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SHORT REPORT

Safe medication use based on knowledge of information about contraindications concerning cross allergy and comprehensive clinical intervention

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Correspondence: Quan Zhou Department of Pharmacy, Second Affiliated Hospital, School of Medicine, Zhejiang University, Zhejiang 310009, People's Republic of China Tel +86 571 8778 4615 Fax +86 571 8702 2776 Email zhouquan142602@zju.edu.cn **Background:** An investigation of safety issues regarding information on contraindications related to cross allergy was conducted to promote clinical awareness and prevent medical errors in a 2200-bed tertiary care teaching hospital.

Methods: Prescribing information on contraindications concerning cross allergy was collected from an information system and package inserts. Data mining and descriptive analysis were performed. A risk register was used for project management and risk assessment. A Plan, Do, Check, Act cycle was used as part of continuous quality improvement. Records of drug counseling and medical errors were collected from an online reporting system. A pharmacist-led multidisciplinary team initiated an intervention program on cross allergy in August 2008.

Results: Four years of risk management at our hospital achieved successful outcomes, ie, the number of medical errors related to cross allergies decreased by 97% (10 cases monthly before August 2008 versus three cases yearly in 2012) and risk rating decreased significantly [initial risk rating: 25(high-risk) before August 2008 versus final risk rating:6 (medium-risk) in December 2012].

Conclusion: We conclude that comprehensive clinical interventions are very effective through team cooperation. Medication use has potential for safety risks if sufficient attention is not paid to contraindications concerning cross allergy. The potential for cross allergy involving drugs which belong to completely different pharmacological classes is easily overlooked and can be dangerous. Pharmacists can play an important role in reducing the risk of cross allergy as well as recommending therapeutic alternatives.

Keywords: clinical pharmacy, contraindications, cross allergy, prescribing information, risk management, safe medication use

Introduction

A drug allergy is an immunologically mediated reaction that exhibits specificity and recurrence on re-exposure to the offending drug. It occurs in 1%-2% of all admissions and 3%-5% of hospitalized patients.¹ Allergic drug reactions account for 5%-10% of all adverse drug reactions and have the potential to cause harm to patients.² However, allergies can be prevented if the patient's history of drug allergy is known and coded.^{3,4} To guarantee safety in medication use, the Joint Commission International requires that a detailed drug allergy history should take into account when doctors prescribe drugs and pharmacists dispense them.⁵

Furthermore, a patient who is allergic to one specific drug may be allergic to other drugs of similar chemical structure. That is known as cross allergy or cross sensitivity.^{6,7}

Some patients who have a sensitized reaction to medications like nonsteroidal anti-inflammatory drugs (NSAIDs) may have trouble taking any drug belonging to that class, and doctors should try other medications first to avoid cross allergy. For example, acetaminophen which shares the analgesic and antipyretic properties of the NSAIDs, can be used for a patient who is running a high fever but has a history of allergy to NSAIDs. If this step is overlooked, pharmacists can still help detect problems with cross sensitivity if they have a clear understanding of what is being prescribed. Therefore, communication and team cooperation between patients, doctors, pharmacists, nurses, and information engineers are very important for safety assurance.

Overlooking the issue of cross allergy may cause medication errors. However, many doctors, nurses, and pharmacists only focus on cross allergy involving drugs within the same therapeutic class, such as NSAIDs, and may not pay enough attention to cross allergies occurring when, for example, two drugs belonging to a completely different pharmacological class can provoke cross sensitivity as a result of a particular formulation excipient in common.

Four years ago, a serious medication error occurred at our hospital in a female cancer patient with a history of allergy to procaine, a local anesthetic. She was receiving intravenous metoclopramide to avoid possible chemotherapyinduced vomiting. When her daughter was reading the package insert for metoclopramide, she noticed that the drug is contraindicated in patients with a history of allergy to procaine. Immediately a senior clinical pharmacist was consulted. The dispensing pharmacist had not been aware of this type of cross allergy because the two drugs were so different in their therapeutic action. Fortunately, the patient did not experience any adverse drug reaction, and although she forgave our medical staff, the case taught us a profound lesson. Subsequently, a systematic investigation was undertaken of prescribing information on contraindications related to cross allergy for all medications used in our hospital and preliminary interventions were implemented, as discussed here.

