

Contact allergy and respiratory/mucosal complaints from heroin (diacetylmorphine)

A. J. HOGEN ESCH^{1,2}, S. VAN DER HEIDE¹, W. VAN DEN BRINK^{3,4}, J. M. VAN REE^{3,5}, D. P. BRUYNZEEL⁶
AND P. J. COENRAADS¹

¹University Medical Center Groningen, University of Groningen, ²Refaja Hospital, Stadskanaal, ³Central Committee for the Treatment of Heroin Addicts (CCBH), Utrecht, ⁴Academic Medical Center University of Amsterdam, Amsterdam, ⁵Rudolf Magnus Institute of Neurosciences, University of Utrecht, Utrecht, and ⁶Free University Medical Center, Amsterdam, the Netherlands

After the start of heroin (diacetylmorphine)-assisted treatment to a selected group of chronic treatment-resistant heroin-dependent patients in the Netherlands, we reported about work-related eczema and positive patch tests to heroin in some nurses and nasal and respiratory complaints. To investigate the prevalence of heroin contact allergy, we started a questionnaire-based study with follow-up by allergological examinations. Of 120 questionnaires sent, 101 (84%) was returned: 67 from nurses and 34 from other employees. Of 101 workers, 38 (38%) had reported work-related complaints: 33 of 67 (49%) nurses and 5 of 34 (15%) other employees. Patch tests to heroin were performed in 24 nurses and were positive in 8 (33%). All the 8 had eyelid or facial eczema and, in 6, accompanied by mucosal or respiratory complaints. The prevalence of heroin contact allergy in this study was 8% (8/101) among all employees and 12% (8/67) among nurses. Respiratory and mucosal complaints could not be ascribed to a contact allergy, and in these cases, serum was analysed for specific immunoglobulin E to heroin. A type 1 allergy to heroin could not be shown. These complaints are possibly due to the histamine-liberating effect of heroin, to atopic constitution, to a combination of these factors or – less likely – to other non-allergic factors.

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4 years ago, a multicentre project was started in 6 cities in the Netherlands to study the effectiveness of medical prescription of heroin (diacetylmorphine) in a selected group of chronic treatment-resistant heroin-dependent patients, in order to improve their health and social function (1). Since the start of this project, in which heroin is taken under medical supervision, several nurses presented with work-related eczema of eyelids, face, neck, hands and arms (2, 3). Patch tests were performed and were positive to diacetylmorphine and related opioids at 48 hr and 72 hr in several tested nurses and negative in control subjects. There were also nurses who had work-related complaints of nasal mucosa or respiratory complaints. In their work at the dispensing unit, the nurses handled capsules containing a mixture of heroin and caffeine. Meanwhile, the project's operating procedures have been changed to reduce the risk of airborne exposure and to avoid manual contact with the capsules, which

are now handed over in small sealed bags. There were no reports of this kind of eczema in the heroin addicts. To investigate the prevalence of heroin-contact allergy among all workers in the heroin delivery project, we started a questionnaire-based study, followed by an allergological investigation.

Subjects and Methods

Questionnaires were developed and sent to the treatment units of the project in all the 6 treatment units in the Netherlands cities (Amsterdam, Rotterdam, Utrecht, The Hague, Groningen and Heerlen) and distributed to all employees by the unit managers. Questions were asked about work-related hand eczema, work-related eyelid eczema, work-related complaints of nasal mucosa and respiratory complaints and about atopy. Employees who reported work-related complaints were invited for a dermatological and allergological examination.

Patch tests were performed with diacetylmorphine in 4 concentrations [0.3% petrolatum (pet.); 1% pet.; 3% pet. and 5% pet.], with caffeine (1% pet.), which was also an ingredient of the capsules and with diacetylmorphine/caffeine 1% pet. The 1% diacetylmorphine-test concentration was based on commonly reported concentrations for related compounds. The 0.3%, 3% and 5% concentrations were chosen as possible safe margins of deviation around the 1%. All these concentrations were checked on non-toxicity by patch testing 5 healthy controls. Initially, some nurses have only been tested with the mixture diacetylmorphine/caffeine 1% pet. Nurses who did not show reactions on diacetylmorphine/caffeine 1% pet. were later tested with diacetylmorphine in other concentrations. In order to study possible cross reactions, employees were also patch tested with the chemically related opioids morphine and codeine. In addition, we patch tested with the chemically less-related, therapeutically used opioids fentanyl, piritramide, buprenorfine, pentazocine, methadone, oxycodon and tramadol. Also, the European standard series and a cosmetics series were tested. Besides, we performed prick tests with common inhalant allergens.

