

EXCIPIENT-RELATED ADVERSE DRUG REACTIONS: A CLINICAL APPROACH

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ABSTRACT

Formulations of the same active pharmaceutical ingredients (API) may contain a variety of inactive pharmaceutical ingredients (IPI) or excipients. Package inserts are important sources of information to clinicians and should provide details of both the API and the excipients in the pharmaceutical preparation. The Medicine Control Council's published guidelines recommend the inclusion of excipients (qualitative) in the package insert, but this is not adequately enforced. Excipient-related adverse drug reactions (ADR) are common in clinical practice. Common adverse reactions caused by excipients are hyperactivity, bronchoconstriction, skin eruptions, angio-oedema and gastrointestinal symptoms. The management of patients with adverse drug reactions thus requires critical observation and judgement of the history and symptomatology of the patient in order to distinguish between an allergy and an intolerance in the clinical situation. It is essential to establish whether it is an API or excipient-related ADR and the Cellular Antigen Stimulation Test (CAST) is recommended as a first line laboratory test to perform in order to come to the correct diagnosis. A clinical approach and guidelines are discussed and a clinical rating scale was compiled by the author that will aid the clinician in the diagnosis and management of excipient-related ADR.

INTRODUCTION

Excipients were previously regarded as merely the vehicle to aid the administration of a pharmaceutical preparation. Their main role was to ensure bioavailability, stability and palatability. Some excipient classifications include twelve different categories and may therefore have at least 12 different functions or activities.¹ Excipients were initially regarded as inert ingredients but several case studies have shown that excipients, rather than the active ingredient, were responsible for several adverse drug reactions.² Several reports describe adverse drug reactions that are attributable to the addition of excipients. In Nigeria (2008), 84 children died after consuming glycerin contaminated with diethylene glycol in a teething formula. In Panama (2006), 46 people died after taking cough syrup also contaminated with diethylene glycol. We have two possible scenarios here: one of mislabelling (pharmaceutical industry neglect) and another of misuse, be it intentional or unintentional.³ If clinicians and patients are better informed about the role of excipients and their possible adverse reactions, many unnecessary adversities can be prevented.

Lactose is an excipient often used as a filler and bulking agent or sprayed on the tablet for a shiny appearance. In patients with lactose-intolerance, it is a clinical problem

if the package insert does not disclose this information, especially if patients take the preparation to improve symptoms due to lactose-intolerance (cramps, bloatedness, diarrhoea).⁴ Another example of a lubricating agent causing unfavourable adverse drug reactions is the generic DS co-trimoxazole preparation. Docusate sodium and magnesium stearate are used in this formulation as lubricating agents and fillers and both have potential laxative effects. In Human Immunodeficiency Virus (HIV) patients, co-trimoxazole is used chronically to prevent *Pneumocystis jiroveci* pneumonia. In Acquired Immunodeficiency Syndrome (AIDS) patients often suffer from chronic diarrhoea and this could impact negatively on patient compliance.⁵

As a result, the purity of excipients have come under the scrutiny of manufacturers, prescribers and consumers. The International Pharmaceutical Excipient Council (IPEC) was founded to regulate the manufacturing process and therefore the quality of excipients.⁶ IPEC has developed guidelines to improve the quality of excipient manufacturing. The Americas, Japan, China, Europe (also representing some Northern African countries) and India (recently joined in 2014) are members of this association.⁷ South Africa is not represented on the IPEC. The Medicine Control Council (MCC), being the regulating controlling

body of all pharmaceutical preparations in South Africa, should ideally be involved in the compilation of these guidelines or alternatively, develop similar guidelines relevant to the South African situation.

THE AVAILABILITY OF EXCIPIENT INFORMATION

The question arises whether the MCC, through Act 101, of 1965 and its guidelines, adequately controls and enforces the inclusion of data on excipient content of registered pharmaceutical preparations in South Africa. The guidelines published by the MCC regarding package insert content recommends the inclusion of excipients (qualitative) except those used for adjusting the product during manufacturing (for example to adjust the pH) and ultimately not present in the final product.⁸ If adequate information is available in the package insert, the clinician is able to search for alternatives in the same therapeutic class in cases of adverse drug reactions. A sample of pharmaceutical preparations' package inserts was studied to address this question. Paracetamol-only preparations listed in the March edition of the 2014 MIMS were used as a sample to investigate whether the guidelines provided by the MCC are strictly adhered to by manufacturers, or not. Paracetamol is widely used and there is no safe alternative, especially in the paediatric population.

Eleven paracetamol-only preparations were listed in the March edition of 2014 MIMS.⁹ In cases where package inserts listed no excipients or where the list was incomplete, the responsible manufacturer was contacted to provide information. In all instances the information provided was not sufficiently detailed, possibly in an attempt by the manufacturers to keep the formulation's ingredients confidential. One manufacturer requested the signing of a confidentiality agreement, illustrating that information on excipients is not easily accessible to the clinician. Two of the eleven preparations listed in the March edition of 2014 MIMS, were intravenous formulations and were not included in the scope of this research as these preparations are only available via prescription and are usually administered in a hospital or clinical setting.

