

Oral drug challenges in NSAID-induced urticaria, angioedema and anaphylaxis

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Background: Urticaria, angioedema and anaphylaxis are common adverse reactions to NSAIDs.

Objective: To investigate the clinical characteristics of NSAID-induced acute hypersensitivity reactions with structured oral drug challenges.

Methods: Patients with NSAID induced urticaria, angioedema or anaphylaxis were challenged with either the homologous NSAID to confirm diagnosis or a heterologous NSAID to investigate cross-reactivity. Data was analysed retrospectively and supplemented by a telephone questionnaire.

Results: 68 patients (mean age 48.3, 53 females,) reported a total of 75 instances of NSAID-induced reactions of which 64% were purely cutaneous and 36% were systemic anaphylaxis. Ibuprofen was the most frequent cause of reactions (35%), however diclofenac was the most frequent cause of anaphylaxis (48%). 17/40 (43%) homologous NSAID challenges were positive; presentation with anaphylaxis or reaction to diclofenac predicted a positive challenge. Only 7 of 28 (25%) of heterologous NSAID challenges were positive. Structured challenges enabled us to identify 23 (34%) patients with selective reactivity to a single NSAID, 19 (28%) patients with cross-reactivity to multiple NSAIDs and 23 (34%) patients in whom NSAID hypersensitivity was not reproduced. Selective reactors presented most often with anaphylaxis and some had a background of beta-lactam antibiotic allergy. Cross-reactive patients often had a background of chronic urticaria and presented with milder reactions.

Conclusion: In the absence of a reliable *in vitro* test, structured drug challenges allow identification of selective and cross-reactive NSAID hypersensitivity syndromes. NSAID-induced anaphylaxis is often associated with selective hypersensitivity and patients may not need to avoid other NSAIDs.

INTRODUCTION:

Non Steroidal Anti-Inflammatory Drugs (NSAIDs) are cyclo-oxygenase inhibitors with analgesic, anti-inflammatory, antipyretic and antithrombotic effects. They are the most commonly prescribed class of drugs in the world¹, are implicated in 20-25% of all adverse drug reactions² and hypersensitivity reactions have a population prevalence of 0.3-2.5%.

Acute NSAID hypersensitivity reactions may take several forms which are not mutually exclusive³. These reaction types may have differing pathogenesis and genetic predisposition⁴, and can be grouped into the following categories⁵:

- Respiratory (rhinoconjunctivitis and/or bronchospasm)
- Cutaneous (urticaria and/or angioedema)
- Systemic (anaphylaxis)
- Mixed

Respiratory reactions usually occur in the context of a background of chronic asthma and polypoid rhinosinusitis (aspirin-exacerbated respiratory disease, AERD or “Samter’s triad”). Patients with chronic urticaria may suffer exacerbations from aspirin or NSAIDs⁶. However, discrete reactions to NSAID may occur in the absence of these conditions, and these are the focus of this paper.

NSAID hypersensitivity may be isolated to a single NSAID, or a syndrome of cross-reactive intolerance to multiple NSAIDs. *Selective NSAID hypersensitivity* has many features resembling Type 1 hypersensitivity⁶, although the mechanism is unknown. The syndrome of *cross-reactive NSAID hypersensitivity* does not have an immunological basis, but is the result of pharmacological inhibition of COX1, and is therefore a class effect; most but not all of these patients tolerate COX2-specific NSAIDs⁷.

In the absence of a reliable *in vitro* test, the accurate diagnosis of NSAID hypersensitivity depends on a careful history and oral drug challenge. Previous studies describing oral drug challenges have largely relied on the use of specific COX2 inhibitors in NSAID intolerant patients, irrespective of the clinical history⁸. While this approach enables identification of a safe alternative, it does not differentiate between selective and cross-reactive NSAID hypersensitivity, and may lead to unnecessary avoidance of potentially useful NSAIDs. We devised a structured protocol for assessment of patients with suspected or confirmed NSAID hypersensitivity and retrospectively examined the results of this approach as a tool for defining and differentiating selective and cross-reactive NSAID hypersensitivity syndromes.