In employees with mucosal or respiratory complaints, serum was analysed for specific immunoglobulin E (IgE) to heroin. Although the existence of IgE antibodies that react with morphine and codeine have been described in literature (4), IgE antibodies and type 1 allergy to heroin have never been detected. Two different methods were used to detect specific IgE to heroin. In the first method, heroin was incubated overnight with bovine serum albumin immobilized to caps in order to conjugate heroin to these caps. Then serum was added. After incubation and washing, labelled anti-IgE was added, followed by substrate incubation. In the second method, heroin was conjugated to epoxy-sepharose according to the procedure described by Harle (4), who conjugated morphine and codeine to epoxy sepharose. Patient serum and labelled anti-IgE were added to this conjugate.

Prick tests with diacetylmorphine were not performed. They were deemed unreliable, because most opioids are histamine liberators (5).

Results

Questionnaires

Questionnaires were distributed to 120 employees (mainly nurses but also security workers, doctors, cleaners, social and other workers). A total of 101 questionnaires were returned (response 84%); 67 by nurses and 34 by other workers (Fig. 1).

There were 38 of 101 (38%) employees who reported work-related complaints. Of these, 29 reported work-related eczema of whom 10 did not have mucosal or respiratory complaints, and 9 reported work-related mucosal and/or respiratory complaints without having eczema. Work-related complaints were mainly reported by nurses. Of 67 nurses, 33 (49%) reported work-related complaints, and of 34 other employees 5 (15%) reported work-related complaints (Fig. 1).

The percentage of atopic subjects was higher among workers with complaints (50%) than workers without complaints (24%) (Table 1). Patch tests were performed in 28 subjects with work-related complaints; 15 (54%) were atopic. In the subgroup of 24 tested nurses, 13 (54%) were atopic.

Patch tests

38 employees with work-related complaints were invited for patch testing, of whom 28 (74%) were tested (Fig. 1). There were several reasons for not testing the other 10 invited employees (9 nurses and 1 medical doctor); some of them were not interested in testing, because symptoms had disappeared after changing the working circumstances and several employees did not work on the project anymore when they were invited for patch testing (most of them were stand-in-workers). Of the 28 workers who were patch tested, 24 were nurses, 2 were security workers and 2 were cleaners.

Of 28 tested workers, 10 (36%) showed reactions on heroin patch tests (Fig. 1). All positive reactions were in nurses (10/24 = 42%), and in two of them, the reactions were doubtful (Table 2). One of the nurses (nurse 2) only had positive reactions on the later tested diacetylmorphine in the higher concentrations 3% and 5%, without reactions on diacetylmorphine in the lower concentrations and without reactions on diacetylmorphine/caffeine 1%. Nurse 4 did not show a reaction on diacetylmorphine/caffeine 1% and reacted positively on the later tested diacetylmorphine 1%, 3% and 5% and doubtfully on 0.3%. The other 6 nurses showed positive reactions on diacetylmorphine/caffeine 1% and 2 of them also on the other diacetylmorphine concentrations (nurse 5 and 7). 4 nurses who were initially only tested with diacetylmorphine/caffeine 1% and reacted positively were not tested with the other diacetylmorphine concentrations (nurses 1, 3, 6 and 8). Cross-reactions with the chemically related opioid morphine were seen in 6 of 8 and cross-reactions with codeine in 4 cases (Table 2). The synthetic opioid Oxycodon, which has some structural similarity, did not show

