

Original article

Patients with drug reactions – is it worth testing?

Background: Unevaluated drug reactions that lead to the prescription of expensive alternative medication is the reason why the European Academy of Allergy and Clinical Immunology guidelines recommend verification. We evaluated whether a structured test procedure in patients with drug reactions is worth the potential risk.

Methods: We retrospectively analysed the charts of a cohort of 291 (220 females/71 males) consecutive patients from January 2003 to June 2004, who presented at the department's allergy outpatient clinic with histories of drug reactions. Twenty-three patients reported more than one independent episode resulting in 325 cases. All patients underwent the following procedure: (1) detailed history; (2) skin test and/or β -lactam-specific IgE and; (3) if inconclusive, each patient was offered provocation testing – if needed with alternative medication.

Results: We evaluated reactions to 130 antibiotics, 90 to nonsteroidal anti-inflammatory drugs, 36 to local anaesthetics and 69 to other drugs. An association between drug intake and reaction was confirmed in 100 and excluded in 157 cases. Fourteen of 104 drug provocation tests (DPT), among these four reactions to placebo, yielded positive results but were managed without difficulty. In 68 cases, the procedure remained inconclusive. Additionally, we recommended 197 safe alternative regimens to 85 patients. Overall, our test procedure resulted in clear-cut recommendations to 82.1% (239/291) of the patients.

Conclusions: A standardized work-up including DPTs in patients with drug reactions leads to clear-cut advice concerning future tolerability or avoidance of certain drugs including recommendations for alternative medication in the vast majority of patients at the cost of only a low risk of mild side effects.

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According to a World Health Organisation (WHO) definition, adverse drug reactions are defined as 'a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function' (1). Adverse drug reactions can be classified into six categories (1): only two classes concern prompt side effects of drug therapy: common predictable reactions occurring in any individual (type A, 'augmented reaction'), and the uncommon,

unpredictable and in susceptible individuals only occurring type B reactions ('bizarre'). Other classes attribute long-term side effects, e.g. teratogenic or carcinogenic (type D, 'delayed') or the adrenal cortex-suppressing effects of corticosteroids (type C, 'chronic').

Type A reactions make up more than 80% of all drug reactions (2) and are usually documented in common prescription manuals. According to Hunziker et al. (2), 13% of adverse drug reactions can be classified as B-type and either be of nonimmunological (intolerance, e.g. to aspirin; idiosyncratic; pseudo-allergic by direct mast cell release, e.g. reactions to radiocontrast media) or immunological origin. According to the new World Allergy Organisation (WAO) nomenclature (3), the term 'drug allergy' should remain restricted to patients with a proven immunological cause. The terms 'immediate' and 'delayed drug allergy' should be used to describe the onset of symptoms and the probable responsible immunological mechanism [IgE, T-cell mediated, rarely IgG mediated (4)].

Adverse drug reactions are an important issue of public health. They rank number one among hospitalizations

Abbreviations: AGEP, acute generalized exanthematous pustulosis; ASA, acetyl salicylic acid = 'aspirin'; DPT, drug provocation test; EAACI, European Academy of Allergy and Clinical Immunology (<http://www.eaaci.org>); EEM, erythema multiforme majus; ESCD, European Society of Contact Dermatitis (<http://orgs.dermis.net/content/e01escd/e01aims/>); ICDRG, International Contact Dermatitis Research Group; IDT, intradermal test; NSAID, nonsteroidal anti-inflammatory drug; sIgE, specific IgE; SJS, Stevens–Johnson syndrome; SPT, skin prick test; TEN, toxic epidermal necrolysis; WAO, World Allergy Organisation (<http://www.world-allergy.org>); WHO, World Health Organisation (<http://www.who.int>).

because of anaphylaxis (5). Gomes et al. (6) report 7.8% of an unselected Portuguese population claiming to suffer from some sort of drug allergy. In selected patient groups, such as surgical patients, this proportion can even reach up to 28.1% (7).

