



Occupational allergy to pharmaceutical products

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Purpose of review

Occupational allergy in healthcare workers is common and can lead to significant costs from both loss of productivity within the workforce as well as those associated with diagnosis and treatment. This review aims to provide an update on drugs implicated in causing occupational allergy.

Recent findings

Drugs traditionally reported as causing occupational allergy, such as penicillin, remain problematic. However, as their use reduces and newer drugs, such as cephalosporins, are used more frequently there is a changing pattern to occupational sensitization. In some studies up to 17% of healthcare workers now appear sensitized to cephalosporins. Other drug classes also reported include proton pump inhibitors and benzodiazepines. Interestingly, drugs such as omeprazole and tetrazepam rarely cause allergy in patients but can be very sensitizing if applied topically or inhaled. Recent studies involving pharmaceutical company employees show that this problem can no longer be considered primarily related to healthcare workers.

Summary

The diagnosis of occupational allergy to drugs can be complicated and has been shown to take up to 5 years from the onset of symptoms. Ultimately, workplace avoidance remains key; however, an up to date awareness of culprit drugs and the patterns of allergy seen are key to a prompt resolution of symptoms.

Keywords

drug allergy, healthcare worker, hypersensitivity, pharmaceutical

INTRODUCTION

Sensitization to drugs can take place in the work place either through topical contact with spilled drugs or by inhalation of powder or foam. Many drugs are able to either irritate or sensitize the skin, eyes, and respiratory tract. Once sensitized re-exposure can lead to a type I (IgE-mediated) reaction with rhinitis, asthma, and urticaria or more commonly a type IV (T cell-mediated) reaction with an allergic contact dermatitis. In contrast to irritant dermatitis, the skin lesions with allergic contact dermatitis tend to extend beyond the site of exposure and can occur at much lower concentrations [1]. That being said clinical examination alone is not accurate at distinguishing between irritant and allergic dermatitis and the correlation between examination and patch testing is inconsistent [2]. The distribution of the dermatitis is also important; if the pattern is centered on the face, neck, and upper eyelids then it is likely the antigen is airborne [3].

Re-exposure can take place in the workplace or when a sensitized individual receives the drug for their own personal need. Although anaphylaxis is rarely encountered there is often a history of milder

self-limiting reactions prior to its development. An example of this includes anaphylaxis to ingested psyllium in two nurses with a prior history of rhinitis to occupational exposure [4].

RISK FACTORS FOR SENSITISATION

Risk factors can include factors associated with individuals as well as the factors relating to the drug that they are being exposed to. Some drugs, such as psyllium, appear to have high risk of sensitization with some studies suggesting that up to 40% of exposed nurses become sensitized with immediate symptoms of rhinitis and ocular symptoms [5]. β -lactam antibiotics also have a propensity for sensitization. One study [6] reported sensitization rates of 12% to penicillin in nonallergic nurses, when skin tests were performed. Two recent studies

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KEY POINTS

- Occupational allergy to drugs is frequently encountered by both healthcare workers and pharmaceutical company employees.
- Owing to poor reporting and lack of awareness it can take several years between the onset of symptoms and a formal diagnosis.
- As prescribing practices change clinicians must be aware of new drugs leading to occupational allergy; many of these have low allergic potential in patients.

demonstrate that 2.6% of Korean nurses were sensitized to a panel of β -lactam antibiotics on skin prick testing [7] and 17.4% had specific IgE to cephalosporins [8]. Interestingly, the risk of sensitization does not always relate to the known allergic potential in patients. Drugs such as tetrazepam and omeprazole rarely lead to reactions in patients but are an increasing cause of occupational allergy [9,10[■]].

It is known that several factors related to the individual can also increase risk of becoming sensitized. Preexisting hand dermatitis, a history of atopy, repeated exposure, and duration of employment have all been reported as leading to increased risk [1,11[■]]. In the report by Choi *et al.* [7] the rate of immediate sensitization to β -lactam antibiotics in nurses with preexisting hand dermatitis was 6.9% compared with the 2.6% overall. This has been seen in other publications [8,12]. Nam *et al.* [13] explored occupational sensitization further and found that the *FcεR1* β -109T more than C polymorphism was significantly associated with IgE sensitization to cephalosporins suggesting a genetic basis for sensitization. The same group also reported genetic polymorphisms ADRB2 46A more than G and IL10-1082A more than G were risk factors that increased IgE sensitization to pancreatic extracts in 39 individuals occupationally exposed to digestive powders [14].