Materials and methods Data collection

This investigation was performed at the Second Affiliated Hospital, School of Medicine, Zhejiang University. The hospital has 2200 beds, with 2.7 million outpatient visits made annually. A conditional search was performed for each drug using the "New Clinical Drug Reference" software jointly developed by Beijing Kingyee Technology Co, Ltd. and the Chinese Pharmaceutical Association (http://www. medscape.com.cn). An informatics pharmacist recorded any information on contraindications related to cross allergy. Full prescribing information for each medication used in the hospital was reviewed for verification. The cross allergy issue was addressed by retrieving all records from drug counseling, medical consultations, and our online no-fault reporting system which accepts reports of adverse events and medication errors from medical staff. A causality assessment of drug allergy was carried out using the adverse reactions probability scale devised by Naranjo et al.⁸

Risk register and intervention procedure

A risk register, a tool commonly used in project management and organizational risk assessments,⁹ was used for prevention of cross allergy. A pharmacist-led multidisciplinary team initiated an intervention program on cross allergy in August 2008. The clinical intervention measures and risk reduction strategies are described in Table 1. Risk likelihood was divided into five levels, ie, almost certain (at least weekly, score 5), likely (monthly, score 4), possible (quarterly, score 3), unlikely (may occur every year, score 2), and remote (may occur every 2 years or more, score 1). Consequences were divided into five grades, ie, extreme (score 5), major (score 4), moderate (score 3), minor (score 2), and insignificant (score 1).

Statistical analysis

A descriptive analysis was performed. According to the Hong Kong Hospital Authority risk quantification matrix and risk register documents, the risk rating is derived from likelihood multiplied by consequences, and the value divided into three risk grades (ie, high risk, ≥ 16 ; medium risk, 6-15; low risk, 1-5).¹¹ The percentage of questions on cross allergy correctly answered the first time by pharmacists was calculated by correct responses in the first instance divided by all responses.

Results

Contraindication information and descriptions of cross allergy

Descriptions of cross allergy in information on contraindications for drugs within the same therapeutic class are listed in Table 2, and include mainly antibacterials, cardiovascular drugs, antitumor drugs, local anesthetics, and endocrine or metabolic agents. Inconsistent descriptions were

Table I Risk register for prevention of cross allergy

Item	Description
Risk owner	Vice dean of pharmacy and vice president in charge of medical care
Risk type	Patient care and safety
Risk description	Risk of medication errors due to cross allergy
Actual or potential risk?	Actual
Existing controls	Simple inquiry by doctors and nurses without standardized recording of drug allergies
Consequences	5
Likelihood	5
Initial risk rating	25
Risk reduction strategies and additional controls required	A pharmacist-led multidisciplinary team initiated an intervention program on cross allergy in August 2008. Clinical intervention measures were as follows:
	bottors must record any real of potential anergies of sensitivities in the electronic medical record which occurred prior to admission or during hospitalization
	Implement maintenance of pharmacy storehouse information management subsystem. For example
	a warning that "Patients who are allergic to an aminoglycoside antibiotic should not receive any aminoglycosides" will appear when doctors prescribe isepamicin for patients with a history of allergy to amikacin.
	• Publish a standard operating procedure for drug allergy management and an updated list of medications
	associated with cross allergy in the local area network. Series of academic lectures, especially typical case analysis, arranged for medical staff.
	 Note skin test results when physicians prescribe special medications for patients. For example, a prescription of penicillamine should contain descriptions of "skin test exemption" or "this test exemption". Otherwise the executive will be interested by additional prescriptions.
	 Adopt a pragmatic approach to use of beta-lactams in patients with penicillin allergy.
	• Install an online database embedded in the hospital information system and electronic medical
	record system. The database, named the Clinical Medication Decision Support System, was developed by Elsevier Datong (http://www.clinicaldecisionsupport.com.cn), and can effectively detect contraindications related to cross allergy.
	• Software modification was implemented to overcome an information design defect, ie, the interface
	of the pharmacy management information system could not show the records of drug allergy (eg, allergy history, medication name, clinical manifestations) so that pharmacists could not detect
	severe pharmacotherapeutic issues in the dispensing process.
	 Implementation of an intrahospital pharmacovigilance system notifying all medical staff when a
	cross allergy occurs in the hospital.
	• Medical staff are encouraged to report any medication errors via a specific spontaneous reporting
6	system. A Plan, Do, Check, Act cycle is built into ongoing quality improvement."
Consequences	3
Likelihood	2
Final risk rating	6
Approximate financial resources required	\$U\$32,000
Priority high/medium/low	High
Responsibility for action	Department of Medical Affairs, Department of Pharmacy, Office of Medical Quality Management
Due date	August I, 2008
Completion date	December 31, 2012
Key indicator(s)	Awareness of cross allergy among doctors and nurses, cases of drug counseling about cross allergy
	from doctors and nurses, percentage of questions on cross allergy answered correctly first time around by pharmacists and number of medical errors
Monitoring and review	Questionnaire survey, application of the tracer methodology, analysis of all records from drug
-	counseling, medical consultation, and online no-fault reporting system which accepts reports
Communication strates (iss)	Cooperation between Department of Information Technology Office of Medical Ousling
Communication strategy(les)	Management, Department of Medical Affairs, Department of Pharmacy, and Division of
Contingency plan(s)	Pharmacist's auditing should be strengthened and electronic medical record system should be installed
consultanty hands	on the pharmacy computer if modification of information system cannot be fulfilled according to the schedule. Pharmacists to review the chart for drug allergy issues

