

Occupational contact dermatitis caused by opioids: A case series

Ursula Flury^{1,2}  | Jennifer L. Cahill² | Rosemary L. Nixon²

¹Zentrum für Dermatologie und Allergologie, Luzerner Kantonsspital (LUKS), Luzern, Switzerland

²Occupational Dermatology Research and Education Centre, Skin and Cancer Foundation Inc., Carlton, Victoria, Australia

Correspondence

Dr Ursula Flury, Zentrum für Dermatologie und Allergologie, Spitalstrasse 6000 Luzern 16, Switzerland.
Email: ursula.flury@luks.ch

Abstract

Background: Opioid-manufacturing facility workers are at risk of developing occupational contact dermatitis.

Objectives: To describe the causes of occupational allergic contact dermatitis caused by opioids in an opioid-manufacturing facility.

Materials and Methods: A retrospective review was performed of patients assessed at the Occupational Dermatology Clinic in Melbourne, Australia from 2004 to 2017.

Results: Fifteen workers from an opioid-manufacturing facility were assessed in our clinic over a period of 14 years. Of these, 11 individuals were diagnosed with occupational allergic contact dermatitis caused by opioids, with seven reacting to thebaine, five to morphine, four to norhydroxymorphinone, two to codeine, and two to oripavine. Two people were suspected of having immediate hypersensitivity reactions to opioids, including one who also had allergic contact dermatitis. Two patients were diagnosed with urticaria, aggravated at work. One patient was diagnosed with a non-occupational rash.

Conclusions: We report a case series of workers with allergic contact dermatitis caused by opioids in a manufacturing facility. With greater awareness, including implementation of an educational programme and improved skin protection, the number of cases declined over time. Interestingly, norhydroxymorphinone had not been reported as an allergen before. Further testing is required to establish optimal patch test concentrations of all opiates.

KEYWORDS

contact allergy, occupational allergic contact dermatitis, opioids, opioid-manufacturing facility, patch test, urticaria

1 | INTRODUCTION

For thousands of years, opioids have been used for the treatment of pain. Although, classically, the term “opiate” was used to mean a drug derived from opium, the term “opioids” is now used to denote all substances, both natural and synthetic, that bind to opioid receptors.^{1,2} They can be divided into four different classes according to their chemical structure: phenanthrenes, benzomorphans, phenylpiperidines, and diphenylheptanes (Figure 1).³

Phenanthrenes are the prototypical opioids. They are all composed of three fused rings, and include natural alkaloids such as morphine, codeine, and thebaine,^{3,4} but also semisynthetic derivatives such as heroin (diacetylmorphine) and hydromorphone⁴ (Table 1).

Opioids can cause true allergies and pseudoallergies. The latter are caused by activation of mast cell degranulation through direct stimulation and opioid receptor activation, resulting in the release of histamine.⁵ This causes skin reactions, such as flushing, urticaria, and pruritus. Not all opioids have the same capacity to release histamine.⁵