Only one of the manufacturers was able to provide a list of excipients that included more than just the preservative, but the list did not mention ethanol, sugar or colourant content. Purified water, sodium meta-bisulphite (preservative), magnesium stearate, pre-gelatinised starch were on the excipient list provided. It was reported that a full list was not available, in order to protect intellectual property. All the manufacturers contacted, save one, provided the minimum excipient information that would typically appear on a package insert of a suspension (preservatives, ethanol concentration and, in some cases, whether the preparation contained tartrazine and sugar). The most common preservatives in these paracetamol-only preparations, were the parabens and benzoates.

One preparation contained metabisulphite and another potassium sorbate. If information on preservatives was available to the clinician, an alternative could be prescribed. In the paediatric population, there are few alternative analgesics to paracetamol that are effective anti-pyretics. In the adult population there are many, including aspirin. There are, for example, many patients that experience an allergic reaction (bronchoconstriction) to the benzoates. These patients may be offered a paracetamol-only preparation with metabisulphite or potassium sorbate as an alternative, still within the paracetamol therapeutic class. This information, however, is not available to the clinician, let alone the consumer.

Table I lists the paracetamol-only preparations (numbered 1 to 9) indicating the combined information from package inserts and the manufacturer. For none of these preparations could a complete list be obtained. This makes it difficult for the clinician to make sound and safe therapeutic choices in the absence of essential information.

EXCIPIENT-RELATED ADVERSE REACTIONS

The most common excipient-related adverse reactions described in the literature are skin eruptions, bronchoconstriction, gastrointestinal symptoms (cramps, flatulence, nausea and diarrhoea) and hyperactivity.¹⁰ These reactions can easily be confused with an allergic reaction or an intolerance due to the API. Many patients consider themselves allergic to penicillin, following a skin eruption as a child, when in fact the reaction may have been to the excipient in the suspension. A clinical study in paediatric patients using amoxicillin-clavulanic acid and sodium benzoate, demonstrated that some patients were allergic to the sodium benzoate in the preparation and not to the antibiotic. There was a different response in terms of time to skin eruption after administration between the amoxicillin-clavulanic acid and the sodium benzoate arm, in the study. The latter caused skin eruptions much sooner after administration than the amoxicillin-clavulanic acid arm, implying a different pathogenic mechanism for the API and the excipient, in this case a preservative.¹¹

It is also known that an underlying viral infection, can

TABLE I: AVAILABLE EXCIPIENT INFORMATION OF PARACETAMOL-ONLY PREPARATIONS

Preparations	1	2	3	4	5	6	7	8	9
Preservatives	•	•		•	•	•	•	•	•
Ethanol		•		•	•	•	•		•
Sugar		•		•			•	•	•
Colourants		•		•	•		•	•	•
Other	•	•	•						

prime the immune system to an allergic reaction to the excipient as well as the API. This observation complicates our assessment and interpretation of the patient's adverse drug reaction.¹¹

Table II indicates the common ADR experienced with popular preservatives used in pharmaceutical preparations as well as in food products.

There is controversy as to whether colouring agents and dyes cause hyperactivity in children.¹² In 2007, in the United Kingdom Food Standards Agency, a study was published linking the use of six colourants (tartrazine, quinoline yellow, sunset yellow, carmoisine, ponceau 4R and allura red) with behavioural problems in children. The European Food Standards Agency reviewed these results but concluded that no change in legislation was needed. It is known that some individuals are in fact prone to hyperactivity following the intake of colouring agents or dyes, whether it is in the food that they eat or in the medicine that they drink.¹⁰ It was also found that not only do colouring agents or dyes cause hyperactivity in children, but that patients may experience other adverse drug reactions as well.⁴ The literature describes post-menopausal women experiencing intolerances after taking Premarin, an oestrogen replacement therapy preparation. This preparation contained 28 excipients and the side-effects experienced were thought to be excipient-related, most probably the tartrazine (colourant) in the preparation and not due to the oestrogen. There are many cases of contact dermatitis described due to neutral red, yellow no. 11 and indigo carmine. Erythrosine, a coal tar based compound is suspected of being carcinogenic. Thyroid tumours were detected in rat studies when high doses of erythrosine were administered.⁴ The use of dyes and colourants could potentially have serious adverse effects. The role of colourants and dyes in terms of marketing, compliance and identification should not overshadow the possible harm it may cause patients.