Table 2 Cross allergy descriptions in information related to contraindications concerning drugs within the same therapeutic class

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does not note any cross allergy issues.		does not note any cross allergy issues.
Ganciciovir Contraindicated in patients who are allergic to aciclovir.	Ganciclovir	Contraindicated in patients who are allergic to aciclovir.

observed for partial agonists, including organic nitrates, angiotensin-converting enzyme inhibitors, local anesthetics, retinoids, 5-HT3 receptor antagonists, and bisphosphonates. Surprisingly, descriptions of cross allergy were also observed to be inconsistent for some drugs with the same generic name but with different pharmaceutical manufacturers.

Prescribing information for certain drugs clearly notes that they are contraindicated in patients who are allergic to drugs belonging to other therapeutic classes. Further, information on contraindications for some drugs which belong to completely different therapeutic classes clearly notes that they are contraindicated in patients who are allergic to structurally similar classes (Table 3). Formulation excipients that provoke cross sensitivity are listed in Table 4.

Information on contraindications related to cross allergy for some drugs does not provide direct guidance on safe use of such medication. Four drugs with inadequate information were identified, comprising: donepezil, which is contraindicated in patients who are allergic to piperidine derivatives; diacerein, which is contraindicated in patients who are allergic to anthraquinone derivatives; bifonazole cream, which is contraindicated in patients who are allergic to imidazoles; and doxofylline, which is contraindicated in patients who are allergic to xanthine derivatives.

Effects of intervention

The outcomes of reducing the risk of cross allergy are shown in Table 5, and indicate that our four-year comprehensive clinical intervention through team cooperation was very effective.

Discussion

Descriptions of cross allergy in information on contraindications for drugs within the same pharmacological class were usually consistent. However, inconsistent descriptions were noted for partial agonists, including organic nitrates, angiotensinconverting enzyme inhibitors, local anesthetics, retinoids, 5-HT3 receptor antagonists, and bisphosphonates (Table 2). To our knowledge, this is a completely new finding and indicates that doctors and pharmacists should carefully select an alternative for patients who are allergic to certain drugs. For example, oral tretinoin and viaminate, instead of acitretin, can

I able 3 Cross allergy involving drugs belonging to completely different pharmacologica	al classes
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Drugs	Description of cross allergy
Metoclopramide	Contraindicated in patients who are allergic to procaine
	and procainamide.
Penicillamine	Contraindicated in patients who are allergic to any of the
	penicillins.
Tacrolimus	Contraindicated in patients who are allergic to other
	macrolides.
Vancomycin	Contraindicated in patients who are allergic to
	aminoglycosides.
Cefoxitin, cefminox, latamoxef, piperacillin-tazobactam, piperacillin-sulbactam	Contraindicated in patients who are allergic to any of the
	cephalosporins.
Bromocriptine, dihydroergotoxine mesylate	The two drugs belong to different therapeutic classes,
	but the contraindication information for both drugs
	indicates that they are contraindicated in patients who are
	allergic to ergotamine.
Sulfonamide derivatives	The six kinds of drugs belong to different therapeutic
Antimicrobial sulfonamides	classes, but the contraindication information for these
 Diuretics: hydrochlorothiazide, amiloride, indapamide 	drugs all indicates that they are contraindicated in patients
 Hydrochlorothiazide-containing antihypertensives 	who are allergic to sulfonamides.
COX-2 inhibitors: celecoxib, parecoxib	
 Hypoglycemic sulfonylureas: tolbutamide, glibenclamide, gliclazide, 	
glipizide, gliquidone, glimepiride	
 Gout suppressant: probenecid 	
Lodine allergy-related drugs	The five kinds of drugs belong to different therapeutic
Diagnostic drug: indocyanine green	classes, but the contraindication information for these
Antiarrhythmics: amiodarone	drugs all indicates that they are contraindicated in patients
Contrast agents: iodized oil injection, compound meglumine diatrizoate injection,	who have a history of iodine allergy.
iopromide	
Cydiodine tablets	
Ophthalmic drugs: prolonium iodide, iodized lecithin tablets	