MATERIALS AND METHODS

Patient selection:

Patients who presented to the Royal Adelaide Hospital (RAH) Clinical Immunology and Allergy Department between Feb 2006 and Jun 2010 with a history of acute cutaneous or anaphylactic reaction to one or more NSAIDs (the index reaction(s)) and subsequently underwent a controlled oral challenge were retrospectively identified from our database. Patients with known AERD, chronic urticaria (ongoing spontaneous urticaria on most days of the week for more than 6 weeks) or aspirin-dependent exercise-induced anaphylaxis were excluded. Anaphylaxis was defined as a rapidly evolving multisystem reaction with any of the features of a grade 2 or 3 generalised hypersensitivity reaction according to the Brown classification⁹, occurring acutely after NSAID ingestion.

Oral Drug Challenge:

Unblinded graded-dose oral drug challenges (ODC) were performed with informed consent as day procedures in the hospital ambulatory day centre where resuscitation facilities were available. The dosing schedule is summarised in Table 1. Antihistamines, monteleukast, cromolyn and inhaled sympathomimetics were withheld at least 48 hours prior to the challenge. The clinical characteristics of each ODC (NSAID involved, symptom pattern, time of onset of reaction) were recorded. A challenge was considered positive if characterised by the development of objective symptoms and signs including urticaria, angioedema, rhinoconjunctivitis or bronchospasm (FEV1 reduced by >15% from baseline). No patient in our cohort had hypotension, laryngeal oedema or required treatment with adrenaline.

The structured protocol is depicted as a flow chart in Figure 1. Patients were assigned to undergo one of two different types of ODC:

- *Homologous ODC*: challenge with the same drug involved in the index reaction. This was primarily to confirm diagnosis when it could not be confidently established from the history. A homologous ODC was sometimes avoided when the patient's index reaction was severe anaphylaxis.
- *Heterologous ODC*: challenge with a different COX1 inhibitory NSAID (usually aspirin). This was done when NSAID hypersensitivity was already confidently established on clinical history (or when the primary homologous ODC was positive) in order to investigate cross-

reactivity. Some patients with a positive heterologous ODC underwent a further challenge with a COX2 selective NSAID.

Not all patients were evaluated strictly in accordance with the final protocol (fig 1) which evolved and was refined over the five years of data collection. In some instances intermediate steps were omitted as dictated by clinical circumstances.

A patient was designated a **selective reactor (SR)** if the reaction was limited to a single NSAID and tolerance was demonstrated to at least one other potent COX1 inhibitor (usually aspirin) in full dosage. Aspirin is an irreversible inhibitor of COX and displays approximately 4-fold selectivity towards COX1¹⁰. Since oral challenges with 30-150mg aspirin typically induce COX1 mediated hypersensitivity reactions in susceptible individuals¹¹, absence of reaction to 600 mg aspirin was deemed to exclude cross-reactive NSAID hypersensitivity.

Cross-reactive (CR) NSAID hypersensitivity was defined as a primary reaction to aspirin or reactions to at least two separate NSAIDs, usually one suspected from history plus a positive ODC to aspirin. Our review of the literature did not identify any reports where aspirin caused selective hypersensitivity, so an index reaction to aspirin was deemed to signify cross-reactive hypersensitivity. This group could be further divided into those in whom the cross-reactivity was limited to the classical COX1-inhibiting NSAIDs with tolerance to the COX2 selective NSAIDs, and those with hypersensitivity to all NSAIDs including COX2 selective agents.

Telephone Questionnaire:

Clinical information obtained from review of referral and discharge letters was further supplemented with data gained from a telephone questionnaire (approved by the RAH ethics committee). The following data were collected: age, sex, concomitant diseases, characteristics of adverse reactions (NSAID involved, dose, time elapsed between administration of drug and onset of reaction, symptoms experienced & treatment given), number of episodes to the same or different NSAIDs, and NSAID use and tolerance after classification. Atopy was determined by a history of doctor-confirmed hay fever, asthma or eczema. Patient-reported history of allergy to other drugs was not confirmed by further testing or challenge.

Statistical Analysis:

Statistical analysis was conducted with PASW Version 18.0. Comparison between two groups of continuous variables was performed with an unpaired t-test. Differences in the frequency of nominal variables were detected with a 2x2 Fisher exact test and a type I error rate of <0.05 was considered significant. Differences in the frequency of ordinal variables was calculated using a likelihood ratio, with a type I error rate of <0.05 considered significant. Where 2 variables were shown to be predictive of an outcome, the contribution of each variable to the outcome was determined by addition to a logistic regression model. The second variable was then added to determine the correlation coefficient, and if this increased, each variable was determined to be an independent predictor of the outcome.

