

Opioid Analgesic Drugs: Misuse, Toxicity, and Hypersensitivity



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Along with salicylate-rich plants and aspirin, the opium poppy and opioid analgesic drugs (OADs) occupy a special place in folk and Western medicine, the development of drug therapy, and the birth of the pharmaceutical industry. OADs are among the most commonly administered drugs in hospitals and are used often and widely in pain management outside the hospital setting. OADs, particularly fentanyl and its analogs alfentanil, remifentanyl, and sufentanil, are extensively used as a high-dose opioid with a low-dose intravenous hypnotic (usually a benzodiazepine) to produce procedural sedation for endoscopy and catheterizations and in various other surgical procedures. Despite the undoubted value of opioids in anesthesia and for treating acute, chronic, and postsurgical pain, the drugs bring their own problems. In what has been described in the United States as an opioid epidemic, in the period 1999–2014, drug overdose deaths increased nearly 3-fold. In 2014, 28,647 of 47,055 drug overdose deaths (60.9%) involved an opioid; in 2015, the corresponding figures were 33,091 (63.1%) and 52,404.¹ In comparison, 35,092 deaths occurred on US roads in 2015.² In 2016, the Drug Enforcement Administration named heroin and fentanyl as the most significant drug-related threats in the United States.³ From 2002 to 2015, heroin deaths increased 6.2-fold.⁴

Apart from “overdose” deaths to OADs, reports of death due to an allergic (anaphylactic) reaction, that is, type I hypersensitivity, are rare as are milder non–life-threatening type I reactions, cytotoxic antibody-mediated type II hypersensitivities, immune complex-mediated type III hypersensitivities, and delayed T-cell–mediated type IV hypersensitive reactions.⁵ This apparent infrequent occurrence of OAD-induced hypersensitivities, reflected, for example, in their relatively superior perioperative safety compared with colloids, hypnotics, antibiotics, latex, and neuromuscular-blocking drugs,^{6,7} is intriguing and largely accounts for the infrequent immunological clinical and laboratory studies on these agents. As a consequence, there is a dearth of literature information concerning adverse reactions provoked by OADs, clinical and laboratory diagnostic methods, symptoms specifically associated with the different

hypersensitivity types and individual OADs, cross-reactivities between the naturally occurring and semi- and fully-synthetic drugs, and the informed selection of alternative OADs in cases of known sensitivity to 1 or more opioids.

It is against this background that the study in this issue by Li et al⁸ of predictors and provocation testing for opioid allergy is a welcome addition to a relatively neglected field of drug hypersensitivity research. Most cases of hypersensitivity to OADs have been diagnosed in a perioperative setting where opioids have been implicated in approximately 2% of agent-induced anaphylactic reactions^{6,7} and although Li et al⁸ acknowledge this and attribute it to the availability of objective measurements such as monitoring of vital signs, ventilator readings, and tryptase results, they also somehow conclude that the perioperative figure of 2% is likely to be an overestimate due to lack of validated tests. Provocation or challenge testing, considered to be the “criterion standard” in diagnosing drug hypersensitivities, is the controlled stepwise administration of a drug in a supervised hospital environment. As well as emphasizing the need for provocation testing with its capacity to avoid incorrect diagnosis and overdiagnosis, perhaps leading to unnecessary drug avoidance, the authors examined the association between index reaction symptoms and drug hypersensitivity, an important but sometimes neglected investigation of drug allergy. Interestingly, multivariate analysis showed that only angioedema and hypotension were significantly associated with allergy, suggesting that these symptoms may be specifically associated with cases of true IgE-mediated reactions to OADs.⁸ Although attention is drawn to the inherent problems associated with OAD skin testing, the histamine-releasing properties of the drugs and the present lack of information on detection of OAD-reactive IgE antibodies should not always preclude application of these tests to the diagnosis of suspected OAD-induced hypersensitivity reactions. Some OADs are more potent histamine releasers than others, so the dilutions used in skin tests are critical.⁶ Morphine, for example, can be tested at low molar concentrations, whereas fentanyl and tramadol produce little or no release of histamine from skin mast cells.^{5,6,8} Note that drugs should also be tested for histamine-releasing and irritant effects in the skin of normal subjects.

There has so far been limited application of immunoassays to detect anti-OAD IgE and IgG antibodies but a few preliminary studies with direct binding and inhibition assays have revealed some rare cross-reacting IgE antibodies recognizing 1 or more of methadone, meperidine, and fentanyl as well as morphine.^{6,9,10} Except for morphine and codeine where the allergenic (ie, the IgE antibody-binding) determinant was shown to be the cyclohexenyl ring with a hydroxyl at C-6 and a methyl substituent attached to the nitrogen,⁹ no structure-activity investigations have been undertaken to identify antibody-binding and cross-reactive structures on the different OADs. Obtaining such

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immune recognition data is potentially important because it may not always be safe to replace, for example, a phenanthrene, say morphine, with a synthetic such as meperidine or fentanyl.⁶ Therefore, before substituting an OAD, the selected opioid should be used to skin test the patient.

As with skin testing using OADs, IgE serum antibody tests must be undertaken with appropriate controls including inclusion of a positive serum control from an OAD-allergic patient, demonstration of specific inhibition of antibody binding by the culprit drug, and cross-reactive inhibition⁶ by other opioids with related chemical structures. It is important that IgE test results are not considered in isolation and, in interpreting results, one needs to be aware of possible antibody recognition of similar structures on drugs not clinically implicated in the hypersensitivity reaction. Examples of this pitfall are antibody cross-reactions due to recognition of substituted ammonium groups present in OADs and unrelated drugs such as neuromuscular blockers and various other agents of diverse pharmacological action.^{11,12} This may be the explanation of the positive serum IgE results to morphine and pholcodine found in 5% of blood donors and 10% of patients with no history of opioid allergy.^{13,14} If necessary, the clinical relevance of drugs identified in antibody-binding studies may be checked by skin testing and graded challenges of patients.

Although drug-induced IgE-mediated mast cell degranulation and anaphylactoid reactions occur independently of opioid receptors, some OADs reveal functional differences between human mast cells and basophils and between mast cells at different anatomical sites.⁵ The most commonly seen clinical features in anaphylactic patients during anesthesia are cardiovascular collapse, bronchospasm, angioedema, and cutaneous symptoms^{7,15} but the complete set of signs and symptoms is not seen in every patient. If bronchospasm is induced by an opioid in an apparent anaphylactoid reaction, the reaction is likely to be immune-mediated, that is, true anaphylaxis. The findings by Li et al⁸ of angioedema in 10 of the 15 allergic patients (67%) while 7 patients (47%) showed respiratory symptoms and 6 (40%) experienced hypotension are potentially useful observations and it will be interesting to see if this relatively high incidence of angioedema as index reaction is borne out in subsequent investigations of opioid-induced anaphylaxis.

Returning to the alarmingly high incidence of "overdose" deaths to OADs, particularly heroin, detection of nonlethal opioid concentrations in postmortem samples from opioid-dependent users,¹⁶ cardiovascular and respiratory clinical features resembling anaphylaxis in heroin intoxication,¹⁶ detection of increased tryptase concentrations in addicts after intravenous injection of heroin,¹⁷⁻¹⁹ and results of immunohistochemical studies on pulmonary mast cells and postmortem blood samples from 48 heroin-related deaths¹⁸ have led to speculation that at least some of the "overdose" deaths are due to an allergic reaction to heroin. Given the extent and significance of the problem of heroin-related deaths and the potential availability of large

numbers of subjects for study, such a project seems worthy of further examination.

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