Drugs	Description of cross allergy
Amifostine, bortezomib, carboplatin, recombinant human epidermal growth factor	Contraindicated in patients who are allergic to mannitol.
Paclitaxel, teniposide, cyclosporin injection	Contraindicated in patients who are allergic to polyoxyethylene castor oil. Contraindication information on paclitaxel for injection (albumin-bound) does not note any cross allergy issues.
Docetaxel, mycophenolate mofetil injection	Contraindicated in patients who are allergic to Tween-80.

be used for patients with acne who are allergic to other retinoids or vitamin A derivatives. Bupivacaine and tetracaine can be prescribed instead of lidocaine for patients who are allergic to local anesthetics. According to our experience, indepth training in this area is essential.

Even for drugs that share the same generic name but have different manufacturers, it is possible to find different descriptions in the information on contraindications, as noted for oxaliplatin (Table 2). The product manufactured domestically is contraindicated in patients who are allergic to platinum derivatives, whereas the information on contraindications for the original imported product contains no mention of cross allergy. To avoid medico-legal disputes between physicians and patients, it is relatively safe to prescribe the original imported product of oxaliplatin instead of domestic oxaliplatin for patients who are allergic to platinum derivatives. An evidence-based meta-analysis indicates that special emphasis should be placed on the role of chemical structure in determining the risk of cross-reactivity between specific agents.¹²

Table 5 Effect	s of intervention	on prevention	of cross	allergy
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Indices	Descriptions of outcomes
Number of drug counseling sessions about	Decreased by 67% (an average of 60 cases monthly before August 2008 versus an average
cross allergy from doctors and nurses	of 20 cases monthly since August 2009).
Awareness rate of special cases of cross allergy	If doctors, pharmacists, and nurses did not read the prescribing information, almost
	no one knew of any contraindications for use of vancomycin in patients who are allergic
	to aminoglycosides, use of metoclopramide in patients who are allergic to procaine, and
	use of piperacillin/tazobactam in patients with an allergy to cephalosporins before August
	2008. Awareness of such types of cross allergy increased to 100% in August 2009.
Percentage of questions on cross allergy correctly	Increased by 30% (60% before August 2008 versus 90% in August 2009).
answered first time round by pharmacists	
Number of medical errors related to cross allergy	Decreased by 97% (10 cases monthly before August 2008 versus three cases yearly
	in 2012).
Percentage of documentation on hypersensitivity	About 20% before August 2008 versus 100% after introduction of a formal history sheet
in clinical notes	in May 2012.
Risk rating	Decreased significantly [initial risk rating:25(high-risk) before August 2008 versus final risk
	rating:6 (medium-risk) in December 2012].

There are practical differences between the professions of medicine and pharmacy, the most obvious one being that the pharmacist has a more indepth understanding of pharmaceutical chemistry. Theoretically, an educational background in pharmaceutical chemistry means that pharmacists have a relatively higher degree of knowledge about cross allergy than doctors or nurses. Therefore, it is necessary for pharmacists to lead the relevant clinical interventions. Pharmacists can play an important role in detecting problems with cross allergy, and are often at the point of care where decisions about cross allergy can impact selection of medication, so they can assist by recommending alternatives.¹³

As an example, in 2011 we handled a successful case involving an elderly female patient suffering from a urinary tract infection who visited our hospital and was found to be allergic to a cephalosporin. She had previously received fluoroquinolone therapy, but the therapeutic effect was very poor. Urine bacterial culture results indicated infection with extended-spectrum beta-lactamase-producing Escherichia coli. The doctor asked a clinical pharmacist for suggestions. Generally, piperacillintazobactam and cephamycins, instead of fluoroquinolones, cephalosporins, aminoglycosides, and oxacephems, are used for treatment of mild to moderate infection caused by extended-spectrum beta-lactamase-producing E. coli.14 However, a patient with a history of allergy to a cephalosporin should not receive fourth-generation cephalosporins, atypical β-lactams (eg, cefoxitin, cefminox, latamoxef), or combination β-lactamase formulations such as piperacillin-tazobactam. Taking into consideration bacterial resistance, the antimicrobial spectrum, and the cross allergy issue, the pharmacist finally recommended intravenous cefmetazole and oral furadantine as alternatives.

