Spanish Society vision of Drug challenge tests


1Servicio de Alergología e Inmunología Clínica, Hospital Universitario Araba, OSI Araba, Vitoria, Spain
2Servicio de Alergología, Hospital Doctor Negrín, Las Palmas de Gran Canaria, Spain
3Sección de Alergología, Hospital Universitario de San Pedro, Logroño, La Rioja, Spain
4Servicio de Alergología, Hospital Universitario Infanta Leonor, Madrid, Spain
5Servicio de Alergología, Hospital del Tajo, Aranjuez, Spain
6Servicio de Alergología, Hospital Quirón Salud Campo de Gibraltar y Hospital Quiron Salud Córdoba, Spain
7Unidad de Alergía, Servicio de Neumología, Hospital Clinic, Institut d'investigacions Biomediques August Pi i Sunyer (IDIPAPS), Barcelona, Spain
8Servicio de Alergología, Hospital San Rafael, La Coruña, Spain
9Servicio de Alergología, Hospital Universitario 12 de Octubre, Madrid, Spain
10Unidad de Alergia, Hospital Universitario Severo Ochoa, Leganés, Madrid, Spain
11Unidad de Alergia, Unidad de Alergoanestesia, Hospital Central de la Cruz Roja, Madrid, Spain

Corresponding:
María Teresa Audicana Berasategui
Servicio de Alergología e Inmunología Clínica, Hospital Universitario Araba.
Organización Sanitaria Integrada Araba.
Edificio de Consultas Externas, 1ª plant. Calle Francisco Leandro de Viana, 1. 01009 Vitoria-Gasteiz. Spain
E-mail: mariateresa.audicanaberasetegui@osakidetz.eus

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0681
RESUMEN
La prueba de exposición controlada a fármacos (DPT) se considera actualmente el estándar de oro para el diagnóstico de alergia a medicamentos. Las reacciones adversas inducidas por medicamentos (RAM) son un motivo creciente de consulta tanto en atención primaria como especializada. Las consultas de Alergología en España son las que habitualmente estudian estas RAM y descartan mecanismos inmunológicos implicados hasta en el 90% de los casos consultados. Un abordaje adecuado de estos casos repercute de una manera evidente en los costes y la eficacia de los tratamientos requeridos por otros especialistas, de modo que, si no empleáramos los DPT, los pacientes requerirían tratamientos más costosos, más tóxicos y menos eficaces en la mayoría de los casos.

En los últimos años se han desarrollado un gran número de nuevos fármacos y este documento pretende ser una guía práctica en la gestión de las DPT con la visión de la Sociedad Española de Alergología. El trabajo de diagnóstico comienza con un historial detallado del paciente. Las pruebas cutáneas solo son útiles en algunos medicamentos y, en la mayoría de los casos, el diagnóstico solo puede confirmarse mediante el DPT. Aunque suele haber reactividad cruzada, las DPT pueden confirmar el diagnóstico y también contribuir a encontrar un fármaco alternativo tolerable. El manejo individual de los pacientes de forma programada, teniendo en cuenta tanto el tipo de fármaco a estudiar como las comorbilidades del paciente, suele permitir encontrar una solución para la mayoría de los pacientes.

Palabras clave: Pruebas de exposición controlada con fármacos. Reacción adversa medicamentosa. Diagnóstico de alergia a fármacos.
ABSTRACT

The controlled drug exposure test (DPT) is currently considered the gold standard for the diagnosis of drug allergy. Drug-induced adverse reactions (ADRs) are a growing reason for consultation in both primary and specialized care. Allergology consultations in Spain are the ones that usually study these ADRs and rule out immunological mechanisms involved in up to 90% of the cases consulted. An adequate approach to these cases has an obvious impact on the costs and efficacy of the treatments required by other specialists, so that if we did not use DPTs, patients would require more expensive, more toxic and less effective treatments in most of the cases.

In recent years, a large number of new drugs have been developed and this document is intended to be a practical guide in the management of PDT with the vision of the Spanish Allergology Society. Diagnostic work begins with a detailed history of the patient. Skin tests are only useful for some medications, and in most cases the diagnosis can only be confirmed by DPT. Although there is usually cross-reactivity, DPTs can confirm the diagnosis and also help to find a tolerable alternative drug. The individual management of patients in a programmed way, taking into account both the type of drug to be studied and the patient's comorbidities, usually allows a solution to be found for the majority of patients.

**Key words:** Drug-controlled exposure tests. Adverse drug reaction. Drug allergy diagnosis.
1. Introduction

Drug provocation test (DPT) is currently considered the definitive tests or the so-called gold standard for the diagnosis of allergy to both food and drugs. In the specific case of drugs, this technique also presents a benefit for three fundamental reasons:

1. Adverse reactions to drugs in the form of rashes are not always allergic and prolonged avoidance of certain drugs has shown to be more toxic and more expensive than a proper allergy study.

2. The use of DPT is often crucial since most drugs - because of their low molecular weight- are not complete antigens but behave as haptens and consequently result in false negatives both in skin tests and in vitro tests.