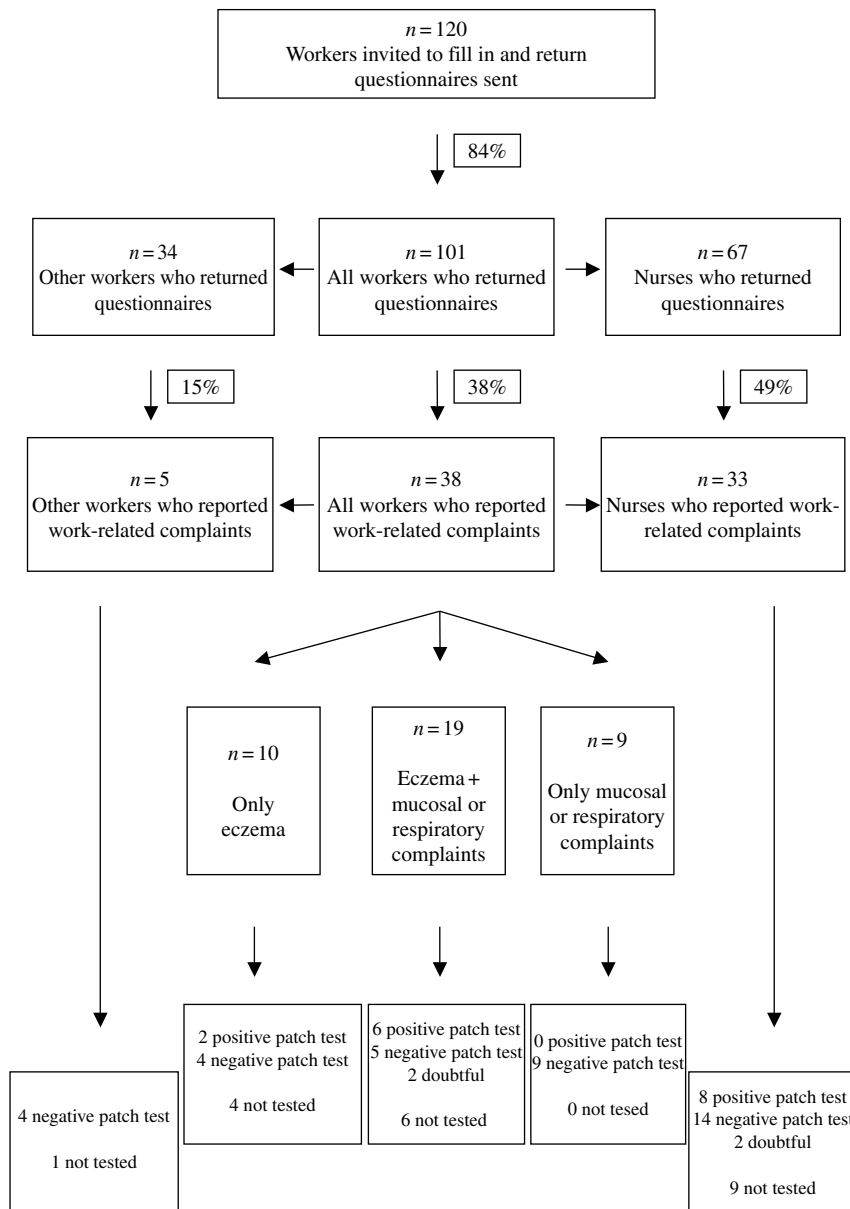


Fig. 1. Numbers of questionnaires (sent and returned), reported work-related complaints and heroin patch test (patch t.) results (pos. is positive and neg. is negative) of nurses and other workers employed in heroin delivery project.

cross-reactions with heroin. There were no cross-reactions with the chemically unrelated opioids like methadone or fentanyl, only 1 doubtful reaction on the opioid piritramide in nurse 9. There

were no positive reactions on the separately tested caffeine (1% pet.). Only nurse 9, who reacted doubtfully on several substances, had a doubtful reaction on caffeine. Table 3 shows that all 8 nurses with positive heroin patch tests reported eczema: 7 eyelid eczema, 6 eczema of other parts of the face or neck, 3 hand or arm eczema. 3 of the 8 nurses had also reported nose/respiratory complaints, and 3 had conjunctivitis. Urticaria was not reported by any of the 8 nurses.

