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Opioids

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OVERVIEW

Introduction

The opioids are a large class of medications related in structure to the natural plant alkaloids found in opium that are derived from the resin of the opium poppy, Papaver somniferum. The natural alkaloids are also referred to as opiates and include morphine and codeine. Synthetic derivatives include heroin, fentanyl, hydromorphone, methadone, buprenorphine and others. The opioids are highly potent and effective analgesics, but most have a high potential for dependency and abuse.

Opioids act by engagement of specific cell surface receptors; the opiate receptors, which are designated μ [mu], κ [kappa] and δ [delta]. These receptors are found predominantly in the central nervous system, brain and spinal column, but are also present on vascular, cardiac, lung, gut and even peripheral blood mononuclear cells. Engagement of the opiate receptors generates a series of intracellular signals, including inhibition of adenylate cyclase, decreased opening of calcium channels, increased potassium currents and activation of protein kinase C (PKC). The major effect of these pathways is reduction in cell excitability and neurotransmission. The natural ligands for the opiate receptors are the so-called endogenous opioid peptides such as the enkephalins, endorphins and endomorphins.

The opioids have a variety of clinical effects, but are predominantly known and used for their profound pain relieving effects. Other effects that are often linked to opiate analgesia include euphoria, changes in mood, drowsiness and mental clouding. However, the distinctive feature of the analgesia induced by the opioids is the lack of loss of consciousness. The pain is often described as less intense, but still present although better tolerated. Thus, the opioids do not decrease or treat the cause of the painful stimulus, but rather decrease its perception.

Other effects of opioids include respiratory depression, decreased gastrointestinal motility, sedation, nausea, vomiting, constipation and intestinal bloating. Opioids also have direct cardiovascular effects, decreasing blood pressure, causing vasodilation and decreasing cardiac work.

Most opioids have similar effects and side effects, although pharmacokinetic differences, tissue distribution, and receptor type specificity probably account for the variation in effects of the various synthetic and semisynthetic derivatives of morphine. Morphine is considered the prototype opiate, against which other agents are measured for their analgesic effects as well as adverse side effects.

The opioids can be categorized into subclasses on the basis of their chemical structure as opium alkaloids (opiates: codeine, morphine), semisynthetic derivatives of the natural alkaloids (hydrocodone, hydromorphone, oxycodone, buprenorphine), and various classes of synthetic opioids such as the anililopiperidines (fentanyl,

alfentanil, sufentanil, remifentanil), diphenylpropylamine derivatives (propoxyphene, dextropropoxyphene, methadone, diphenoxylate, loperamide), and others (pentazocine, butorphanol, nalbupine, levorphanol, tramadol), and, the opioid antagonists (nalmefene, naloxone and naltrexone). They can also be informally classified based upon their major use such as anesthesia (fentanyl, alfentanil, remifentanil, sufentanil), severe pain (morphine, hydromorphone, levorphanol, merperidine), moderate to severe acute or chronic pain (transdermal or transbuccal fentanyl, codeine, oxycodone, hydrocodone, levorphanol, methadone), diarrhea (loperamide, diphenoxylate), and cough (codeine, hydrocodone). Finally, opioids can be categorized on the basis of their action as full agonists, partial agonists or mixed agonists/antagonists, and antagonists of opiate receptors.

Opioid receptor antagonists are used to reverse the effects of opioids and are invaluable in the management of opioid overdose (naloxone, naltrexone, nalmifene). Specialized opioid antagonists can be used to reverse unwanted opioid effects, such as constipation in patients with chronic pain on long-term opioids. These agents (naldemedine, naloxegol) are generally modified so as not to cross the blood brain and reverse the central nervous system effects of opiates.

Opioids are rare causes of drug induced liver disease and are not mentioned in large case series of clinically apparent liver injury caused by medications. In physiological, pain relieving doses, opioids have not been implicated in causing clinically apparent liver injury, acute liver failure, chronic hepatitis or vanishing bile duct syndrome. However, overdoses of the more potent opioids have been linked to cases of acute liver injury, usually with a precipitous onset and pattern of acute toxicity with marked elevations in serum aminotransferase levels and early onset of signs of hepatic failure. This syndrome has been best characterized after buprenorphine overdose or abuse, but likely occurs with others. It is possible that the implicated opioids are not directly toxic to the liver, but cause ischemic liver injury due to respiratory failure, cardiovascular collapse, shock and anoxia that can occur with severe opioid overdose. The clinical syndrome resembles acute hepatic necrosis and liver failure, but is rapidly reversible and rarely the primary cause of death from overdose.