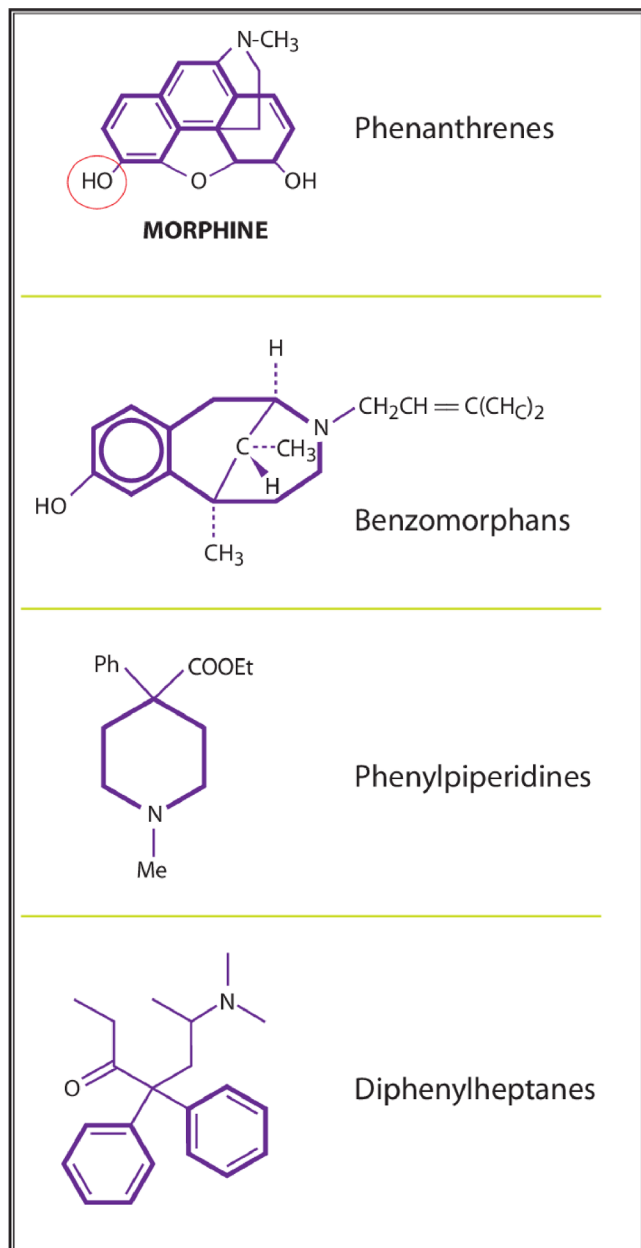


FIGURE 1 Chemical classification of opioids³

TABLE 1 Four classes of opioids and their subtypes

Phenanthrenes	Benzomorphans	Phenylpiperidines	Diphenylheptanes
Morphine	Pentazocine	Fentanyl	Propoxyphene
Codeine		Alfentanil	Methadone
Hydromorphone		Sufentanil	
Norhydroxymorphinone		Meperidine (= pethidine)	
Hydrocodone			
Oxymorphone			
Levorphanol			
Palbuphine			
Buprenorphine			
Oxycodone			
Heroin			
Oripavine			
Thebaine			

Opioid-plant workers risk becoming sensitized by exposure during the processing procedures. Cutaneous sensitization to topical opioids was first described in 1882, according to Touraine's extensive review.⁶ Subsequently, cases of occupational allergic contact dermatitis (ACD) have been reported in morphine-industry workers, doctors, nurses, and pharmaceutical workers.⁶⁻¹¹ In 2012, Wootton et al were the first to describe occupational ACD caused by oxycodone, in three pharmaceutical workers.¹² Recently Dekeyser reported ACD caused by oripavine (tested at 5% pet., ethanol and aq.) for the first time, in a 35-year-old male working in a drug-manufacturing plant who was also allergic to thebaine.¹³

Australia is one of the global players concerning the production and processing of poppy straw, but no cases of occupational ACD have been reported to date.¹⁴ We report a case series of workers from an opioid-manufacturing facility who were referred to our clinic for patch testing over a 14-year period.

2 | CASE SERIES

Sixteen workers were referred from a single opioid-manufacturing plant to our Occupational Dermatology Clinic, Melbourne, Australia for patch testing from 2004 to 2017. Patch testing was performed with our baseline series, any additional relevant allergen series, and a selection of opioids supplied from the workplace. The patches were removed on day (D) 2, and readings were performed on D2 and D4. Opioids were initially tested with the concentrations and vehicles reported,¹¹ but these were subsequently modified after discussions with factory chemists regarding the solubility of opioids in different vehicles. The series as shown in Table 2 was devised. The first patient, who described immediate symptoms, underwent both prick testing and patch testing. However, opioids are direct mast cell degranulators, and comparison with controls soon showed that such testing was not informative.

The patients' characteristics and patch test reactions are summarized in Table S1. Sixteen patients, with a mean age of 36 years, were assessed; 14 were patch tested, and one was diagnosed with a non-

TABLE 2 Opioids used for testing

Opioid	Concentration	Vehicle
Morphine	10%	2% Acetic acid
Morphine	5%	2% Acetic acid
Morphine	3%	3% Acetic acid
Oripavine	5%	2% Acetic acid
Oripavine	3%	2% Acetic acid
Thebaine	1%	Ethanol
Codeine CBA	2.5%	Ethanol
Noscarpine	0.5%	2% Acetic acid
Noscarpine	0.3%	2% Acetic acid
Control	2% and 3% acetic acid	aq.
Norhydroxymorphinone	3%	pet.

occupational skin problem (details not included). The majority ($n = 15$, 80%) were male. Most reported facial dermatitis, indicative of airborne contact dermatitis, although the hands and arms were also often involved. Eleven patients were diagnosed with occupational ACD caused by opioids, with seven reacting to thebaine, five to morphine, four to norhydroxymorphinone (NHM), two to codeine, and two to oripavine. Three patients also had positive patch test reactions to substances other than opioids. One reacted to nickel sulfate and propyl gallate, and another reacted to nickel sulfate, thiuram mix (including two thiuram constituents), and fragrance mix I. The third patient had a positive reaction to methylchloroisothiazolinone. None of these reactions was thought to be relevant to the presenting skin condition.