RESULTS

Patients:

Sixty-eight patients (53 females) were included in the study. Mean age was 48.5 (range 16 to 73) years. These patients reported a total of 75 acute NSAID hypersensitivity reactions of which 27(36%) were systemic anaphylaxis and 48(64%) pure cutaneous reactions (urticaria and/or angioedema). Five patients had reacted to two and one patient to three different NSAIDs. The NSAIDs involved are presented in Table 2. In order of frequency, these include ibuprofen (n=26 reactions, 35%), diclofenac (n=14, 19%), aspirin (n=11, 15%) and paracetamol (n=11, 15%). Naproxen, celecoxib, lumiracoxib, meloxicam and indomethacin were responsible for the remaining 13 reactions (17%). In the anaphylaxis subgroup, diclofenac was the most commonly incriminated drug (n=13, 48%) followed by celecoxib (n=5, 18%). No cases of anaphylaxis were seen with aspirin. Except for one patient (topical), all NSAIDs were taken orally for acute (63%) or chronic (37%) pain. Systemic anaphylaxis was associated with NSAID use for acute pain (duration <7 days) in 25 of 27 patients (92%). Time intervals between drug intake and reaction onset were less than 1 hour in 60%, between 1-6 hours in 32% and >6 hours in 8% of patients. 44(64%) of all patients were successfully contacted by telephone. Supplementing this information with case records, a personal history of atopy was found in 19 (27%), family history of atopy in 14 (20%) and a patient-reported history of beta-lactam antibiotic allergy in 23 (33%) patients.

Homologous ODC

40 patients (33 females, mean age 43.8 years) were subjected to a homologous ODC because of diagnostic uncertainty. Seventeen had a positive challenge. Challenges were more frequently positive when the index reaction was anaphylaxis (10/15, 66%) compared with urticaria and/or angioedema (7/18, 39%) (p=0.024). Challenge with diclofenac was most commonly associated with a positive outcome (8/11, 73%) compared with other NSAIDs combined (9/29, 30%) (p=0.031). Logistic regression analysis indicated that anaphylaxis as the index reaction and diclofenac as the index drug independently predicted the ODC outcome. There was a trend towards increased likelihood of a positive challenge when there was a shorter index reaction to challenge interval- <6 months (10/21, 48%), and >6 months (7/19, 37%) (p=0.54). 14 patients who had a positive homologous ODC subsequently underwent a secondary heterologous ODC with an alternative

NSAID. Three patients declined a secondary ODC and preferred to avoid all NSAIDs. Five of the 6 (83%) diclofenac-intolerant patients subsequently tolerated aspirin in a secondary ODC, suggesting that they had selective diclofenac hypersensitivity. For ibuprofen, reproducibility of the index reaction was lower (4/13 positive, 30%) and most of the positively identified intolerant patients (3/4, 75%) were also intolerant to aspirin, indicating a cross-reactor status.

Heterologous ODC

28 patients (20 females, 8 males, mean age 53.3 years) had reliable evidence on clinical grounds to satisfy a diagnosis of acute hypersensitivity to the index NSAID and hence underwent an ODC with a heterologous NSAID. These patients were considered in two subgroups. **Sub-group 1** comprised 21 patients who had previously reacted to a single NSAID and were therefore challenged with aspirin to determine cross-reactivity. Seven of these reacted, whereas 14 tolerated the aspirin ODC and were thus designated cross-reactors (CR) and selective reactors (SR) respectively. **Sub-group 2** comprised of 7 patients in which cross reactivity was already apparent on history by virtue of reactions to two or more different NSAIDs and further aspirin ODC was therefore not required.

A total of 19 confirmed CR (including some who started with a primary homologous challenge) underwent a further challenge with a COX2 selective NSAID. Tolerance was 72% (8 of 11) for meloxicam, 100% (4/4) for celecoxib and 75% (3/4) for paracetamol. 3 patients declined a secondary NSAID challenge and could not be classified.

Overall, by means of homologous and heterologous ODC, in our cohort of 68 patients we identified 23(34%) SR, 19(28%) CR and 23(34%) NSAID-tolerant individuals.