Unevaluated drug allergies lead to the prescription of less effective or more expensive alternative drugs, thus laying high economic burdens on public health care systems (8–10). Therefore, a clinical work-up is recommended by the guidelines of the European Academy of Allergy and Clinical Immunology (EAACI) (11) and the 'Société Française d'Anesthésie et de Réanimation' (12).

Currently, validated, commercial *in vivo* and *in vitro* test materials are available only for type-1 β -lactam allergies and some cephalosporins. There are recommendations for *in vivo* and *in vitro* tests for diagnosing aspirin (ASA)-hypersensitivity (13). Sensitive and specific commercial *in vitro* tests would be more than desirable; however, most tests available are of questionable sensitivity and reproducibility so that they are used in studies but not routine settings (e.g. CD63 activation tests, lymphocyte transformation tests, CAST-ELISA). Therefore, a thorough work-up of patients with a history of adverse drug reactions, usually includes re-administration of the suspicious drug (14). This poses risk to patients at times when they do not need the drug.

Although the above-mentioned guidelines (11, 12) recommend testing in patients with drug reactions, there are no data about the overall effectiveness of such a procedure. In this study, we tried to assess the risk-benefit ratio of our structured approach consisting of a fixed sequence of history, (if available) measurement of specific IgE, skin test and, finally, drug provocation test (DPT). We did this by retrospectively analysing the charts of 291 consecutive patients with drug reactions, who were referred to our allergy outpatient clinic from January 2003 to June 2004.

Patients and methods

Patients

We retrospectively analysed the charts of a cohort of 291 consecutive patients (220 female/71 male, average age 44.9 ± 16.0 years) referred to our allergy outpatient clinic from 1 January 2003 to 30 June 2004 by primary care physicians, specialists or, from other departments of our institution for the evaluation of a drug reaction.

Informed written consent had been obtained from all patients subjected to skin and/or provocation tests.

Multiple drug reactions

Twenty-three patients reported more than one independent event: 15 subjects two, six subjects three, one subject four and another five. These events were analysed independently resulting in 325 cases.

The 21 patients with ASA-hypersensitivity and multiple reactions to ASA and other nonsteroidal anti-inflammatory drugs (NSAID) were considered as single cases.

Clinical work-up

We started with obtaining a detailed history from each patient. Depending on the history, we planned an individual but structured approach in all patients (Fig. 1). The patient underwent skin tests [patch testing, scratch testing or, depending on the pharmaceutical form of the drug, skin prick (SPT) and intradermal tests (IDT) (15)] and/or, in the case of β -lactam antibiotics, tests for specific IgE in the peripheral blood [penicilloyl G + V (c1 + c2), amoxicilloyl (c6), ampicilloyl (c5), cefaclor (c7); cut-off > 0.35 kU/l; ImmunoCAPTM, PharmaciaDiagnostics, Uppsala, Sweden]. Antihistamines were stopped 1 week and oral corticosteroids and the suspicious drugs themselves 1 month before performing skin tests. Antidepressive therapy with antihistamine side effects and antihypertensive therapy with β -blockers and ACE-inhibitors were switched over to alternative regimens before testing.

Scratch tests with material for oral use crushed in a mortar were only performed when material for parenteral use was not available. Parenteral drugs were tested at a dilution of 1 : 100 in 0.9% saline, local anaesthetics at dilutions of 1 : 10, and bupivacaine at 1 : 5.

Skin prick test, scratch test and IDT were read after 20 min and after 24 hours. Positivity of skin tests was established with a diameter > 3 mm for SPT and > 10 mm for IDT according to the EAACI and European Society of Contact Dermatitis (ESCD) guidelines (15, 16). Scratch tests with a clear wheal and flare reaction were considered positive as published previously (17).