Table 1. Number and percentage of atopics from questionnaires

Workers	n	Atopics n (%)
Workers who returned questionnaires	101	34 (34)
Workers with complaints	38	19 (50)
Workers without complaints	63	15 (24)
Nurses who returned questionnaires	67	23 (34)
Nurses with complaints	33	17 (51)
Nurses without complaints	34	6 (18)
Patch-tested workers	28	15 (54)
Patch-tested nurses	24	13 (54)

In 20 of 28 tested workers with work-related complaints, heroin patch tests were not clearly positive (18 negative and 2 doubtful reactions). 9 of them only had mucosal/respiratory complaints (without eczema), 5 only had eczema (without mucosal/respiratory complaints), and 6 had both eczema and mucosal/respiratory

Table 2. Patch-test results on diacetylmorphine (heroin) and other opioids, caffeine, European standard and cosmetics series in 24 nurses and 4 other workers

	Heroin 0.3% in pet.	Heroin/caffeine 1% in pet.	Heroin 1% in pet.	Heroin 3% in pet.	Heroin 5% in pet.	Morphine 1% in pet.	Codeine 1% in pet.	Other opioids*	European standard and caffeine 1% in pet.	Cosmetics series
Nurse 1	NT	+	NT	NT	NT	+	+	-	-	-
Nurse 2	-	-	+	+	+	-	-	-	-	-
Nurse 3	NT	+	NT	NT	NT	+	-	-	Nickel	-
Nurse 4	?	-	+	+	+	-	-	-	Nickel	-
Nurse 5	+	+	+	+	+	+	+	-	-	Cocamidopropylbetaine
Nurse 6	NT	+	NT	NT	NT	+	+	NT	-	-
Nurse 7	+	+	+	+	+	+	-	-	Balsam peru, fragrance mix, nickel	-
Nurse 8	NT	+	NT	NT	NT	+	+	-	-	-
Nurse 9	?	-	?	?	?	?	?	---	Caffeine?	-
Nurse 10	?	-	-	-	-	-	-	-	-	-
Nurses 11-24	-	-	-	-	-	-	-	-	Nickel 5, woolalcohol 2, thiomersal 1, fragrance mix 1, wood tar 1 Nickel 1	Hydroxycitronellal 1, isoeugenol 1
Workers 25-28	-	-	-	-	-	-	-	-	-	-

NT = not tested.

*This series includes fentanylcitrate 0.1% in pet., oxycodone 1% in pet., piritramide (ampul 10 mg ml⁻¹ aq), buprenorfine 0.1% in pet., pentazocine (ampul 30 mg ml⁻¹ aq), methadone 1% in pet. and tramadol 1% in pet.

**This nurse had a doubtful reaction on piritramide and negative reactions on all the other opioids in this series.

Table 3. Work-related complaints and atopy in 8 nurses with positive heroin patch tests

	Eyelid eczema	Hand/ arm eczema	Face/ neck eczema	Nose/ respiratory complaints	Conjunctivitis	Headache	Urticaria	Atopy
Nurse 1	+	+	+					
Nurse 2	+	+	+	+				
Nurse 3	+		+	+				
Nurse 4	+			+				
Nurse 5		+	+		+	+		+
Nurse 6	+		+		+			
Nurse 7	+		+					+
Nurse 8	+				+			+
Total	7	3	6	3	3	1	0	3

complaints. Of the 18 heroin patch-test negative employees, 5 had a positive patch test on nickel; 1 on woolalcohol; 1 on a combination of nickel, woolalcohol, thiomersal, wood tar and fragrance mix and 1 on a combination of hydroxycitronellal and isoeugenol.

IgE serum tests

In the 28 workers with work-related mucosal or respiratory complaints, blood was taken to look for specific IgE to heroin. Using the first method where heroin was tried to conjugate to albumin which was immobilized to a solid phase (caps), we found that there was not any response after adding serum and labelled IgE in any of the sera. Using the second method, where heroin was conjugated to epoxy-sepharose, we found that there was a positive fluorescence signal after adding patient serum and anti-IgE antibodies in all subjects. However, control sera also showed increased fluorescence.