SR (mean age 38.7, 53% females) presented almost exclusively with anaphylaxis (20/23, 87%, compared to 5/19 (26.3%) for CR ($p=0.001$). All but one of the 23 SR had prior history of intake of the same NSAID (without reaction). SR more commonly had a self-reported history of allergy to beta-lactam antibiotics (9/23 (39%) vs. 1/19 (5.3%); $p=0.013$). CR were older (mean age 62.1) ($p<0.001$), mostly females (74%) and the predominant presentation was angioedema (14/19, 73%). CR had a significant association with a history of chronic urticaria (CU) (10/19 (52.6%), compared to 1/23 (4.3%) for SR, ($p<0.001$). Although patients with AERD were excluded, 1/23 SR patients had a history of asthma compared with 3/19 CR patients (NS). Many CR gave a history of reaction on first exposure to a NSAID.

The NSAID-tolerant group was contacted by telephone to confirm out of hospital tolerance. 18 patients responded of which 7 confirmed tolerance. 11 however continued to avoid NSAID despite a negative ODC.

DISCUSSION

This study addresses the optimal diagnostic procedure to define NSAID hypersensitivity reactions. The main limitation of the study is the retrospective design. However, the importance of oral drug challenges (ODC) in the diagnosis of NSAID hypersensitivity is highlighted by the observation that less than 50% of patients in our series with a history of suspected NSAID hypersensitivity demonstrated reactivity in the controlled ODC. Reasons for this might include temporary hypersensitivity, cofactors no longer present, or misattribution to the NSAID when it was a different trigger such as another drug, a food or a viral illness. These patients would have unnecessarily continued to avoid NSAIDs. The clinical parameters that significantly predicted a positive challenge outcome in this series were anaphylaxis as the index reaction and diclofenac as the index NSAID, whereas the reaction-to-challenge duration of less than 6 months appeared to be predictive but did not reach statistical significance.

Selective NSAID Hypersensitivity:

This is defined by reactivity to a single, specific NSAID with good tolerance to other NSAIDs. *Selective reactors* (SR) were distinguished from *cross-reactors* (CR) in our patient group by presentation with more severe reactions (anaphylaxis) and a higher rate of a self-reported history of allergy to beta-lactam antibiotics. Most SR had a history of prior exposure to the same drug, especially when used intermittently for acute pain. SR was most commonly associated with reactions to diclofenac and celecoxib; selective hypersensitivity was uncommon to ibuprofen and not seen with aspirin.

The mechanism for selective NSAID hypersensitivity appears to relate to the molecular structure of the drug rather than its pharmacological activity. Studies^{12,13} have validated this concept in patients with anaphylaxis to a single NSAID, using multiple challenges which showed tolerance to a number of structurally unrelated NSAIDs. Cross-reactivity between structurally similar NSAIDs does occur (eg. aceclofenac/diclofenac, dipyrone/propyphenazone) but these are not used in Australia. NSAID

currently available in Australia are structurally diverse and there is no evidence that any two are sufficiently similar to cross-react on the basis of structure⁵.

Several features of the clinical pattern of selective NSAID hypersensitivity are consistent with a type-1 (IgE-mediated) hypersensitivity model: the dependence on molecule structure rather than function, the history of prior exposure and intermittent use (consistent with immunological sensitisation), reproducibility in challenge (anamnesic response) and diminution of response over time (waning of immunological memory). The delayed and variable timing of anaphylaxis following NSAID ingestion may argue against an IgE mechanism. Specific IgE to the pyrazolone class of NSAIDs (not used in Australia) was identified in-vitro more than 20 years ago¹⁴ however there have been no convincing demonstrations of specific IgE to other NSAIDs. Despite the relatively common association of diclofenac with anaphylaxis, only a single case report claims to identify *in vitro* evidence for specific IgE¹⁵. A recent comprehensive investigation of 41 individuals with a history of anaphylaxis to diclofenac failed to identify specific IgE to the drug or its phase 1 metabolites despite 4 different assay systems; indeed given the well-controlled experimental systems used, the authors concluded that drug-specific IgE is excluded as a mechanism¹⁶. Therefore despite circumstantial indications, there is no evidence of a role for IgE in most cases of selective NSAID anaphylaxis and the mechanism remains unknown.