Patch tests were performed with either the crushed pill/tablet or the liquid drug on Finn Chamber[®] (Epitest Ltd Oy, Tuusula, Finland) and on Scanpor[®] (Alpharma AS, Oslo, Norway) and read after 24 and 48 h. Scoring of the patch tests followed the International Contact Dermatitis Research Group (ICDRG) recommendations (18).

Positive skin tests of drugs, that had not been performed before in our outpatient clinic, were evaluated by repeating the test under the same conditions in healthy volunteers as proposed by the ESCD guideline (16).

All patients with a history to penicillins were skin prick tested with a standard series consisting of PPL/MDM/penicillin G (Sandoz, Kundl, Austria)/amoxicillin and clavulanic acid (Augmentin[®], GlaxoSmithkline, Vienna, Austria) and scratch tested

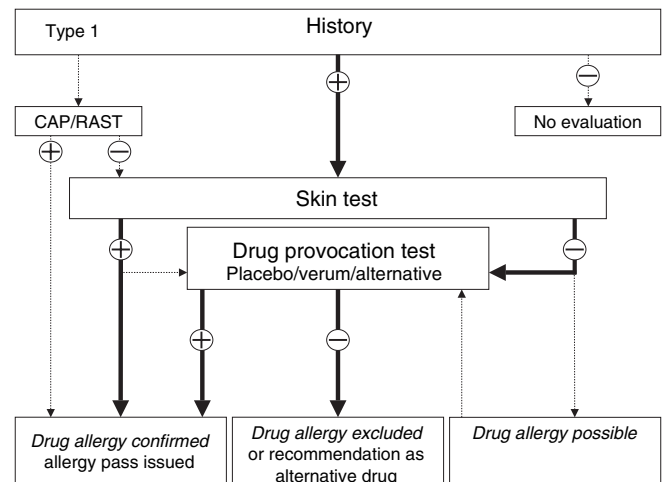


Figure 1. Flow chart for the evaluation of the adverse drug reactions.

with pure amoxicillin (Ospamox®, Sandoz, Kundl, Austria) as pure amoxicillin for parenteral use is not commercially available in Austria. PPL and MDM were bought from Allergopharma (Reinbek, Germany); 0.1 ml of PPL, MDM, 100 IE penicillin G and 0.05 mg amoxicillin (containing also 0.0125 mg of clavulanic acid) were used for IDT.

Planning the drug provocation tests

In the case of inconclusive skin and blood tests, each patient was offered a DPT according to EAACI guidelines (19) with the exception of the three patients with vasculitis-like reactions and the eight patients with severe delayed type hypersensitivity reactions in their history [acute generalized exanthematous pustulosis (AGEP), erythema multiforme majus (EEM), Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)]. In some of the latter, positive patch tests confirmed the reaction (details in Table 1).

Drug provocation tests inflict potential harm on patients and, for ethical reasons, may only be performed if valuable to the patient's future. Depending on the drug, we followed three different strategies.

- 1 Antibiotics.** Antibiotic intake is limited to a certain time period, mostly during infection, and the future need of a certain antibiotic is uncertain. Therefore, DPTs primarily aimed at verifying the plausibility of the drug reaction and were usually planned with the suspicious drug. We only included recommendations for alternative antibiotics if there was an immediate need for.
- 2 Local anaesthetics.** These patients were usually referred by dentists with the need for a safe local anaesthetic after a history of a possible adverse reaction. After negative SPT and IDT to the suspicious drug, one local anaesthetic was selected and the patient received increasing subcutaneous dosages up to a therapeutic dosage as recommended by the EAACI guidelines (15). In contrast to the provocations with all other drugs, the DPTs with local anaesthetics were performed in outpatient settings and because of organizational reasons usually without placebo control.

3 Other drugs. Usually, we conceived DPTs with alternative medication (in most cases analgesics, see Table 2). Sometimes, however, we planned DPTs with the suspicious drug either for excluding hypersensitivities in nonsuggestive histories, or to utilize a negative DPT for demonstrating tolerance to anxious patients.

