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A Study of Occupational Contact Dermatitis in the Pharmaceutical Industry

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Introduction

Workers in the pharmaceutical industry are considered to be particularly at risk for irritant and allergic contact dermatitis. Ireland is the largest net exporter of medicines in the world.¹ Cork, where our department is based, is one of the manufacturing hubs for the industry in Ireland because of the available links to R&D in third level institutions, a flexible, educated workforce and its logistic advantages as one of the largest natural harbours in the world, amongst others. We reviewed the case notes of those patients referred to our department over a 15 year period from 1997 to 2012 to determine the common clinical presenting features and the causes of occupational skin disease.

Methods

A database of patients referred from the pharmaceutical industry between 1997 and 2012 was maintained over the study period. Each patient was seen and interviewed by the same specialist consultant dermatologist (JB). Site visits were also conducted where permitted. Patch testing was carried out with the British Society for Cutaneous Allergy standard series, with the patients' work materials and other allergens as indicated on clinical grounds. Allergens were ap-

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plied using Finn Chambers® (SmartPractice, Phoenix, Arizona, USA) and secured with Tegaderm® (3M Health Care, Neuss, Germany). Raw materials were obtained from the companies as indicated clinically and diluted for patch testing in water, white soft paraffin or methyl ethyl ketone (MEK).

Results

Over the 15-year period, 73 patients were patch tested, 59 male (81%) and 14 female (19%). 32 were diagnosed with allergic contact dermatitis (ACD) and 24 with irritant contact dermatitis (ICD). One patient had an immediate hypersensitivity reaction to pyridine and 19 were diagnosed with a variety of other dermatoses. The recorded primary site was the face in 66% of patients with allergic contact dermatitis. Of particular interest was the range of drug allergens to which patients had a confirmed ACD by patch testing (see Table 1). This, to our knowledge, is the first report of contact allergy to imatinib, fluvastatin, abacavir, ziprosidone, and the class 1a antiarrhythmic medication, pirlmenol hydrochloride. One of the patients was found to have contact allergy to olanzapine (the third reported case)^{2,3} and another to simvastatin (the fifth reported case)⁴⁻⁶ and also, as previously reported in 3 cases, bibeal (a precursor component of atorvastatin).⁷ We identified three cases of omeprazole allergy, which has been reported in four other cases.^{8,9} Chlorpromazine allergy was identified in a maintenance technician, affecting the malar area (allergic not photoallergic in nature). Several cases of airborne allergy to chlorpromazine have been reported in members of the public, often carers, but not in pharmaceutical workers to date.¹⁰⁻¹² We identified four cases of probable contact allergy to ranitidine (only one was confirmed by patch testing). Ranitidine has been reported to cause contact allergy in many settings, including during its manufacture.¹³⁻¹⁵ One case of acrylate allergy was identified in a patient us-

ing UV-cured acrylates in Loctite® glue in the manufacture of drug-eluting coronary stents. Of the other patients with ACD the implicated agents included colophonium, neomycin, tixocortol pivalate, sodium metabisulfite, nickel, cobalt, mercaptobenzathiozole, isopropyl alcohol, HBTU (o-(benzotriazol-1-yl)-n n' n'-tetramethyluronium hexafluorophosphate), palladium, and balsam of Peru. There were three cases of tetramethylthiuram monosulfide allergy. Amongst the above, the following were designated as non-occupational allergens; colophonium/rosin, sodium metabisulfite, and neomycin.

Several patients presented with endogenous eczema including discoid eczema, atopic dermatitis (n=4), and seborrhoeic dermatitis (n=5), rosacea (as a non-allergic reaction to carbamazepine and carprofen), infections, psoriasis and nodular prurigo.

Personal protective equipment (PPE) was identified as the culprit exposure in several cases (see Table 2). All gloves used were tested by direct application to the back. There was only one case of foot dermatitis in this cohort. There were seven cases of ACD to thiurams in latex gloves.

10-20 controls were patch tested to any allergen that proved positive, at all dilutions to which the index patient was tested. All were negative.

Discussion

Several case reports and case series exist in the literature on occupational allergens in the pharmaceutical industry. Because of the abundance of pharmaceutical plants in our catchment area, we were able to study the spectrum of skin disease and the potential allergens encountered by workers in the pharmaceutical sector.

Our study identifies a range of previously unreported allergens in the pharmaceutical industry. This to our knowledge is the first report of contact allergy to imatinib, fluvastatin, abacavir, ziprosidone, and pirfenolol hydrochloride. Several previously identified allergens were detected including simvastatin, bibea (atorvastatin precursor), chlorpromazine, tixocortol pivalate, ranitidine, olanzapine and omeprazole.

The primary site was the face in 66% of patients and where a more specific site was documented, this mainly indicated eyelids. Large studies of occupational dermatoses cite mainly the hands as the primary site affected. From our study, hand dermatitis is more commonly due to irritants if encountered in this setting. Drugs and their various intermediates are often airborne during manufacture which increases the risk of contact with workers' skin. While most of our patients were process operators who charge reactors, there were also tradesmen and laboratory staff found to have been sensitised. Three of our cases were involved in maintenance of machines. Some allergens would have been missed had a site visit not been conducted. Work practices influenced the rate of ACD encountered, with some clustering of cases seen in plants where cases occurred partly because workers disregarded recommended practice (as in the statin cases) and partly because of an unexpected hazard (as in the cases of the omeprazole allergy where the company were not informed of problems at the plant which previously manufactured omeprazole).

New exposures may emerge when working conditions are changed, and therefore vigilance on behalf of workers needs to be constant and dynamic. Any changes implemented to protect workers need to be monitored for effectiveness. Collaboration between dermatologists and occupational physicians and industry is necessary to detect and limit skin disease in pharmaceutical workers.

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Table 1: Range of Drugs Causing Contact Allergy in Pharmaceutical Workers

Allergen	Drug class	Age	Occupation	Primary site
Pirmenol Hydrochloride	Antiarrhythmic	31	Process operator	Eyelids
Abacavir (n=2)	Nucleoside analog reverse transcriptase inhibitor (NRTI)	48, 51	Process operators	Eyelids, hands
Imatinib (n=2)	Tyrosine kinase inhibitor	54	Process operator	Face
Tixocortol Pivalate	Corticosteroid	34	Process operator	Face, arms
Omeprazole (n=3)	Proton pump inhibitor	33, 43, 56	2 process operators 1 organic chemist	Face, ears

Ranitidine (n=1+/-3) (only one confirmed by patch testing)	H2 receptor antagonist	37, 40, 42, 46	2 process operators, 1 maintenance technician, 1 compression operator	Hands, face, trunk, elbows
Fluvastatin	Statin	35	Process operator	Eyelids, neck
Simvastatin	Statin	41	Maintenance engineer	Eyelids
Bibea (atorvastatin intermediate) (n=3)	Statin	46, 46, 52	Process operators	Eyelids, face, anterior chest
Chlorpromazine	Dopamine antagonist (Typical antipsychotic)	42	Maintenance technician	Malar region
Olanzapine	Atypical antipsychotic	51	Process operator	Eyelids Hands
Ziprosidone	Atypical antipsychotic	52	Process operator	Hands

Table 2: Personal Protective Equipment Identified as an Allergen

Allergen	Item
Thiurams (N=7)	Latex Gloves
Tetramethylthiuram monosulfide (TMTM)	Rubber face mask
Uncertain	Nitrile gloves
Nickel	Metal clasp
Uncertain	Boots