Selective NSAID hypersensitivity is more common than often recognized. In a recent study, 75% of patients with history of allergy to a single (non-aspirin) NSAID were able to tolerate aspirin in an oral challenge test¹⁷.

Cross-Reactive NSAID Hypersensitivity:

The syndrome of cross-reactive NSAID hypersensitivity is characterised by intolerance to multiple COX1-inhibiting NSAIDs which may extend to the selective COX2 inhibitors. Aspirin exacerbated respiratory disease (AERD) and chronic urticaria (CU) are commonly associated with cross-reactive NSAID hypersensitivity^{11,18}.

Statistically significant clinical observations regarding (CR) from our study include greater mean age, presentation with angioedema and/or urticaria more commonly than anaphylaxis and history of chronic urticaria; there were trends to female predominance, index reaction to aspirin or ibuprofen and reactions to the first exposure to a NSAID. .

The likely explanation for cross-reactive NSAID hypersensitivity is the inhibition of COX1 by NSAIDs which makes the protective prostaglandin E2 unavailable to prevent 5-lipoxygenase mediated biosynthesis of sulfidoleukotrienes from arachidonic acid and the release of histamine and PGD2 from mast cells and basophils¹¹. Hence the balance between the anti- and pro-inflammatory arachidonic acid metabolites is acutely disturbed by the NSAID. Observations from other studies which lend support to this hypothesis include a relationship between the potential to cause reactions and the COX1 inhibitory potency of the drug, tolerance to selective COX2 inhibitors, elevation of basal leukotriene E4 levels in patients with NSAID-intolerant asthma or urticaria,¹⁹ and the ability of leukotriene receptor antagonist drugs to suppress reactions to NSAIDs²⁰.

In our cohort of cross-reactive NSAID intolerant patients, 72% were able to tolerate meloxicam, 75% paracetamol and 100% celecoxib. Although numbers are small, this parallels the degree of COX2 selectivity of these drugs.

Diagnostic approach to patients with NSAID-induced reactions:

ODC is the primary tool available to the clinician for diagnosis and management of NSAID hypersensitivity^{21,22}. Diagnostic drug challenges must be carried out under close supervision by experienced medical and nursing staff in a centre with facilities to treat anaphylaxis. The history is crucial; the presence of current or recent asthma, nasal polyposis or chronic urticaria (not discussed in this paper) suggest cross-reactive NSAID intolerance and investigation generally commences with aspirin challenge for diagnosis if required, and if positive, subsequent challenge with a COX2-selective agent which will be tolerated in most but not all cases. In the absence of these conditions, in patients with discrete NSAID reactions, our experience led us to devise a structured approach, as shown in Figure 1, resulting in a high diagnostic yield and acceptable patient safety. If the diagnosis is not clinically certain then a homologous challenge will confirm or refute hypersensitivity to the index NSAID. However if this is reliably evident on the history, one may directly proceed to the second step of heterologous challenge with another COX1 inhibitor such as aspirin to allow distinction between SR and CR. Those who tolerate aspirin can be considered SR (to the index drug) and should tolerate any other NSAID. A positive aspirin challenge indicates CR. The options for CR are to avoid NSAIDs altogether and use alternative analgesics or to consider further challenge with a COX2-specific NSAID. Avoiding all COX1 inhibitors in patients with a

reaction to one NSAID without first defining their status as SR or CR significantly limits the NSAID repertoire.

We have found that certain features of the history or presentation are associated with challenge positivity and with SR or CR status, however we advise against any assumptions on the basis of history alone in the absence of challenge confirmation. When the diagnosis has been established, a MedicAlert® should be considered to guard against inadvertent NSAID administration, such as during emergency surgery in injectable or suppository form.

Conclusion

Hypersensitivity reactions to NSAIDs are commonly encountered adverse drug reactions. In the absence of a reliable *in vitro* test, a structured approach based on history and standardised oral drug challenges is essential for diagnosis and subsequent management of selective and cross-reactive NSAID hypersensitivity syndromes. Patients who suffer acute hypersensitivity reactions to a NSAID must initially avoid all NSAIDs but with appropriate investigation as outlined above, the majority can resume tailored NSAID therapy.