A special form of liver injury linked to opioid use occurs with their fixed drug combinations with acetaminophen. These combinations are commonly used for moderate to moderately severe pain and can lead to abuse. If taken too frequently, acetaminophen doses may reach toxic levels, particularly with overuse for several days in the face of malnutrition, alcohol abuse or intercurrent illness. These other stresses can lower hepatic glutathione levels and predispose to acetaminophen hepatotoxicity. This constellation of events is referred to as inadvertent or unintended acetaminophen overdose or more colloquially as a “therapeutic misadventure”. For this reason, the FDA has recommended that physicians not use opioid combinations in which the dose of acetaminophen is greater than 325 mg per tablet or unit dose.

References to the safety and hepatotoxic potential of the various opiate agonists are given together at the end of this Overview section. References to the opioids and the opiate antagonists used to treat substance abuse are given separately with each agent (buprenorphine, methadone, nalmefene, naloxone, naltrexone). The opioids are discussed individually or as groups of agents and links to each are given below.

Full and partial agonists:

- Alfentanil
- Butorphanol
- Codeine
- Diphenoxylate
- Fentanyl
- Heroin
- Hydrocodone
- Hydromorphone
- Levorphanol

- Loperamide
- Meperidine
- Methadone
- Morphine
- Opium
- Oxycodone
- Oxymorphone
- Pentazocine
- Remifentanil
- Sufentanil
- Tramadol

Opiate antagonists:

- Naldemedine
- Nalmefene
- Naloxegol
- Naloxone
- Naltrexone

ANNOTATED BIBLIOGRAPHY

References updated: 25 April 2019

Zimmerman HJ. Narcotic analgesics. Miscellaneous drugs and diagnostic chemicals. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999: pp. 710-11.

(Expert review of hepatotoxicity published in 1999 discusses morphine, heroin, methadone and codeine, mentioning that studies in humans "have shown little evidence of hepatic injury").

Larrey D, Ripault MP. Illegal and recreational compounds. Hepatotoxicity of psychotropic drugs and drugs of abuse. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 456-7.

(Review of hepatotoxicity discusses buprenorphine, an orally available morphine analogue, which has been linked to cases of severe acute liver injury, usually as a result of intravenous administration).

Yaksh TL, Wallace MS. Opioids, analgesia, and pain management. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 481-525.

(Textbook of pharmacology and therapeutics).

Edland JF. Liver disease in heroin addicts. Hum Pathol 1972; 3: 75-84. PubMed PMID: 5060682.

(Review of autopsy findings in the liver of heroin addicts mentions the frequency of nonspecific portal inflammation, lymph node enlargement in the porta hepatis, typical changes of viral hepatitis including subacute hepatic necrosis with 3 representative case histories).

Stimmel B, Vernace S, Tobias H. Hepatic dysfunction in heroin addicts. The role of alcohol. JAMA 1972; 222: 811-2. PubMed PMID: 4677931.

(Among 46 heroin users admitted for methadone maintenance, 85% admitted to excessive alcohol intake, and 10 of 12 patients with unexplained liver test abnormalities had changes of alcoholic hepatitis on liver biopsy).

Ireton HJ, Gust ID, Moon WJ, Lehmann N, Stening GF, Smallwood RA. The covert liver disease of drug addicts. Aust N Z J Med 1974; 4: 444-9. PubMed Citation

(Among 20 injection drug users, 11 [55%] had abnormal liver tests [AST 41-98 U/L] and 19 [95%] had abnormalities on liver biopsy, often being mild; none of the patients had HBsAg in serum).

Gorodetzky CW, Sapira JD, Jasinski DR, Martin WR. Liver disease in narcotic addicts. I. The role of the drug. Clin Pharmacol Ther 1968; 9: 720-4. PubMed PMID: 5721975.

(20 male prison inmates were given morphine daily for 6-8 months and then switched to methadone that was slowly withdrawn; monthly testing demonstrated that serum ALT and AST values did not change appreciably during periods of morphine or methadone administration).

Sapira JD, Jasinski DR, Gorodetzky CW. Liver disease in narcotic addicts. II. The role of the needle. Clin Pharmacol Ther 1968; 9: 725-39. PubMed PMID: 5721976.

(Among 32 prison inmates with a history of heroin use, 26 [81%] had some clinical or biochemical evidence of liver disease, and the frequency of chronic hepatitis increased with number of years of injection use).

Lapierre J. Possible hepatotoxic effect of methadone. Can Med Assoc J 1969; 10: 113. PubMed PMID: 5794138.

(Long term heroin user developed nausea and dizziness within a week of starting methadone with atypical lymphocytosis; liver tests were not done until after stopping methadone and then showed minor abnormalities only [bilirubin normal, ALT 56 U/L, Alk P normal]; no further follow up available).

Tartakow IJ. Narcotic-induced hepatitis. Am J Med 1971; 50: 313-6. PubMed PMID: 5553950.