Literature Review and Discussion

Literature review

Heroin contact allergy has never been described before. Contact dermatitis from other opioids, either therapeutically or occupationally applied, has been documented.

Work-related skin problems and opioids. Work-related skin problems caused by opioids have been documented in literature since the end of the 19th century. In 1893, it was first mentioned by De Lewin (6) who reported about a 61-year-old worker engaged in the manufacturing of apomorphine who developed fever, malaise and an itchy squamous eruption starting on forearms with subsequent spread to the upper part of the body. In the first decades of the last century, several cases of occupational skin problems have been documented in morphine industry workers, in nurses, doctors and in pharmaceutical workers (7–11). In many cases, it was about

allergic contact dermatitis caused by morphine or by codeine and confirmed by positive patch tests, often showing cross-reactions between both opioids. Some workers who were occupationally sensitized by external contact with opioids developed the same or even more extensive skin eruptions after oral intake of the opioids in tablet or cough mixture (9–11). More recently, occupational opioid contact dermatitis was described by Romaguera (12) in workers engaged in manufacture of opium alkaloids and in a female laboratory worker manufacturing opiates by Waclawski (13).

Skin problems and therapeutically used opioids. Contact dermatitis from externally therapeutically used opioids is documented since the 19th century. Comanos in 1882 (14) was the first to describe a case of dermatitis from opium compounds. In the course of the last century, more case reports were published (15, 16). Subcutaneous administration of morphine and hydromorphone can give local intolerance (17) and has caused generalized dermatitis with positive patch tests in case of hydromorphone (18).

Cutaneous drug eruptions from systemic therapeutic use of opioids have been documented by many authors, probably first by Von Essen in 1894 (19). The systemic cutaneous reactions can be divided in four groups: (i) scarlatiniform erythemas (8, 18–23), (ii) eczematous reactions (8–11, 16, 18, 24, 25), (iii) pruritus and urticaria (probably also caused by direct histamine release) (8, 22, 26, 27) and (iv) other drug eruptions like erythema multiforme (11, 28), fixed drug eruptions (29–31) and erythema nodosum (32).

Heroin and skin problems. Although there are only few publications about skin problems caused by heroin, Pignot in 1931 (33) already described an itchy erythema of the face, later accompanied by vesicles and oedema, especially of the eyelids in 18 workers in a factory in Paris, who worked with morphine, codeine and heroin. He noted this work-related dermatitis most

commonly in workers engaged in the purification of heroin. In this publication, Pignot did not report patch testing.

Skin problems from therapeutically used heroin were described by Scott and Fischer (34) in a patient with facial itching 5 hr after she was given diacetylmorphine hydrochloride intrathecally.

Although there are no reports about contact dermatitis from heroin in addicts, there are publications about several other skin complications appearing in heroin addicts by Young and Rosenberg (29). They described skin disorders as local complications from injections such as scars, abscesses, ulcers, thrombophlebitis and bullae but also more systemic skin effects such as eyelid oedema, urticaria, fixed drug eruptions, purpura and pruritus. Weidman and Fellner found cutaneous signs of adverse effects in 86 of 100 cases of drug abuse. They found hyperpigmentation at the injection side to be the most frequent finding. In 3 cases of heroin abuse, urticaria was seen and, in one case, eyelid oedema. They noted a maculopapular-generalized eruption in 2 heroin abusers but did not report about contact dermatitis from heroin (35). Gendelman et al. (36) described a case of leucocytoclastic vasculitis from intravenously heroin use, and Westerhof et al. (37) described some cases of fixed drug eruptions on the tongue in addicts inhaling heroin.

Just like many other opioids, heroin is a strong histamine liberator. Cutaneous reactions such as erythema, urticaria and itch have been described in intravenous drug use (38), and anaphylactoid reactions especially severe asthma and also urticaria have been described as a result of inhaling heroin (39–41).

Discussion

The results of this study suggest a high, possibly airborne, allergenic potential of heroin. Although, also, other employees reported skin and other symptoms, positive patch tests were only seen in nurses, probably because only they were in direct contact with heroin.