Performing the drug provocation tests

The patients were hospitalized for the DPTs. Emergency medication (i.v. corticosteroid, antihistamine, adrenaline, theophylline and inhalant β -mimetic) was at hand. The patients had intravenous

Table 2. Recommendations for alternative medication, listed if proposed at least five times

Generic name	Drug class	Recommended (n)	Of which proven through negative challenge (n)
Mefenamic acid	Analgesic	32	13
Diclofenac	Analgesic	18	8
Mepivacaine	Local Anaesthetic	16	13
Paracetamol (Acetaminophen)	Analgesic	16	6
ASA	Analgesic	11	1
Cefalexin	Antibiotic	11	9
Rofecoxib	Analgesic	11	1
Articaine*	Local Anaesthetic	9	8
Lornoxicam	Analgesic	8	8
Lidocaine	Local Anaesthetic	7	4
Penicillin V	Antibiotic	6	3
Metamizole (Dipyrone)	Analgesic	5	3
	Other	41	17
Total		191	94

The tolerability of some alternative regimens was demonstrated in drug provocation tests that all yielded negative and are listed in the right column.

*Contained adrenaline as vasoconstrictor.

Table 1. Plausibility of the reported drug reactions

After testing, the drug reaction was	Reaction type	Drug class					Total
		Antibiotic	NSAID	Local Anaesthetic	Ophthalmic	Other	
Confirmed	I	17	17	2	0	8	44
	IV	17	4	0	3	5	29
	ASA	0	20	0	0	0	20
	hypersens						
	other	5	0	0	0	2	7
Excluded	Subtotal	39	41	2	3	15	100
	I	25	21	25	0	10	81
	IV	19	5	1	11	13	49
	other	8	7	6	0	6	27
	Subtotal	52	33	32	11	29	157
Still possible	I	17	10	1	0	6	34
	IV	21	2	0	0	5	28
	other	1	4	1	0	0	6
	Subtotal	39	16	2	0	11	68
	Total	130	90	36	14	55	325

Test results are given per case (not per patient). 'ASA hypersens': aspirin hypersensitivity. NSAID, nonsteroidal anti-inflammatory drug. Ophthalmic, ophthalmic, topical drug. Details are only given for reactions occurring at least five times.

catheters in place and were monitored for blood pressure, heart rate, oxygenation and cardiac function during the whole DPT.

We preferred performing oral DPTs. These were started with the smallest dosage that could be achieved by separating a commercial preparation of the referring drug, incrementing the dose in hourly intervals until reaching a normal daily dose or until symptoms occurred, e.g. diclofenac 1/2 25 mg, 25 mg, 50 mg (total dose 87.5 mg, normal daily dose around 75–150 mg). Parenteral DPTs worked the same way except that we used a logarithmical dose escalating scheme, e.g. 0.001, 0.005, 0.01, 0.05, 0.1, 0.5 times the total daily dose.

All DPTs were patient blinded and preceded by a controlled challenge with placebo (lactose pills or 0.9% saline for i.v.). Several patients were challenged with more than one drug. These patients received an incremental dosage of a single drug up to a therapeutic dosage on 1 day until a reaction occurred as described above or, if not, the DPT was continued with the next substance the following day.

Plausibility

The WHO classification scheme for the probability of adverse drug reactions (1) is usually applied for assessing type A reactions in premarketing safety studies. For assessing a risk–benefit ratio, we applied a scheme for classifying type B reactions according to the following algorithm: ‘excluded’: negative DPT or implausible history, ‘unlikely’: negative skin test and very improbable history, ‘possible’: negative skin test, undecided history and no DPT; ‘likely’: positive skin test and convincing history, ‘confirmed’: positive DPT or positive CAP/RAST; controversial cases were categorized only after two of the authors (KV and SW) had agreed on the classification.