OCCUPATIONS AFFECTED

An individual developing an occupational allergy can have major implications for their work productivity as well as the cost of investigating and treating them. Occupational skin diseases in particular represent over 30% of all occupational diseases [15]. Although the incidence of occupational contact dermatitis is not fully known it is estimated to be between 11 and 86 cases/100 000/year [16]. Traditionally, healthcare workers, in particular nurses and pharmacists, have been identified as being at high risk of developing occupational allergy.

Pesonen *et al.* [15] recently reported a relative risk of 5.86 of nurses developing occupational contact dermatitis compared with the general population. Although contact allergy to antiseptics, disinfectants, and gloves account for the majority of cases a substantial number can be attributed to drug exposure. In a recent retrospective review, Schwensen *et al.* [11[■]] described the results of investigating 1402 healthcare workers who had experienced dermatitis. Patch test positive cases included 12 study participants to budesonide, 17 to neomycin, 10 to tixocortol, and one to benzocaine. In another retrospective case series, Breuer *et al.* [17] included 16 healthcare workers (five veterinarians and 11 nurses) with delayed airborne contact dermatitis. Positive patch test was confirmed in six individuals: four to tetrazepam, one to tylosin, and one to pantoprazole.

Pharmaceutical workers are another high-risk group. Bennett *et al.* [18[■]] recently reported 32 cases of delayed contact dermatitis in individuals involved in the manufacturing process. Included in her cohort were the first reported cases of occupational contact allergy to imatinib, fluvastatin, abacavir, ziprasidone, and pirlmenol. Interestingly, seemingly unrelated occupations can also lead to exposure to antigens that indirectly lead to drug sensitization. In the past this type of indirect sensitization was seen with pholcodine and the risk of reaction to neuromuscular blocking agents in a non-occupational setting [19]. More recently in hairdressers positive IgE antibodies against quaternary ammonium ions found in cosmetics were shown to crossreact with neuromuscular blocking agents used in anesthesiology [20].

SPECIFIC DRUG CAUSES OF OCCUPATIONAL ALLERGY

Although there is a long list of drugs that can cause occupational allergy the following section will highlight classes of drugs that over the past few years have become implicated as established causes. Table 1 [6,9,10[■],11[■],12,17,18[■],21–71] provides an overview of commonly used medications that have been reported to cause occupational allergy.

ANTIBIOTICS

The natural and semisynthetic penicillins have historically been a common cause of allergic contact dermatitis in nurses [6,22]; however, the incidence is now significantly lower as most preparations are in single dose packaging and do not require substantial preparation with aerosolization of product. In addition as the usage of penicillin reduces there has been an increase in the number of reported cases

Table 1. Commonly used medications that have been confirmed as causing occupational allergy in healthcare or pharmaceutical workers

Drug	Reference
Antibiotics	
β-lactams	
• Penicillin (penicillin G and penicillin V)	[6,21]
• Semisynthetic penicillins	[22–24]
• Cephalosporins	[12,25–27]
Macrolides	[17,28–31]
Tetracyclines	[32,33]
Aminoglycosides	[34]
Others	
• Vancomycin	[35]
• Metronidazole	[36]
• Colistin	[37]
• Chloramphenicol	[33]
Antimalarials	
Chloroquine	[38]
Quinine	[39]
Hydroxychloroquine	[40]
Tafenoquine	[41]
Antiretroviral	
Abacavir	[18 ^a]
Anti-inflammatory agents	
Paracetamol	[42]
Carprofen	[43,44]
Piroxicam	[45]
Corticosteroids and immunosuppressive drugs	
Budesonide	[46]
Tixocortol	[11 ^a ,18 ^a]
Azathioprine	[47]
Methotrexate	[48]
Cisplatin	[49]
Etoposide	[50]
Mitoxantrone	[51]
Imatinib	[18 ^a]
Neurological drugs	
Tetrazepam	[9,17,52,53]
Levopromazine	[54]
Chlorpromazine	[18 ^a ,55]
Olanzapine	[18 ^a ,56]
Zolpidem	[57]
Ziprasidone	[18 ^a]
Gastrointestinal drugs	
Ranitidine	[18 ^a ,58,59]
Famotidine	[60]
Omeprazole	[10 ^a ,18 ^a ,61,62]
Lansoprazole	[63]
Pantoprazole	[17,64]