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FIGURE LEGENDS

Figure 1: Structured approach to NSAID challenges in patients with discrete acute NSAID reactions (no history of asthma/polyposis or chronic urticaria). Conclusion/outcome numbers shown in a total of 68 patients.

Figure 2: relationship between mode of presentation and selective vs. cross-reactive hypersensitivity status at conclusion of challenges.

Figure 3: Prevalence of background medical conditions in SR and CR (healthy=absence of the other conditions mentioned).

TABLE 1: NSAID doses used for ODC

Category	Drug	Dose (mg) *
Potent, nonselective COX1/COX2 Inhibitor	aspirin	20,75,150,600
	ibuprofen	40,120,400
	diclofenac	5,15,50
	naproxen	50,150,500
Weak nonselective COX1/COX2 Inhibitor	paracetamol	150,500,1500
Preferential COX2 Inhibitor	meloxicam	1.5,5,15
Selective COX2 Inhibitor	celecoxib	50,100,200

*
All doses 120 min apart

TABLE 2: Reported NSAID adverse reactions in 68 intolerant patients

Drug	Reactions	SA	PA	U & A[*]
aspirin	11	0	7	4
ibuprofen	26	7	11	8
paracetamol	11	1	6	4
diclofenac	14	13	0	1
naproxen	4	1	2	1
celecoxib	6	5	0	1
lumiracoxib	1	0	0	1
meloxicam	1	0	1	0
indomethacin	1	0	0	1
Total	75	27	27	21

^{*} SA-systemic anaphylaxis, PA- isolated periorbital angioedema, U & A- urticaria and angioedema

