Gillis MC, ed. Compendium of pharmaceuticals and specialties, 31st ed. Ottawa: The Canadian Pharmaceutical Association, 1996:341.

[21] **Camfield** P, Camfield C. Acute and chronic toxicity of antiepileptic medications: A selective review. Can J Neurol Sci 1994;21:S7-11.

[22] **Bohan** TP, McDonald II, Konig S, Helton E. Treatment and clinical characteristics of valproate induced hepatotoxicity. Ann Neurol 1995;38:505-6.