Table 1 (Continued)

Drug	Reference
Pancreatic enzyme	[65–67]
Biodiastase	[68]
Antiarrhythmic drugs	
Pirmenol	[18 ^a]
Carvedilol	[57]
Statins	
Simvastatin	[18 ^a ,57,69]
Atorvastatin	[18 ^a]
Fluvastatin	[18 ^a]
Anesthetic drugs	
Succinylcholine	[70]
Sevoflurane	[71]

of occupational reactions to cephalosporins [25–27,72] as well as other β-lactams such as meropenem [24] and piperacillin [23]. As with penicillin the risk of sensitization to certain cephalosporins appears to be high with 8.9% of 457 Korean nurses self-reporting contact urticaria, while preparing intravenous antibiotics [7]. The second generation cephalosporin cefotiam in particular is strongly associated with occupational allergy in Korea and Japan. Tadokoro *et al.* [12] described eight nurses who suffered anaphylactic/systemic reactions to cefotiam at work. Interestingly, five of these nurses had a history of hand dermatitis. Further cases have been reported in the literature to cefotiam [73,74]. Kim *et al.* [8] identified specific IgE to cefotiam in 10.4% of 161 healthcare workers. In the same study [8], 17.4% of individuals reported immediate work-related symptoms when preparing cephalosporins; there was no association seen between symptoms and the IgE positivity.

The macrolide antibiotics azithromycin and tylosin have also been reported to cause allergic contact dermatitis. Tylosin is mainly used in animals and cases of occupational allergy have occurred in farmers or those involved in veterinary medicine [17,28]. Malaiyandi *et al.* [29] reported two cases of occupational delayed airborne contact dermatitis to tylosin in pharmacy technicians; both were patch test positive. Azithromycin-induced allergic contact dermatitis has been reported in pharmaceutical employees [30,31]. In one case series, 25% of the workers manufacturing azithromycin developed occupational allergy [30]. Although most cases developed delayed airborne contact dermatitis some individuals also reported immediate symptoms with rhinitis and urticaria.

Other non- β -lactam antibiotics have also been shown to cause occupational allergy. These include vancomycin [35], metronidazole [36], and colistin [37].

PROTON PUMP INHIBITORS

There have now been over a billion omeprazole treatment courses prescribed since the product first launched in 1979 [10[■]]. Despite the widespread use of this and other proton pump inhibitors (PPI), the incidence of hypersensitivity in patients is very low [75]. In the occupational setting, however, there have been multiple reports of sensitization to PPIs. The explanation for this is related to the strong sensitizing capacity of theazole containing structures, when applied topically [76]. This effect is not seen in patients as these medications are mostly used systemically in tablet or capsule form.

Ghatan *et al.* [10[■]] investigated a large cohort of pharmaceutical company employees in Sweden who had become sensitized to omeprazole. They assessed 96 workers who reported symptoms following occupational exposure to omeprazole. The majority of cases had developed symptoms consistent with delayed contact dermatitis with a smaller number having features of an IgE-mediated process with rhinitis and ocular symptoms. A total of 31 of the 96 study participants had a positive lymphocyte transformation test and 28 of 84 study participants positive patch testing; there was excellent correlation between investigations with 23 of the positive patch test patients also having a positive lymphocyte transformation test. Bennett *et al.* [18[■]] reported three further patients with delayed contact dermatitis to omeprazole on the face and ears; all of these worked as process operators or chemists in industry.

Other recently reported delayed contact dermatitis to omeprazole includes two separate studies [61,62] of horse trainers who became sensitized to an omeprazole paste used to treat horses. Both study participants were patch test positive.