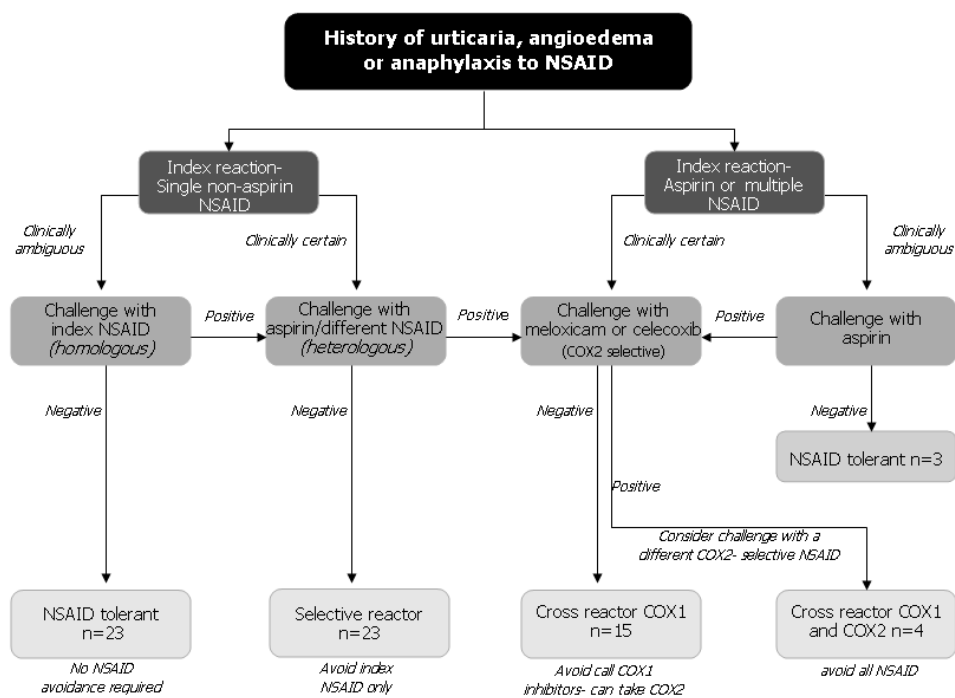


Figure 1

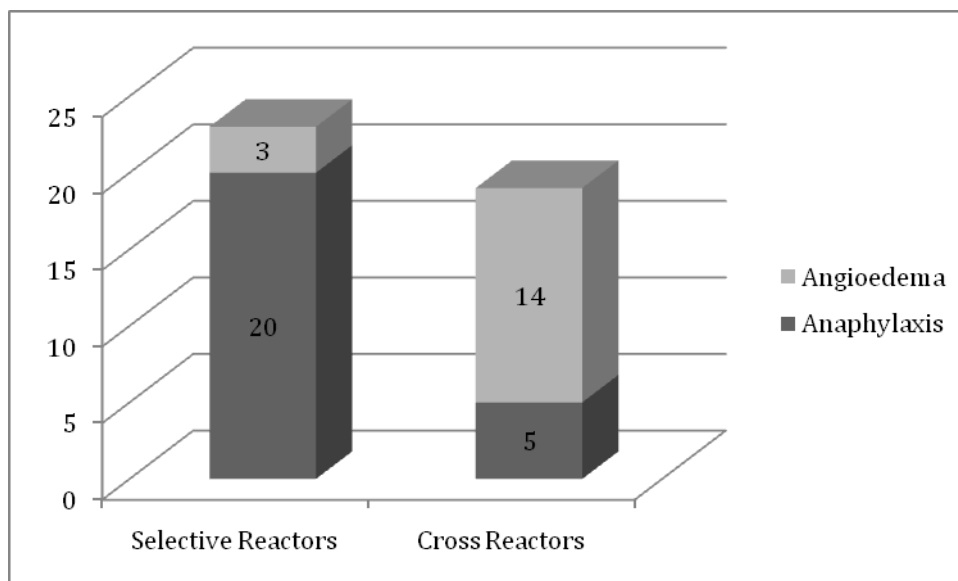


Figure 2

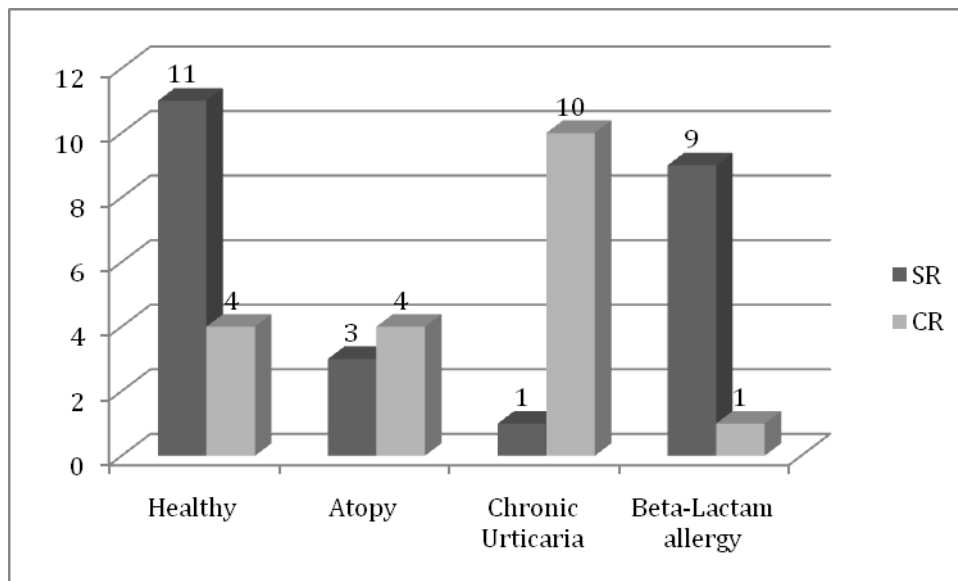


Figure 3