For the risk–benefit assessment, the reactions classified as ‘confirmed’ and ‘likely’ were subsumed as ‘confirmed’, ‘unlikely’ and ‘excluded’ as ‘excluded’ and ‘possible’ as ‘not useful’.

Statistics

Chi-squared tests were used for calculating statistical significances of categorical data. $P < 0.05$ was considered statistically significant. Statistical analysis was performed with the software package SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Patients and histories

Two hundred and ninety one subjects presented for the evaluation of adverse drug reactions. As already observed before (20), the majority of the presenting patients were female (220/291, 75.6%). The rates of multi-drug reporters (20 females, 9.1%; three males, 4.2%), those owning pre-existing ‘allergy passes’ (14 females, 6.4%; four males, 5.6%) and also the final outcome did, however, not differ significantly between the sexes ($P \geq 0.05$, chi-squared test).

Twenty-five patients had more than one reaction, resulting in 325 cases (details in Multiple drug reactions). The drugs suspected were 130 antibiotics, 90 NSAIDs, 36 local anaesthetics, 14 ophthalmologic topical therapy, six opiates and 49 other drugs (details in Table 1). According to the patients’ histories, there were 182 type I reactions (90 grade I, 62 grade II, 28 grade III and 2 grade IV

according to the classification by Ring and Messmer (21)). Among the delayed-type reactions, there were 101 maculo-papular eruptions, three fixed drug eruptions and nine of the severe delayed type (AGEP/EEM/SJS/TEN). Three patients reported a possible type-3 (vasculitis) reaction and 24 reactions could not be classified by history. Another three cases asked for evaluation of a possible drug reaction simply out of concern without a history.

A total of 70.2% of the reactions were recent events that had happened less than 6 months ago. Only 9.9% were historic with a time lag of more than 10 years between evaluation and reported reaction.

Two hundred and ninety one patients representing 325 single cases were submitted to the structured algorithm presented in Fig. 1. Twenty-eight cases were not evaluated further because an adverse drug reaction could already be excluded by history and two patients representing two cases refused testing because of needle phobia.

Skin and *in vitro* tests

Commercial tests for specific IgE were only available for β -lactams and cephalosporins (cefactor) and were performed in all subjects with a penicillin-history irrespective of the reported reaction pattern. Eight of 449 CAP assays yielded positive results in 4/116 cases (three to penicilloyl V, two to each penicilloyl G, amoxicilloyl, ampicilloyl and none to cefactor), of which 52 had a history suggestive for a type I reaction. All four cases with β -lactams-specific IgE were classified as ‘certain’ without any further examination. Hence, 283 cases were subjected to 1225 skin tests, of which 111 scored positively in 69 cases. Often, there were several positive skin tests in one individual, especially in the penicillin-reacting individuals with reactions to several components of the penicillin test series (see Clinical work-up).

Drug provocation tests

Drug provocation tests were proposed to 151 patients, 70 patients agreed and 81 declined. Fourteen of 166 DPTs in 70 patients yielded positive results. Remarkably, four of these happened after testing with placebo. The other 10 positive reactions happened after DPT with the suspicious drugs and were mimicking the original reactions. Two were exanthemas to enoxaparin and penicillin V that went away without treatment. The other eight were type I reactions: one grade I reaction to mefenamic acid, six grade II reactions to mepivacaine, articaine (with the vasoconstrictor adrenaline), ASA, mefenamic acid and two to propyphenazone and, finally, one grade III to articaine (with the vasoconstrictor adrenaline). One of the grade II reactions to articaine consisted of elevated heart rate and anxiety and was probably caused psychogenically.

All reactions either needed no therapeutic intervention or were controlled with i.v. antihistamine and corticosteroids. Additional i.v. ephedrine was needed in one patient with a bronchial reaction. Adrenaline or epinephrine was not needed in any case. All patients recovered immediately without any sequelae.

Alternative medication. One hundred and ninety one alternative medications were recommended to 85 patients (Table 2), most often analgesics (116) and local anaesthetics (34). The tolerability of these recommendations was demonstrated in 94 negative DPTs.