BENZODIAZEPINES

The incidence of allergic reactions to benzodiazepines is very low in patients; however, as with PPIs there is a growing number of studies [9,52,53] of occupational contact dermatitis, in particular to tetrazepam. It is felt that sensitization occurs via airborne exposure when healthcare workers crush tablets for patients with swallowing difficulties. Swinnen *et al.* [9] reported three cases (two nurses and one pharmacy assistant) who developed repeated episodes of airborne facial dermatitis after crushing tetrazepam. All patients were patch test

positive and interestingly crossreacted to a range of benzodiazepines, including lorazepam and diazepam. The same group previously reported a further 10 nurses who suffered a delayed dermatitis and were patch test positive to tetrazepam [53]. Of these nurses five suffered airborne facial dermatitis, two from hand dermatitis, and three from both airborne and hand dermatitis. In a similar case series, Landeck *et al.* [52] reported 10 nurses suffering from airborne facial dermatitis secondary to tetrazepam; none had a prior history of atopy. All study participants were patch test positive to tetrazepam and three also were positive to diazepam.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Over recent years there have been several studies [43,44,77] of pharmaceutical workers developing a delayed photoallergic contact dermatitis to carprofen. Carprofen is a nonsteroidal anti-inflammatory drug that was withdrawn from use in humans in the 1990s but continues to be used for veterinary use. Kerr *et al.* reported two cases of dermatitis in photo-exposed sites after exposure to carprofen in a factory. Diagnosis was confirmed by photopatch test, with conventional patch testing being negative. Subsequently, a further three cases were identified at the same factory. Other cases, also confirmed by photopatch, have been reported because of occupational exposure [44,77]. This included a 28-year-old pharmaceutical worker with an itchy facial erythema after working with carprofen powder in the laboratory [44] and a 27-year-old factory worker who developed a photoallergic dermatitis on the arms and face, which coincided with a period of sunny weather [77].

ASSESSMENT AND MANAGEMENT OF AFFECTED INDIVIDUALS

When assessing these patients it is best done by a specialist in the field. Establishing the causative agent can be difficult and relies heavily on patient history and the timeline with exposures. When drugs are suspected the suspicions can be confirmed with patch testing or prick testing depending on the mechanism. Unfortunately, it can take 2–5 years between the onset of symptoms and diagnosis [78].

The management of occupational allergy to drugs involves two different approaches: firstly modifications to the work place and secondly medical management of the individual. In terms of the workplace, avoidance of the drug is the main objective and individuals should be counselled about this. If this cannot be achieved then any

potential exposures should be minimized by the use of gloves, masks, and goggles. If the allergy is felt to be airborne then preparation in well ventilated rooms and the use of crushing devices that do not allow tablet powder to be aerosolized can also be useful. In the telephone follow-up of the 10 nurses identified with dermatitis secondary to tetrazepam nine of the them had improvement in symptoms by using protective measures, such as gloves, masks, or goggles [53].

It is important that other members of staff wipe the outside of the drug bottles if they are to be reused and work surfaces should be wiped or disposable plastic covering used. This was highlighted in a recent case of two pharmacy technicians who developed allergic contact dermatitis to diphencyprone, a drug that is used for alopecia areata. As part of their investigation, the team identified sensitizing concentrations of the drug on the outside of the bottles and the work surfaces [79].

Medication should be given to optimize the control of dermatitis, rhinitis, or asthma. For allergic contact dermatitis, the use of topical steroids, emollients, and soap substitutes is recommended [78]. Prompt treatment of mild disease may allow more effective outcomes before a condition becomes more chronic and severe. For individuals with difficulty to control IgE-mediated disease Lavaud *et al.* [80] reported a case series of 10 patients with occupational asthma who received omalizumab for uncontrolled symptoms. Asthma control improved in nine study participants and seven were able to continue working in the same workplace. None of these study participants, however, was sensitized to drugs.

CONCLUSION

With increasing numbers of drugs becoming available there is a need for constant vigilance and good reporting of allergic manifestations in the occupational setting. There is often not a good correlation between the allergic potential of a drug in a patient in comparison to the effect on employees. Once there is a suspicion of occupational allergy individuals should be diagnosed promptly and management plans established to limit the impact upon their employment.

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- of special interest
- of outstanding interest

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