Interestingly, no obvious information on cross allergy involving drugs belonging to completely different pharmacological classes appeared in the package inserts. For example, information on contraindications for vancomycin mentions that the drug should not be prescribed for patients who are allergic to glycopeptide antibiotics and aminoglycosides. However, the information on contraindications for aminoglycosides does not note cross allergy related to vancomycin. Metoclopramide is contraindicated in patients who are allergic to procaine and procainamide, whereas the information on contraindications for procaine and procainamide do not note cross allergy in relation to metoclopramide. Almost all doctors, pharmacists, and nurses did not know this important information before August 2008.

International Union of Pure and Applied Chemistry names of metoclopramide, procaine, and procainamide are 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxybenzamide, 2-(diethylamino)ethyl 4-aminobenzoate, and 4-amino-N-[2-(diethylamino)ethyl] benzamide, respectively, and their chemical structures are shown in Figure 1. Procaine carries an ester moiety whereas metoclopramide and procainamide carry an amide moiety. Ester and amide are mutual isosteres, so may share the same cross-reactivity pattern, just like amide-type lidocaine and ester-type procaine. A case of immunoglobulin E-mediated anaphylaxis induced by metoclopramide has been documented.¹⁵ Therefore, doctors need to take a careful patient history of allergy and select an appropriate medication prior to initiating treatment of nausea and vomiting for patients who are allergic to procaine.

Sometimes information on contraindications gives descriptions of cross allergy related to formulation excipients. However, this aspect seems of less concern to clinicians.



Figure I Chemical structures of metoclopramide $(\boldsymbol{A}),$ procaine (\boldsymbol{B}) and procainamide $(\boldsymbol{C}).$

Paclitaxel containing Cremophor is contraindicated in patients with a history of allergy to polyoxyethylene castor oil. However, the prescribing information on contraindications for nanoparticle albumin-bound formulations does not note any cross allergy issues. Therefore, this novel formulation of paclitaxel may have certain advantages.¹⁶ Some descriptions are so unintelligible and obscure that they lack practical value in guiding safe use of medication, and can cause tension between doctor and patient. For example, Aricept® (donepezil hydrochloride, Eisai Inc, Woodcliff Lake, NJ, USA), a drug widely used in the treatment of Alzheimer's disease, is contraindicated in patients with known hypersensitivity to donepezil hydrochloride or to piperidine derivatives. However, very few hospital staff except pharmaceutical chemists would know which drugs are piperidine derivatives. Such a description may help to understand an allergy that has already happened, but has a limited role in preventing cross allergy, so there is a need to standardize further the information on contraindications related to cross allergy, including specific structural chemical classes, in the future.

A good medication history should encompass all currently and recently prescribed drugs, previous adverse drug events, including hypersensitivity reactions, any over-the counter medications, including herbal or alternative medicines, and adherence with therapy. Documentation of allergies occurring during medical admissions is also very necessary, but hypersensitivity reactions are often poorly documented or not explored in detail, which may lead to potential cross allergy.¹⁷ Bruce Bayley et al introduced a medication reconciliation service and recommended identification of allergy as a key contribution at admission and in the follow-up plan at discharge.¹⁸ Barton et al reported that involvement of clinical pharmacists leads to improved documentation.¹⁹ We introduced a tracer methodology and a work pattern of pharmacist review to address the problem. Collaboration among doctors, nurses, pharmacists, and information engineers is very important. Integration of our clinical information system technology, including computerized entry of physician orders, pharmacy and laboratory information systems, clinical decision support systems, an electronic drug dispensing system, and a bar code point-of-care medication administration system decreased medication errors involving cross allergy. Multidisciplinary teams provide a vital safety net for their patients and colleagues.²⁰

Conclusion

Use of medication can be potentially hazardous if adequate attention is not paid to information on contraindications

related to cross allergy. A systematic investigation of this problem was undertaken in a 2200-bed tertiary care teaching hospital. A pharmacist-led multidisciplinary team initiated an intervention program on cross allergy at our institution, and a risk register was used in the management of this project. Four years of experience in risk management at our hospital indicates that comprehensive clinical intervention including team cooperation can play an important role in detecting problems with cross allergy as well as the ability to recommend safer alternatives.

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Disclosure

The authors report no conflicts of interest in this work.

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