One patient (case 9) reported rhinitis and asthma-like symptoms, with no rash, and was diagnosed with an immediate hypersensitivity reaction to morphine derivatives. Patch testing was not performed, and the patient was referred to an allergist, but no follow-up information was available. Another two patients (cases 12 and 14) had negative results on patch testing, and were subsequently diagnosed with urticaria, although both had a clear history of aggravation in the workplace and improvement off work.

3 | DISCUSSION

We present 11 cases of occupational ACD caused by opioids from a manufacturing facility in Australia. Two cases were suspected of having immediate hypersensitivity reactions, including asthma, and two had urticaria that was exacerbated by their work exposure. Four of these reported cases were diagnosed as occupational ACD caused by NHM. To our knowledge, NHM has not been described as an allergen, although it is classified as a phenanthrene. The substance was first tested by us in 2004, and the concentration of 3% pet. was chosen after testing several dilutions; however, we no longer have information about the testing performed at that time.

Many of the early cases were assessed some years ago in 2004, when it became clear that workers were being exposed inappropriately to opioid substances, leading to sensitization. This had occurred especially when substances were scraped out of a centrifuge and transferred to a different container. A worksite visit was undertaken, and subsequently an educational programme highlighting the dangers of any skin contact with opioids was implemented. Very few cases of ACD were reported subsequently, until cases 11 and 13 were reported recently. We believe this to be the largest case series from an opioid-manufacturing facility reported to date, although we recognize that such problems may often be dealt with in-house and thus be under-reported.

The majority of our workers with ACD experienced facial involvement, some with a clear-cut clinical pattern of airborne exposure. This made avoidance of the allergen in the workplace difficult, and, in a number of cases, workers had to leave their employment because of ongoing ACD. Many of the cases reported in the literature have described cross-reactions between different opioids within the same class.^{4,15,16} Our data show that, of 11 patients with ACD, six reacted to at least two substances. This might be indicative of cross-reactivity, or, alternatively, multiple exposures.

Some older reports have mentioned that workers with occupational ACD have developed the same or even more extensive skin eruptions after oral medicament intake of opioids.^{9–11} None of our workers described reactions to systemic opioids, but they were warned about this possibility. In the event that a sensitized person requires narcotic analgesia, it would be useful to organize further investigations to answer this question. Mucosal and respiratory complaints caused by opioids have already been reported by Hogen Esch et al. They analysed serum for IgE specific for heroin, but a type I allergy to heroin could not be shown. They assumed that the complaints were attributable to the histamine-liberating effect of heroin, to atopic constitutions, to a combination of these factors, or to other non-allergic factors.¹⁷ Two workers described aggravation of urticaria at work. It was thought that this most likely resulted from systemic exposure to small amounts of opioids, which are direct mast cell degranulators. In at least one case, it was necessary for the worker to leave the workplace.

In conclusion, we report a case series of workers with ACD caused by opioids in a manufacturing facility. There is no doubt that morphine, thebaine, NHM, oripavine and codeine are skin sensitizers. However, information is lacking with regard to the optimal patch test concentrations, and further research is necessary.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