(Among 1015 cases of viral hepatitis reported in one county in NY over a 3 year period, 162 were believed to be serum hepatitis, of which 107 [66%] occurred in injection drug users).

Kreek MJ, Dodes L, Kane S, Knobler J, Martin R. Long-term methadone maintenance therapy: effects on liver function. Ann Intern Med 1972; 77: 598-602. PubMed PMID: 4629927.

(Among 214 patients with opioid dependency treated with maintenance methadone therapy for up to 3 years, there were no significant changes in liver tests and no deaths from liver disease).

Seeff LB. Hepatitis in the drug abuser. Med Clin North Am 1975; 59: 843-8. PubMed PMID: 1095845.

(Review of the frequency and clinical features of viral hepatitis in injection drug users, including the frequency of chronic hepatitis and history of multiple bouts of hepatitis, only one of which is associated with HBsAg positivity).

Gelb AM, Mildvan D, Stenger RJ. The spectrum and causes of liver diseases in narcotic addicts. Am J Gastroenterol 1977; 67: 314-8. PubMed PMID: 879147.

(Among 42 heroin users with liver disease, 79% were also heavy alcohol users and all 17 patients with cirrhosis also abused alcohol, suggesting that alcohol plays a major role in serious liver disease among drug users).

Vandelli C, Piaggi V, Battilani R, Cariani E, Sirotti MA. Relationship between HBV markers and heroin as a cause of liver injury in drug addicts. Drug Alcohol Depend 1984; 14: 129-33. PubMed PMID: 6510216.

(Among 50 injection drug users admitted to start methadone maintenance who had liver tests abnormalities and underwent liver biopsy, 36 had chronic active hepatitis, 4 had chronic persistent hepatitis, and 10 had nonspecific reactive changes, and all 23 patients with HBsAg in serum had chronic active hepatitis).

Joehl RJ, Koch KL, Nahrwold DL. Opioid drugs cause bile duct obstruction during hepatobiliary scans. Am J Surg 1984; 147: 134-8. PubMed PMID: 6537876.

(32 year old woman with abdominal pain and fever treated with meperidine had an abnormal hepatobiliary scan, but on subsequent laparotomy had a normal biliary system without gallstones; in subsequent volunteer studies, opioid drugs caused delayed clearance of technetium labeled iminodiacetic acid and scans suggested bile duct obstruction).

Bickel WK, Stitzer ML, Bigelow GE, Liebson IA, Jasinski DR, Johnson RE. A clinical trial of buprenorphine: comparison with methadone in the detoxification of heroin addicts. Clin Pharmacol Ther 1988; 43: 72-8. PubMed PMID: 3275523.

(Among 45 patients with opioid dependency treated with either buprenorphine or methadone for up to 90 days, no discussion of side effects or ALT levels).

de Araújo MS, Gerard F, Chossegros P, Porto LC, Barlet P, Grimaud JA. Vascular hepatotoxicity related to heroin addiction. Virchows Arch A Pathol Anat Histopathol 1990; 417 (6): 497-503. PubMed PMID: 2125388.

(Histological analysis of liver biopsies from 39 injection drug users with ALT elevations found sinusoidal dilatation and centro-lobular inflammation were more prominent in actively using compared to previous heroin users, but fibrosis was less).

Drummer OH, Opeskin K, Syrjanen M, Cordner SM. Methadone toxicity causing death in ten subjects starting on a methadone maintenance program. Am J Forensic Med Pathol 1992; 13: 346-50. PubMed PMID: 1288269.

(Among patients starting methadone maintenance who died acutely, the cause of death was respiratory depression in 5 patients and, while all ten had chronic hepatitis, liver disease did not appear to be the cause in any).

Thompson DR. Narcotic analgesic effects on the sphincter of Oddi: a review of the data and therapeutic implications in treating pancreatitis. Am J Gastroenterol 2001; 96: 1266-72. PubMed PMID: 11316181.

(Systematic review of the literature on the effects of opioids on sphincter of Oddi spasm, found little difference among the various opioids in causing an increase in sphincter pressure or symptomatic pancreatitis; recommending use of morphine for pain management, even in acute pancreatitis).

Economou G, Ward-McQuaid JN. A cross-over comparison of the effect of morphine, pethidine, pentazocine, and phenazocine on biliary pressure. Gut 1971; 12: 218-21. PubMed PMID: 4928171.

(Among 31 patients after cholecystectomy with T tubes, morphine, meperidine and pentazocine caused increased bile duct pressure; no mention of abnormal liver tests).

Johnson RE, Jaffe JH, Fudala PJ. A controlled trial of buprenorphine treatment for opioid dependence. JAMA 1992; 267: 2750-5. PubMed PMID: 1578593.

