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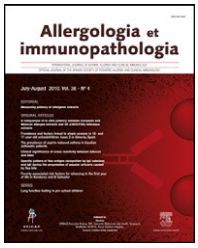

REVIEW

Airborne contact dermatitis to drugs

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Abstract Contact dermatitis is defined as ''airborne'' when the causative factor is present in the environment and may determine irritative or allergic skin reactions. It is often work-related.

In this review of the literature, we focus our attention on airborne contact dermatitis due to pharmaceutical compounds. Contact reactions to medications, often occupation-related, occur mainly in two exposed groups: employees of pharmaceutical industries involved in the production of the drugs and healthcare workers who use the drugs for therapeutic aims.

Introduction

Contact dermatitis is one of the most common skin diseases. It is defined as ''airborne'' when the causative factor is present in the environment and may determine irritative or allergic skin reactions.

Many agents have been reported as causes of airborne contact dermatitis: plants, natural resins, wood, plastic, rubbers, glues, metals, agricultural dusts, and industrial and pharmaceutical chemicals. In fact, this affection has often been described in the context of occupational setting.[1]

The skin reactions caused by airborne agents may be distinguished into airborne irritant contact dermatitis, allergic contact dermatitis, photoallergic or phototoxic reactions, contact urticaria, photocontact urticaria, acne-like lesions, fixed drug eruptions, lichenoid eruptions, exfoliative dermatitis, teleangectases.[2,3]

Airborne agents consist of volatile substances, droplets of the causative agent, and solid particles originated from powdery dust of various materials.[2]

In this review of the literature, we focus our attention on airborne contact dermatitis due to pharmaceutical compounds. Contact reactions to medications are often occupation-related and occur mainly in two exposed groups: employees of pharmaceutical industries involved in the production of the drugs, and healthcare workers who use the drugs for therapeutic aims. However, other categories may be interested. As regards the male:female ratio, women seem to be the most affected, especially nurses.[4]

The irritant substances or the chemically reactive intermediates of the drugs that may be potential sensitisers usually determine skin lesions located at the site of contact, especially the hands. Airborne reactions involve exposed areas, such as the face, the neck, the hands, wrists, underarms; however, reactions on non-exposed areas (by particles trapped under clothing) have been also reported. Generalised reactions may occur due to inhalation or transcutaneous absorption.[5]

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Patch tests with the drugs to which workers are exposed are necessary to make a diagnosis.

Here we report the molecules described as cause of airborne contact dermatitis and the cases associated to them. The pharmaceutical contact allergens belong to many different pharmacological classes.

Antibiotics

Beta-lactams

The natural and the semi-synthetic penicillins are some of the main allergens responsible for occupational allergic contact dermatitis in healthcare workers. Airborne contact urticaria has been described after administration of amoxicillin.[6,7]

Veterinarians and nurses have been described by Gielen and Goosens as subjects affected by penicillins and less frequently by cephalosporins contact dermatitis localised at fingers, palms of both hands, face, eyes and secondary at arms, face, neck. The manifestations are probably caused by airborne agents but it is not well specified.[4]

A diagnosis of occupational contact dermatitis to cefradine and cefazolin was made in a nurse who presented with a history of hand and palpebral eczema explained by needle gushing, hand contact, or airborne diffusion since the patient used to preparare intravenously administered drugs.[8]

Ceftiofur is another cephalosporin described as a drug responsible for airborne occupational contact dermatitis together with cefazolin.[9]

Meropenem was also reported as airborne causative agent of allergic contact dermatitis. A nurse, who prepared intravenous infusions of several antibiotics, reported recurrent periorbital erythema accompanied by itching and runny eyes. Patch test resulted positive to meropenem only.[10]

Aminoglycosides

Gielen and Goosens[4] recorded a positive patch test to aminoglycosides (amikacin and gentamycin) in two nurses affected by contact dermatitis, presumably airborne, respectively localised at fingers, wrist and mouth and at arm and wrist.

Macrolides

Airborne contact dermatitis to macrolides, particularly to tylosin, azithromycin, kitasamycin and midecamycin have been described.[4,11–13]

Tylosin and its phosphate and tartrate salts are usually used in veterinary medicine in the prophylaxis and treatment of various infections, so it may cause allergic contact dermatitis in farmers, animal caretakers, and veterinary surgeons.[11,14] A pharmacist who used it in compounding was also reported.[4]

A case of a man who presented occupational allergic contact dermatitis caused by azithromycin was described by López-Lerma.[12] The patient reported initial pruritus on the head and neck, which had spread to the rest of the body later, and skin lesions appeared on his face, neck and forearms. He worked at a pharmaceutical company and his problem started two months after moving to a new workplace, where he was occupationally exposed to the final pure powdered form of clarithromycin and azithromycin. The sensitisation to azithromycin was confirmed by Patch test.