ORCID

Ursula Flury  <https://orcid.org/0000-0002-5670-4045>

REFERENCES

1. Royston D, Hemmings HC. Physiology and Pharmacology for Anesthesia: Foundations and Clinical Application: Expert Consult—Online and Print. Elsevier. p. 253; 2013. <http://www.clinicalkey.com/dura/browse/bookChapter/3-s2.0-C20090417124>. Accessed May 19, 2019.
2. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain Physician*. 2008;11(2 suppl):S105-S120.
3. Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. *Pain Physician*. 2008;11(2 suppl):S133-S153.
4. Sasseville D, Blouin M-M, Beauchamp C. Occupational allergic contact dermatitis caused by morphine. *Contact Dermatitis*. 2011;64:166-168.
5. Zhang B, Li Q, Shi C, Zhang X. Drug-induced pseudoallergy: a review of the causes and mechanisms. *Pharmacology*. 2018;101:104-110.
6. Touraine A. Les dermatoses de l'opium. *Revue de Médecine*. 1936;53:449-460.
7. Low RC. *Anaphylaxis and Sensitization*. Edinburgh, Scotland: W. Green and Son, Ltd.; 1924:182.
8. Palmer RB. Contact dermatitis due to codeine. *Arch Dermatol*. 1942;46:82.
9. Jordon JW, Osborne ED. Contact dermatitis from opium derivatives: with special reference to occupational aspects. *JAMA* [Internet]. 1939;113:1955-1957. <http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.1939.02800470031007>. Accessed December 16, 2016.
10. Dore SE, Prosser Thomas EW. Contact dermatitis in a morphine factory. *J Allergy*. 1945;16:35-36.
11. Waclawski ER, Aldridge R. Occupational dermatitis from thebaine and codeine. *Contact Dermatitis*. 1995;33:51.
12. Wootton CI, English JS. Occupational allergic contact dermatitis caused by oxycodone. *Contact Dermatitis*. 2012;67:383-384.
13. Dekeyser S, van Tomme M, Boone B, van Geel N, Lapeere H. Occupational allergic contact dermatitis caused by thebaine and oripavine. *Contact Dermatitis*. 2017;76:120-122.
14. International Narcotics Control Board, United Nations, Narcotic Drugs 2015. Estimated World Requirements for 2016, Statistics for 2014. comments_E.pdf [Internet]. https://www.incb.org/documents/Narcotic-Drugs/Technical-Publications/2015/comments_E.pdf. Accessed December 17, 2016.
15. Rodriguez F, Fernandez L, Garcia-Abujeta JL, Maquiera E, Llaca HF, Jerez J. Generalized dermatitis due to codeine. *Contact Dermatitis*. 1995;32:120.
16. Rodriguez A, Barranco R, Latasa M, de Urbina JJO, Estrada JL. Generalized dermatitis due to codeine. Cross-sensitization among opium alkaloids. *Contact Dermatitis*. 2005;53:240.
17. Hogen Esch AJ, van der Heide S, van den Brink W, van Ree JM, Bruynzeel DP, Coenraads PJ. Contact allergy and respiratory/mucosal complaints from heroin (diacetylmorphine). *Contact Dermatitis*. 2006;54:42-49.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Flury U, Cahill JL, Nixon RL. Occupational contact dermatitis caused by opioids: A case series. *Contact Dermatitis*. 2019;81:332–335. <https://doi.org/10.1111/cod.13305>

Online supplemental Table 1. Summary of participants with conditions related to opioid exposure

No	Sex/ age	Initial appt	Duration of work	Atopy	History of immediate hypersensi-tivity to opioids	Site of rash	Positive reactions	Relevant diagnosis
1	M/31	March 2004	3.5 yrs	Nil	Nil	Hands, legs, neck, arms	NHM ++	ACD to NHM
2	F/28	March 2004	2 yrs	Asthma	Nil	Neck, abdomen, face, chest, axilla	Morphine + NHM ++	ACD to morphine and NHM
3	M/25	March200 4	16 mths	Asthma	Nil	Chin, forehead	Morphine ++	ACD to morphine
4	M/28	March.200 4	12 mths	Nil	Nil	Face	NHM +	ACD to NHM
5	M/32	August 2004	17 mths	Asthma	Nil	Face	Thebaine ++ NHM + nickel sulfate + propyl gallate ++	ACD to thebaine and NHM

6	F/44	Oct 2004	4 yrs	Nil	Nil	Hands, neck, arms	Thebaine + codeine + nickel sulfate + thiuram mix + fragrance mix + tetramethyl-thiuram disulfide ++ dipenta-methylene-disulfide +	ACD to thebaine and codeine
7	M/36	Nov 2004	18 mths	Asthma eczemaallergic rhinitis	Nil	Face, hands, arms	Morphine + thebaine +	1.ACD to morphine and thebaine 2. Suspected immediate hypersensitivity 3.Endogenous eczema
8	M/28	Dec 2007	-	Nil	Nil	Face	Thebaine +	ACD to thebaine
9	F/33	July 2011	-	Allergic rhinitis	Allergic rhinitis, asthma-like reactions in work-place	Nil	Not performed - referred to allergist	Suspected immediate hypersensitivity
10	M/49	Aug 2013	3.5 yrs	Nil	Nil	Face	Oripavine ++ thebaine ++	ACD to oripavine and thebaine

11	M/38	Nov 2016	4.5 yrs	Nil	Nil	Face, neck, hands	Morphine ++ codeine + thebaine ++ methylothiazolinone ++	ACD to morphine, codeine and thebaine
12	M/40	Feb 2017	3 yrs	Asthma	Unknown	Head, Trunk, Limbs	Negative	Urticaria, exacerbated by work environment
13	M/42	June 2017	20 yrs	Asthma	Nil	Face	Thebaine ++ morphine+ oripavine+	ACD to thebaine, morphine, oripavine
14	M/51	Nov 2017	16 years	Nil	Nil	Generalised itch, urticaria	Negative	Urticaria, exacerbated by work environment