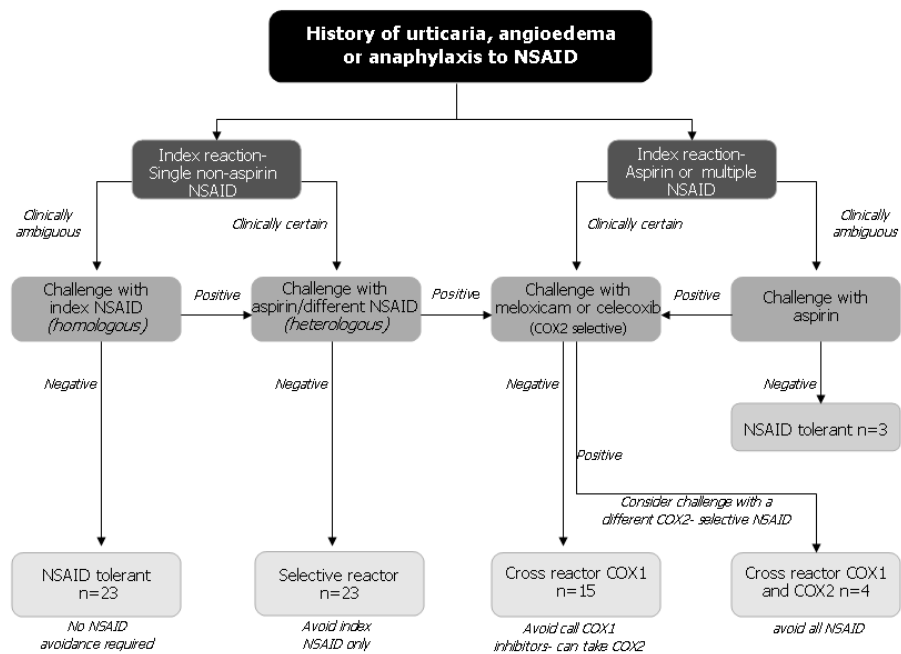


Figure 1

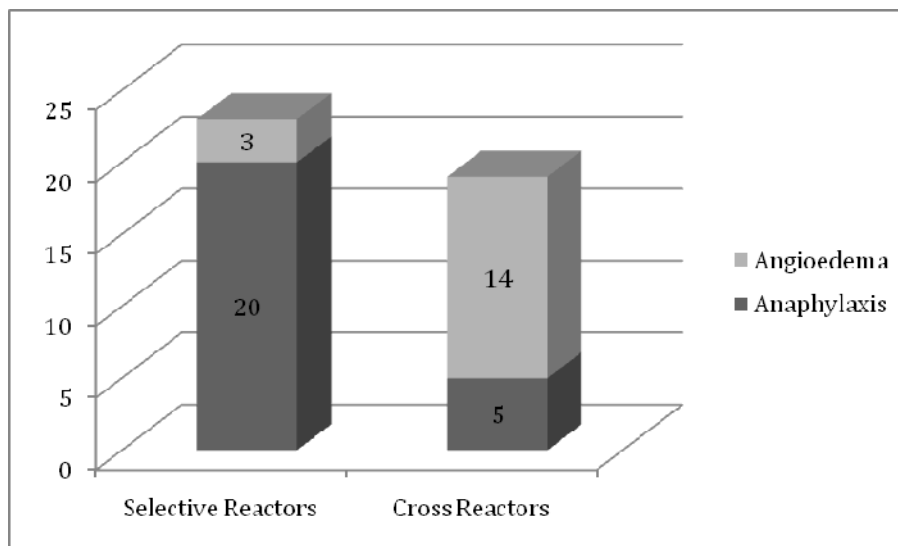


Figure 2

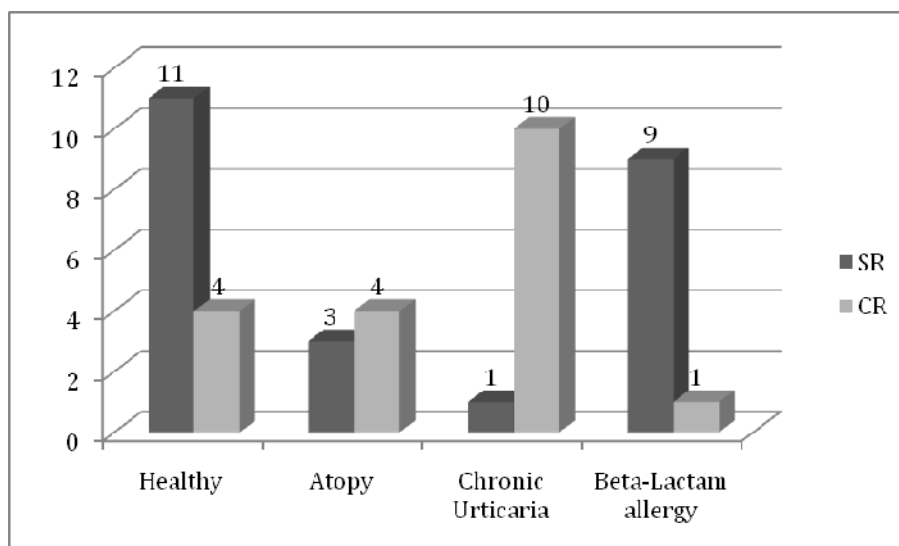


Figure 3