There are a few reports of airborne contact dermatitis caused by azithromycin. Milkovic-Kraus and Kanceljak-Macan[15,16] published a case series of seven pharmaceutical workers with skin and/or respiratory manifestations who were occupationally exposed to azithromycin. They observed that occupational hypersensitivity to azithromycin was present in about 25% of workers synthesising the drug. Mimesh and Pratt described two other cases of two men who were employed in a pharmaceutical company to add water to the powdered form of various chemical substances and to bake them. One patient reported an itchy vesicular eruption first on the head and neck and then into the rest of the body. The second man presented with itching acute eczema on the left cheek that later spread to the rest of the face.[17]

Pristinamycin

Pristinamycin is an antibiotic of the streptogramin group. Allergic contact dermatitis from this antibiotic was first observed by Pillette et al.[18]; after this report, Blancas-Espinosa et al. described a case of occupational allergic airborne contact dermatitis from pristinamycin in a man working for a pharmaceutical company, within the department of granulation and compression of the medicament. He was exposed to powder of various substances and presented with pruritic dermatitis involving the neck, eyelids and cheeks. Skin lesions improved during holidays and after treatment with topical corticosteroids and relapsed at work. Patch tests with pristinamycin 1%, 5% and 10% in aq./alc. showed positive reactions at days 2 and 4.[19]

Nitrofurazone

Nitrofurazone is bactericidal for many Gram-positive and Gram-negative bacteria causing disease in fresh water and marine fishes.

Allergic contact dermatitis to nitrofurazone has been reported from the use of eye drops and topical ointments. Some authors described a case of contact dermatitis from airborne nitrofurazone secondary to a powdered aquarium water additive.[20]

Corticosteroids and immunosuppressive drugs

Budesonide

Cases of allergic contact dermatitis due to topical budesonide (creams, spray and aerosols) are described in the literature.[21–23] Airborne allergic contact dermatitis was reported in a patient treated with aerosols of budesonide,[24] in a nurse, and in a babysitter who administered the aerosolised drug.[25,26]

In both work-related cases, the patients presented with eczematous areas on face, neck, and upper limbs. Patch

tests were positive for budesonide and hydrocortisone-17-butyrate, which probably cross-react to each other.

Azathioprine

In the literature, a case has been reported of a woman who developed eczema on her face, neck, hands and soles after contact with azathioprine. Her son was affected by leukaemia and treated with marrow transplantation took this immunosuppressive drug and the woman crushed the tablets to help him swallow them. On patch testing, crushed and diluted azathioprine tablet gave a positive reaction.[27]

Methotrexate

Some authors observed that methotrexate may cause airborne allergic contact dermatitis. The reports were about a ventilation engineer and a production engineer working in methotrexate manufacture.[28,29]

The man employed in the production took contact with the two precursors that reacted together to form methotrexate (2,4-diamino-6-chloromethylpteridine hydrochloride and N-methyl-N-formyl-p-aminobenzoylglutamateethyl derivate). Acute eczema on the face and neck was the first clinical manifestation, followed by vesicular and exudative erythema spread to thorax and volar forearms.

Patch test performed with substances from workplace resulted positive for 2,4-diamino-6-chloro methylpteridine hydrochloride and methotrexate.

Inhibitors of gastric secretion

Omeprazole

The first cases of occupational contact dermatitis due to omeprazole were reported in two pharmaceutical workers, who presented lesions localised to the eyelids.[30]

Two other cases have recently been described. A man exposed to substances used in the manufacture of omeprazole in a pharmaceutical company showed skin lesions involving eyelids, neck and hands. The other case refers to a man working as supervisor at the same pharmaceutical company. He developed an itchy dermatitis affecting the eyelids, nose, and perioral area during supervision of the area of omeprazole production. The causative agent was confirmed by patch test with omeprazole 0.1%, 0.5% in alcohol. Both patients had become free from skin lesions since they changed the job posts.[31]