All nurses with positive patch tests to heroin (8/67 = 12%) had work-related eczema, most commonly on neck or face, especially the eyelids; eyelid eczema seems to be the most common symptom of heroin contact allergy and was seen in 7 of 8 allergic nurses (88%). This is in concordance with the 'dermatitis of especially the eyelids' described by Pignot (33) in 18 factory workers, who worked with heroin. Hand or arm eczema was seen in 3 allergic nurses (38%). In 6 of 8 cases, eczema was accompanied by mucosal or respiratory complaints (75%).

Just like the other authors who published about opioid allergy, we saw cross-allergic reactions to the chemically related opioids. Cross-reactions to morphine were seen in most cases of heroin allergy (6/8 = 75%) and to codeine in half of the cases (4/8 = 50%). Contrary to what we expected, there were no cross-reactions with the structurally related synthetic opioid Oxycodon. Not unexpectedly, we saw no cross-reactions to chemically unrelated, synthetic opioids such as methadone and fentanyl. These findings indicate that nurses with work-related allergies because of the handling of diacetylmorphine can use other prescribed opioids in cases of medical necessity without any medical risk.

In 16 of 24 tested nurses with work-related complaints (66%) and in 20 of 28 tested workers (71%), no heroin contact allergy was found. Of these nurses, 4 had only eczema (25%), 6 only mucosal/respiratory complaints (38%) and another 6 had eczema as well as mucosal/respiratory complaints (38%). The complaints in these 16 nurses must have been caused by other factors. We suggest 3 possible heroin-related reasons. First, these complaints might have been caused by non-immunological histamine release. Heroin is a potent histamine liberator and cutaneous reactions such as erythema, urticaria and itch in intravenous drug use (38) as well as anaphylactoid reactions such as asthma in inhaling heroin (39–41) have been described. Second, we have considered and studied the possibility of a type 1 allergy to heroin as a cause of these complaints. However, specific IgE to heroin has never been described in literature. IgE antibodies reacting to morphine and to codeine have been described by Harle (4) in the serum of a subject who experienced a life-threatening reaction following administration of papaveretum (an opioid mixture). Because of lack of a positive-control serum, our IgE assay for heroin could not be validated. Therefore, the existence of IgE antibodies in the patient serum cannot be excluded completely. Third, the complaints might be associated with atopy. The percentage of atopics was indeed higher in workers with complaints than in workers without complaints (Table 1). The percentage of atopics was higher in nurses with a negative heroin patch test (10/16 = 63%) than in nurses with a proven heroin contact allergy (3/8 = 38%). This is in line with our reasoning that atopy might be (jointly) responsible for the complaints in nurses without a heroin-contact allergy. Atopic individuals may also be more sensitive to the effects of the histamine release by heroin. From the literature, it is known that broncho-constriction and local oedema produced by histamine release through opiates is especially

seen in atopics (39). Finally, it can not be excluded that some of the reported work-related problems are not attributable to contact with heroin particles at all. The higher rate of complaints in nurses (49%) compared with other workers (15%) and the fact that positive patch test were seen only among nurses support the role of heroin contact as one of the most plausible reasons for the reported work-related problems, but other potential causes can not be excluded completely.

In conclusion, it is found that, in a dispensing unit where patients are treated with inhalable heroine, almost 50% of the nurses report work-related problems that are most likely related to contact with the prescribed medication (heroin). In about 1/3 of these cases, a positive patch test was found, indicating the presence of a heroin-contact allergy. In the remaining 2/3, the reported work-related problems are probably caused by (a combination of) non-immunological histamine release, the presence of IgE antibodies against heroin or the pre-existence of an atopic constitution. Fortunately, a change in the delivery procedure effectively prevented further cases of work-related complaints. Finally, it should be noted that there were no cross-reactions with opioids chemically unrelated to heroin. This finding precludes the occurrence of adverse reactions to prescribed opioids for pain relief in nurses who were sensitized for heroin during their work in the heroin-dispensing unit.

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Address:
P. J. Coenraads
Dermatology UMCG
PO Box 30001
9700 RB Groningen
the Netherlands
e-mail: p.j.coenraads@med.umcg.nl