(Trial comparing buprenorphine vs two doses of methadone for opioid dependence for 17 weeks found no serious adverse events in either group; no mention of liver injury or ALT elevations).

Clark RF, Wei EM, Anderson PO. Meperidine: therapeutic use and toxicity. J Emerg Med 1995; 13: 797-802. Review. PubMed PMID: 8747629.

(Review of the efficacy and safety of merperidine, a synthetic opioid used in emergency departments; it has variable absorption and bioavailability and toxicities include seizures and neuropsychiatric reactions, making it a second line agent for treatment of severe pain).

Ling W, Wesson DR, Charuvastra C, Klett CJ. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. Arch Gen Psychiatry 1996; 53: 401-7. PubMed PMID: 8624183.

(Among 225 patients with opioid dependency treated with either buprenorphine or two doses of methadone over a one year period, adverse events were similar in both groups and there were no serious liver related events).

Petry NM, Bickel WK, Piasecki D, Marsch LA, Badger GJ. Elevated liver enzyme levels in opioid-dependent patients with hepatitis treated with buprenorphine. Am J Addict 2000; 9: 265-9. PubMed PMID: 11000922.

(Among 120 opioid dependent patients treated with buprenorphine, ALT and AST levels did not change in patients whose levels were normal initially, but increased slightly in those with preexisting abnormalities [median ALT increase=8 U/L]).

Mattick RP, Ali R, White JM, O'Brien S, Wolk S, Danz C. Buprenorphine versus methadone maintenance therapy: a randomized double-blind trial with 405 opioid-dependent patients. Addiction 2003; 98: 441-52. PubMed PMID: 12653814.

(Controlled trial in 405 patients with opioid dependence found similar rates of adverse events with buprenorphine and methadone; one patient had hepatitis C, but no other liver related adverse events reported).

Ho V, Stewart M, Boyd P. Cholestatic hepatitis as a possible new side-effect of oxycodone: a case report. J Med Case Rep 2008; 2: 140. PubMed PMID: 18452597.

(A 34 year old man developed jaundice 6 weeks after outpatient surgery and while receiving oxycodone [bilirubin 8.2 mg/dL, ALT 295 U/L, Alk P 358 U/L], having received cephalosporin at the time of surgery, with slow but ultimately complete recovery).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease collected in the US between 2003 and 2008, no cases were attributed to an opioid analgesic).

Pinto H, Maskrey V, Swift L, Rumball D, Wagle A, Holland R. The SUMMIT trial: a field comparison of buprenorphine versus methadone maintenance treatment. J Subst Abuse Treat 2010; 39: 340-52. PubMed PMID: 20817384.

(Patient preference controlled trial comparing buprenorphine and methadone for up to 6 months in 361 opiate dependent subjects; no discussion of hepatotoxicity or ALT elevations).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, but none to methadone or other opiates or agents used to treat substance abuse).

Gibson A, Randall D, Degenhardt L. The increasing mortality burden of liver disease among opioid-dependent people: cohort study. Addiction 2011; 106: 2186-92. PubMed PMID: 21749525.

(Among 2489 people enrolled in methadone maintenance programs in Australia between 1980 and 1985 who were tracked using the National Death Index, the standardized mortality rate was increased compared to the general population [SMR = 4.6] and 17% of deaths were due to liver disease [SMR 28 for women and 14.5 for men]).

Saxon AJ, Ling W, Hillhouse M, Thomas C, Hasson A, Ang A, Doraimani G, et al. Buprenorphine/Naloxone and methadone effects on laboratory indices of liver health: a randomized trial. Drug Alcohol Depend 2013; 128: 71-6. PubMed PMID: 22921476.

(Among 731 patients with opioid dependency treated with either buprenorphine and naloxone vs methadone for at least 24 weeks, 12.6% vs 17.9% developed ALT elevations [>2 times ULN] which were "extreme" in only 2.1% vs 3.6% [bilirubin 0.7-3.7 mg/dL, ALT 418-6280 U/L], usually attributable to underlying HBV or HCV infection).

Drugs for Pain. Treatm Guidelines Med Ltr 2013; 11 *(128): 32-43.* *PubMed Citation* (Concise summary and recommendations for use of analgesics including aspirin, acetaminophen, NSAIDs, opiates and adjuvant pain medications).

Naloxegol (Movantik) for opioid-induced constipation. Med Lett Drugs Ther 2015; 57 (1478): 135-7. PubMed PMID: 26393826.

(Concise review of the mechanism of action, efficacy and safety of naloxegol shortly after its approval for use in the US; mentions dose related gastrointestinal side effects, but not ALT elevations or hepatotoxicity).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-1352.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, none were attributed to opiates or opiate antagonists).