Pantoprazole

Neumark et al. reported a case of contact dermatitis caused by pantoprazole in a male referring to their clinic with a history of facial and eyelid dermatitis. He had worked as a machine operator in a pharmaceutical factory for the six years prior to presentation. The dermatitis resolved with exfoliation and hyperpigmentation of the eyelids. At readings on D4, patch test resulted positive for omeprazole 10%(+) and pantoprazole 5% (++).[32]

Lansoprazole

Allergic contact dermatitis caused by lansoprazole has been reported in the setting of the pharmaceutical industry. A man who worked in the section where lansoprazole was made developed pruritic papules on the face, neck, upper arms and forearms. At D4, patch test resulted positive for lansoprazole 10% (++++), lansoprazole 50% (++), omeprazole 10% (+++) and omeprazole 50% (++). After restriction from further work with lansoprazole, the patient experienced no further symptoms.[33]

Ranitidine and famotidine

Some cases of airborne contact dermatitis to ranitidine localised at wrist, fingers, face, mouth, hands were reported especially in nurses. Patch test performed with the drug confirmed the diagnosis.[4,34–36]

Airborne contact sensitivity to ranitidine hydrochloride has been demonstrated by Ryan in six symptomatic exposed pharmaceutical manufacturing employees.[37]

Occupational airborne allergic contact dermatitis from intermediate products in famotidine synthesis has been described by Guimaraens et al.[38]

Analgesics

Propacetamol

Propacetamol is the injectable form of paracetamol. After intravenous administration, this prodrug is hydrolysed into paracetamol within 10 min.[39]

Gielen and Goosens reported nine nurses and one medical doctor affected by contact dermatitis by propacetamol. Skin lesions were present in both hands in almost all the patients. The medical doctor and one of the nurses showed manifestations on face, mouth and eyes.[4]

Another case of a nurse, who prepared injections of cephotaxine and propacetamol and showed erythematous, pruritic and micropapular lesions affecting the face, neck and forearms, has been described. The patient did not have eczema on her hand because she wore latex gloves. Patch test was performed with propacetamol chlorhydrate (50% aq.), sodium citrate (50% aq.) and paracetamol (50% aq); at D2, only propacetamol was positive.[40]

There are two reports of airborne contact dermatitis to p-aminophenol, which is a breakdown product of paracetamol under moist or wet conditions at room temperature. Two men employed as process workers in the production of paracetamol powder developed a dermatitis affecting the face and also the hands and forearms in the second case. Patch tests were performed to standard series, face series and the pharmaceutical powders they came into contact with at work. They resulted positive to p-phenylenediamine (PPD, 1% pet), p-aminophenol (PAP, 1% pet) and m-aminophenol (1% pet) in the first patient and to PPD (1% pet), PAP (1% pet), p-aminoazobenzene (0.25% pet) and Disperse orange 3 (1% pet) in the second patient. In both cases, there was no reaction to paracetamol itself.

These examples demonstrate that it is important to consider breakdown products as responsible allergens in

individuals who are exposed to paracetamol in the pharmaceutical industry.[41]

3-(Aminomethyl)-pyridyl salicylate

Two females with acute allergic contact dermatitis from 3-(aminomethyl)-pyridyl salicylate have been described in the literature. This substance is contained in topical analgesic sprays. Clinical manifestations were characterised by eczema, angio-oedema and respiratory symptoms. In one patient, airborne elicitation was suspected.[42]

Neurological drugs

Tetrazepam

Landeck et al. presented 10 health care professionals who developed airborne contact dermatitis due to occupational exposure to tetrazepam dusts. Affected individuals were employed as geriatric nursing staff; they were exposed to tetrazepam when crushing tablets for their patients. Patch test performed with commercial and customised allergens revealed strong positive reactions to tetrazepam in all patients. Additional diazepam sensitisation was observed in three subjects.[43]

Previously other cases of airborne allergic contact dermatitis from tetrazepam had been reported.

A geriatric nurse, who crushed some drugs to make them simpler to swallow for old people, resulted positive to tetrazepam on patch testing. She presented with intermittent skin reactions involving the whole face. At weekends or on holidays, she was symptom free.[44]

A diagnosis of occupational airborne allergic contact dermatitis due to sensitisation to tetrazepam was made on another geriatric nurse,[45] in a pharmaceutical factory working with tetrazepam powder[46] and in a woman crushing tablets with her fingers.[47]

Levopromazine

Airborne contact urticaria from levomepromazine was described by Johansson[48].