Plausibility

Considering patients' histories and test results, we judged the plausibility of the adverse drug reaction for each case in each patient. Notably, this classification did not pay attention to the pathogenesis of the reaction (i.e. immunological vs non-immunological), but whether the drug had been the true cause of the adverse drug reaction (Table 1). The drug reaction was confirmed in 100 cases (30.8%). The patients were advised to avoid the drug in the future and received an 'allergy pass' documenting their drug intolerance as recommended by the EAACI guidelines (15). We could exclude a connection between drug intake and reaction in 157 cases (48.3%) meaning that a future intake of the originally suspected drug would be well tolerated.

The category 'possible' implicated an inconclusive test result and hence, no advice could be given to these patients. For this minority of 68 cases (20.9%) including the four patients with placebo reactions, testing was not worth the effort. The outcome 'possible' statistically significantly

depended on a refusal of a DPT ($P < 0.001$, chi-squared test). Nevertheless, 'allergy passes' were issued to most of these patients for security reasons.

The outcome varied considerably depending on the class of drug (Fig. 2). While excluding nearly all reactions to local anaesthetics, we confirmed half of the reactions to analgesics, among these 20 ASA-hypersensitive subjects. Turning to antibiotic reactions, one-third was confirmed, the other third excluded and the last third remained unresolved.

Risk-benefit assessment

The test procedure led to clear results in 79.1% cases (257 confirmed/excluded vs 68 possible). However, the effectiveness of our test procedure depended on the drug type. Highest effectiveness was achieved in judging reactions to topical ophthalmic therapy and local anaesthetics where there was a clear decision in 100% (14/14) and 94.4% (34/36) respectively (Fig. 2). Although antibiotics are the only drug class for which commercial *in vitro* tests are available, the highest rate of unresolved cases remained in this group (30.0%, 39/130).

On a per patient basis, 82.1% patients (239/291) received advice through the test procedure. This seems to be a very favourable risk-benefit ratio based on the small number of the regularly mild side effects through testing (for details see Drug provocation tests).

Additionally, 29.0% (85/291) received recommendations about possible alternative treatment.

Discussion

In this study, we assessed how often a structured approach for evaluating drug reactions (Fig. 1) leads to clear-cut answers to the patient's vital question: 'Which are the drugs for my coming needs?'. In other words, we tried for a fine-tuning of the patient's individual pharmacotherapy. 79.1% of the cases were clearly answered. Half of the patients could reuse the drug on future occasions, one-third should avoid it (Table 1). Only the remaining sixth part remained unresolved. In addition, we recommended alternative medication to 85 patients. In our eyes, this risk-reward ratio is a favourable one.

In general, there are two main counterarguments against DPTs with suspicious drugs. First, they cause high costs of inpatient treatment for otherwise healthy individuals for safety reasons only. Although the prescription of alternative drugs in penicillin allergic patients is known for causing high costs *per se* (9), an evaluation of the total cost-effectiveness of testing for drug reactions remains an open issue (8). A possible cost-effectiveness of DPTs in the German healthcare system was suggested by Blaschke and Fuchs (22). Secondly, exposing otherwise healthy patients in advance of need to drugs having caused – at least by history – some kind of adverse