ALLERGIES AND THE LABORATORY

It is necessary to distinguish between an allergy and an intolerance in this clinical context. The former implies immune system involvement whereas the latter has no immunological response. An allergy has several aetiological

TABLE II: COMMON ADVERSE REACTIONS DUE TO PRESERVATIVES IN PHARMACEUTICAL PREPARATIONS

ADVERSE REACTIONS	URTICARIA	ANGIO-OEDEMA	ASTHMA	LUNG IRRITATION	HYPERACTIVITY
Benzoates	•	•	•	•	•
Sulphites	•		•	•	
Parabens	•	•	•	•	



Figure 1: Flow Cytometre

factors: genetic, environmental, lifestyle differences and allergen exposure. This explains why non-allergic parents can have allergic children – it is a multifactorial disease. Allergic reactions can be divided into IgE mediated and non-IgE mediated reactions. This has an impact on the choice of laboratory testing. Non-IgE mediated reactions include the basophil, T-cell and eosinophil mediated reactions. Less than 5% of IgE mediated reactions are caused by pharmaceutical formulations. If an allergy due to a pharmaceutical formulation is suspected there is little value in testing patients' IgE levels. In patients with asthma, the reactions are 70 to 90% IgE mediated and in food allergies 40 to 60%¹³ in the laboratory.¹⁴ Basophils in the patient's blood sample are stimulated during the CAST and the serum-leukotriene concentration (usually more than 200 picogram/ml) is a strong indication of an allergy to a specific ingredient.¹⁵ Basophils have IgE receptors on their surfaces therefore both IgE and non IgE-mediated reactions can be measured. This test is useful in allergies caused by food, preservatives, colourants and pharmaceutical formulations.¹³ Different generics of a single API can be tested to rule out an excipient-related ADR.

Cross-sensitivity between APIs and excipients adds complexity to the evaluation of symptoms of a possible causative ingredient. For example, patients who are allergic to saccharin and aspartame, might also have a sensitivity to sulphonamides and some patients have cross-sensitivity between aspirin and the azo-dyes. This stresses the importance of obtaining a detailed history from the patient in terms of food and pharmaceutical preparations. It also demonstrates that in cases where information is lacking, the clinician may have the wrong approach when evaluating the patient. The laboratory test most useful when cross-sensitivity is suspected is the ISAC test. The Memory Lymphocyte Immuno-Stimulant Assay (MELISA) is a valuable test in cases where symptoms are delayed (up to 6 days), which is typical of the delayed type IV hypersensitivity reaction.

TABLE III: RATING SCALE AND SCORE CARD FOR DIAGNOSING AN EXCIPIENT-RELATED ADVERSE DRUG REACTION

	CRITERION	SCORE	TOTAL SCORE
1.	Time between intake and adverse reaction is less than 3 days	4	
2.	Symptoms appear to worsen with repeated dosing or increase in dosage	4	
3.	Skin eruption: urticaria or erythema or both (maximum of 4)	4	
4.	Upper airway and respiratory symptoms (rhinitis 1, sinusitis 1, bronchospasm 2, coughing 1)	5	
5.	Gastrointestinal symptoms (diarrhoea 1, bloatedness 1, cramps 1)	3	
	Maximum Score	20	

A complete history of the allergic symptoms and the time between exposure and symptoms experienced should be the clinician's focus. IgE-mediated reactions cause immediate symptoms such as erythema, itching, urticaria, coughing, bronchospasm, angio-oedema and anaphylaxis. Basophil mediated reactions can be immediate (within minutes) or delayed (within hours and usually less than 3 days). It often presents as rhinitis, urticaria, gastrointestinal symptoms and asthma. Important here is that reactions are dose-dependent and cumulative, therefore the patient will experience more severe symptoms with repeated dosing and with up-titration of the dosage. T-cell mediated reactions are delayed immunological reactions. These reactions usually occur more than three days after exposure to the pharmaceutical preparation and most frequently present as skin eruptions (especially maculo-papular) and respiratory symptoms.

CLINICAL GUIDELINES AND APPROACH

A comprehensive patient history is key to the approach of excipient-related ADR evaluation. The clinician should focus on timeframes and factors that can influence interpretation, e.g. a family history of atopy, underlying infections, a recent change in diet and concomitant medications.

The following criteria and rating scale was compiled by the author and can be used to direct the clinician in making a diagnosis of excipient-related ADR in a particular clinical context. If the patient presents with a recent history of exposure to a pharmaceutical formulation, regardless of novel or past exposure and no recent change in dietary intake, the following rating scale can be used to guide the clinician to a specific diagnosis.

A score should be assigned to each positive finding as indicated in Table III. If the total score is 10 or more, there is a high index of suspicion that the patient is suffering from an excipient-related ADR. The maximum score (when all criteria are met) is 20. The first two criteria listed are considered major criteria.

A score of 10 indicates a high level of suspicion of an excipient-related ADR. The CAST can confirm this diagnosis. A high leukotriene concentration (more than 200 pg/ml) is a good indication of an allergic reaction towards a specific component. The laboratory can, in the same process, test for an alternative pharmaceutical formulation in another thera-

peutic class, should the clinician need additional guidance.

CONCLUSION

According to the assessment of the information on excipient content in package inserts of the paracetamol-only preparations, the MCC does not adequately regulate and enforce its guidelines on the information requirements of package inserts. Information on excipient content could prove helpful in a clinical setting where no alternatives are available. A complete patient history will guide the clinician to the appropriate laboratory test and will be advisable in the clinical situation where an adverse drug reaction has to be excluded. The CAST is a useful first-line test to perform in cases where excipient-related adverse drug reactions are suspected. Different generics can be tested with the CAST in order to eliminate the ingredient responsible for the adverse drug reaction.

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