Chlorpromazine

Airborne photoallergic contact skin lesions by chlorpromazine have been reported. Two females who used to give their husbands an oral solution of chlorpromazine for senile dementia presented with eczematous lesions affecting the face (particularly forehead, eyelids, periocular region, chin), the back of fingers and hands.[49] A patient with photocontact urticaria and a self-employed farmer and pig breeder with a severe persistent photoallergic contact dermatitis due to direct occupational dermal and airborne contact to chlorpromazine and olaquindox (antibiotic and animal growth promoter) have also been observed.[50,51] In these cases the diagnosis was confirmed by the positive reactions at photopatch testing.

Antihypertensives

Carvedilol, propranolol, oxprenolol

A case of airborne contact dermatitis to carvedilol in association to simvastatin and zolpidem has been reported in a male who worked as a machine operator in a pharmaceutical factory. His dermatitis involved eyelids, cheeks, lips, nose, and the nasolabial folds. Patch tests were performed with his own samples of work chemicals appropriately diluted. Readings at D2 and D4 were positive to simvastatin 1% pet. (+/+), simvastatin 0.1% pet. (+/+), carvedilol 10% pet. (+/+), and zolpidem 10% pet. (+/++).[52]

Epichlorohydrin, oxprenolol hydrochloride and propranolol hydrochloride have been described as airborne agents of contact dermatitis.[53]

Others molecules

Albendazole

Albendazole is an anthelmintic drug used for the treatment of a variety of worm infestations. Macedo et al.[54] reported contact urticaria and contact dermatitis from this substance in an occupational setting.

Simvastatin

A facial eruption with desquamative erythema was observed in two patients (a male and a woman) who worked in the same pharmaceutical industry in the department of quality control in simvastatin synthesis.[55]

Airborne occupational allergic contact dermatitis to simvastatin has previously been cited in association to carvedilol[51] and it has also been described by Field et al.[56]

Diphencyprone

Diphencyprone is used in the treatment of alopecia areata, recalcitrant warts and melanoma. It has been recognised as airborne sensitisation agent in a male employee in a hospital pharmacy presented with acute contact dermatitis on the exposed skin of the face and hands with spread to the forearms.[57]

2-Aminothiophenol

2-Aminothiophenol (also known as 2-aminobenzenethiol or *p*-mercaptoaniline) is an aromatic hydrocarbon used for chemical and biomedical research and for the synthesis of various drugs. A case of occupational contact dermatitis in a chemical technician involved in the production of intermediate pharmaceutical substances was reported. He developed recurrent episodes of eczema of the face, with improvement of the symptoms when away from work. The onset of the skin manifestations was related to the accidental exposure to vapours of 2-aminothiophenol coming from the heating chambers. Recurrences of the dermatitis occurred after inspection visits in the plant department and when drainage

procedures of containers with residual 2-aminothiophenol were carried out.[58]

In the literature another case had been previously described, consisting of recurrent airborne contact dermatitis which arose in a development technician who used 2-aminothiophenol for a chemical process.[59]

Cyanamide and dibenzyl phosphate

Cyanamide is an organic amide used in different settings, such as in chemistry, in antirust solutions, or in drugs for treating alcoholism. Dibenzyl phosphite is a substance used in the pharmaceutical industry as a phosphorylating agent for converting pro-drugs. The two substances are reagents involved in the synthesis of phosphorylcreatine. Some authors reported them as responsible for airborne contact dermatitis. A chemical worker, who supervised phosphorylcreatine synthesis, developed severe eczematous dermatitis with diffuse, symmetrical involvement of the face, including the eyelids, the region under the chin and the retroauricular folds. Patch testing was performed with the substances used in the synthesis of phosphorylcreatine and resulted positive to dibenzyl phosphite, cyanamide and phosphorylcreatine. Sensitisation to phosphorylcreatine was due to the presence of dibenzyl phosphite and cyanamide residues, because patch tests with phosphorylcreatine pure grade 5% and phosphorylcreatine pure grade 1% gave a weak positive and a negative reaction, respectively.[60]

Conclusions

The cases reported show airborne contact dermatitis to drugs as often being an occupational disease; in fact most of the subjects affected by the dermatitis handle the drug at work, being pharmaceutical industry employers or healthcare workers.

Airborne causes are still greatly underestimated because reports in the literature often omit this term when dust or volatile substances are responsible for skin reactions. Taking a careful history and a clinical examination, and applying specific patch tests with the suspected drugs are necessary to make a proper diagnosis, to provide an appropriate control of the affection and to enact effective prevention measures.

Conflict of interest

The authors have no conflict of interest to declare.

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