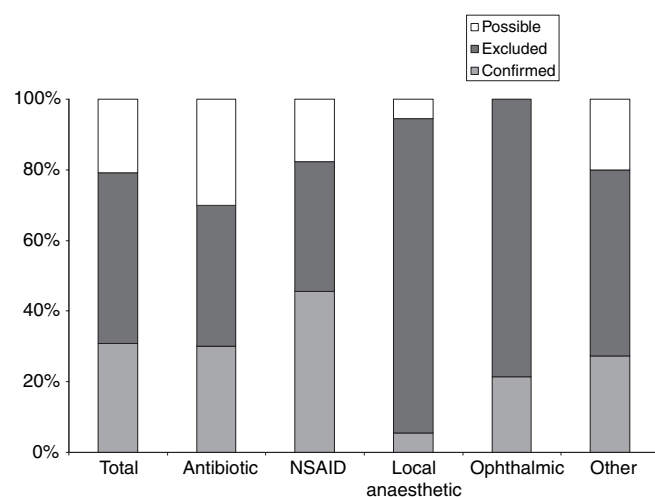


Figure 2. The outcome of the test procedure for the work-up of the drug reactions depended on the drug class. While reactions to local anaesthetics were most often excluded, nearly half of the reactions to NSAIDs (nonsteroidal anti-inflammatory drugs) were confirmed.

reaction, is an ethical caveat. Usually, the gain of knowledge leading to an optimization of the patient's therapy is seen as favourable compared with the risks of a DPT (23). Even large scale DPTs with suspicious drugs in patients with a history of type-1 reaction to drugs in two recent studies from France with 1372 adults (24) and Serbia-Montenegro in 1170 children (25), reported no sequelae from provocation-testing. In our patients, DPTs were also safe. There were reactions in 20.0% (14/70) patients including the four reactions to placebo. Hence, the inclusion of placebo-challenges was essential in our patients to avoid false positive reactions especially in patients with histories of type-1 bronchial and cardiovascular reactions, that are hard to objectify. The remaining 15.2% (10/66) responders to *verum* correspond well with the 17.6% reported by the above-mentioned study of Messaad et al. (24). We think that the low risk of mild reactions upon DPTs with suspicious drugs and the risk-free DPTs with alternative medication were well worth the outcome. However, the need for a DPT will always remain a careful case-by-case decision according to the caring physician's personal risk-benefit estimation.

As already highlighted by others (26, 27), many patients are falsely labelled as 'allergic to local anaesthetics' although allergic reactions to local anaesthetics are very rare. We confirmed only two reactions and could exclude nearly all the others (Fig. 2). Often, we even recommended the suspicious local anaesthetic as proven alternative in a therapeutic dosage for common local interventions.

In contrast to data by Blanca et al. (28), who found sIgE to amoxicilloyl in 53% and to benzylpenicilloyl in 68% in 129 patients with type-I reactions to penicillins, measuring specific IgE to β -lactams was insensitive in our patients (4/116 subjects, 3.4%). Only half of these cases (52/116, 44.8%) had a type-1 suggestive history which can partly explain this difference but, probably, Blanca et al. (28) had described a more preselected population.

Our focus in patients requiring analgesics primarily aimed at finding alternative medication. Apart from experimental systems such as an ELISA against propyphenazone (29), *in vitro* tests are currently not available. Skin tests with NSAIDs bear the risk of false positive reactions because of their high irritancy (30). The high didactic value of negative DPTs with alternative drugs in patients with adverse reactions to analgesics including patients with ASA-hypersensitivity was already stressed by Laking et al. (31). Because of their low risk of side effects and their good tolerability even in ASA-hypersensitivity patients (32, 33), mefenamic acid and paracetamol (acetaminophen) were the first line alternatives that we recommended to our patients (Table 2). However, these two analgesic drugs are not very potent and, therefore, diclofenac was the other most often proposed alternative. Laking et al. (31) also mentioned that these patients should stick to the recommended analgesics for a better quality of life. However, to 11 patients, we recommended rofecoxib (Vioxx®, MSD, Vienna, Austria) as alternative medication, a drug that was withdrawn later on from the market worldwide for safety concerns in patients with a high risk of cardiovascular disease (34).

Conclusions

A clear-cut result in 82.1% patients clearly outweighed the low risk of mild side effects. Bearing in mind this favourable benefit-risk ratio, patients with a history of drug reactions need testing including DPTs. A thorough work-up should also comprise recommendations for alternative drugs when needed.

Disclosure

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