3. In case of a positive allergy confirmation to a pharmacological group, it is often necessary to evaluate the tolerance of a therapeutic alternative.

However, this practice demands compliance with a set of requirements beginning with a medical history, skin tests and/or patch tests and in vitro tests. Unfortunately, excluding the medical history, none the above are available for all drugs.

In usual clinical practice, there are situations in which the vital risk demands a quick action. In these cases, the so-called graded challenge and desensitization, which differs from the DPT, would be the most sensitive approach.

A DPT is a diagnostic procedure performed when the patient is in good health with no sign of active disease in order to find a well-tolerated drug that could potentially be useful for the patient in the future[1]. Graded challenge and drug desensitization, however, are therapeutic procedures, and are likely to be performed at the time that the
patient requires immediate treatment with the medication in question. As indicated in the recent US-updated practice parameter on drug hypersensitivity reaction (HSR), graded challenge should be carried out in patients who are unlikely to be allergic to the drug and with no intention to induce tolerance. Thus, patients who tolerate a graded challenge are considered not to be allergic to the drug. However, when a patient has a relatively high risk of being allergic to a drug, drug desensitization (or an induction of drug tolerance) it should be considered. This procedure allows temporary modification of a patient's immune response to safely tolerate the drug as long as the patient continues to take the specific drug.

It is clear that a large number of new drugs have been developed in recent years, for the diagnosis and treatment; this paper aims to be a practical guide in the management of drug challenge test.

1. **Indications and contraindications.**

Indications for the controlled exposure tests will vary depending mainly on the drug to be studied, its relevance in the patient's pathology and the patient's comorbidities [1,2].

There are three basic situations in which a DPT is considered to:

1- Confirm tolerance of a drug with were there was a reasonable doubt of an allergic or idiosyncratic reaction, either by negative study, concurrence of other drugs or inconclusive anamnesis.

2- Establish a firm diagnosis of drug allergy in case of inconclusive study by in vivo and in vitro tests.

3- Confirm the absence of cross-reactivity with related drugs in order to have alternative medication.
Some authors propose a direct DPT with beta-lactams when adverse reactions occurred more than 10 years ago and or are poorly defined [3,4]. We do not consider this procedure to be sensible without a prior skin test and in vitro test, with the only exception of non-severe cases in children [4-6].

Regarding the contraindications, it may depend on the reaction presented on the patient and the drug itself:

1. Severe reactions: severe cutaneous syndromes, vasculitis, severe anaphylaxis especially if the patient has other comorbidities that could interfere in the treatment of the reaction.

2. Patient: Pregnant women, severe comorbidities (infections, poorly controlled asthma, heart disease, hepatic or renal disease), human leukocyte antigen (HLA) associations with increase the susceptibility of adverse drug reactions (ADR) to a particular drug.

3. Drug: currently unused drugs such as streptomycin, drugs with doubtful therapeutic value or alternatives with a supporting literature, unpredictably required drugs (anesthetics), implicit toxicity drugs (iodinated and gadolinium contrast) or the ones requiring complex testing techniques (sedation, intubation, etc.).

These general considerations should be assessed in each case as previously discussed by contextualizing the needs and circumstances of each patient. In this sense, patients treated with angiotensin converting enzyme inhibitors (ACE-inhibitors) and beta-adrenergic blockers, increase the susceptibility to adverse reactions and treatments instituted in the case of anaphylactic reactions are less effective [2-7]. In addition, the management of drug reactions in patients with mast cell activation syndrome (MCAS) is difficult and not well researched.
Drugs such as antibiotics, NSAIDs, narcotics or neuromuscular blocking agents and radiocontrast media are known triggers in MCAS patients [3,8].


The process of controlled drug exposure (DPT) consists essentially in the administration of the drug involved in progressively increasing doses, usually in 15-to-30-minute intervals, under careful patient monitoring.

An exhaustive allergy control is mandatory for risk-free practice. Therefore, the patient must sign a consent. Providing that the patient is not able to do it on its own (only in case of incapacitation or because the patient is under legal age), a close relative could sign it. It is worth to mention that according to the Spanish legislation, children with 12 years on, must be able to understand the procedure and sign the corresponding consent themselves as well as their parents/legal guardians.

Vital signs should be monitored (pulse, blood pressure) and observe periodically the patient's subjective symptoms and skin, as in all exposure tests. Adrenaline and other indicated anaphylaxis treatments should be readily available, as well as equipment and trained health personnel. The most optimal situation is that the medication to be administered is well labeled and at least the adrenaline is pre-filled at the head of the patient. It is also considered advisable to have antihistamines and parenteral corticosteroids, saline solution and bronchodilators in solution with inhalation system.

Patients are usually required to be treated with an adequate, gradual and personalized protocol of exposure.

2.1. Initial premises.

DPT requires continued monitoring of the patient undergoing drug administration to recognize possible adverse reactions at all times. The key for success
resides on the concept of risk stratification by individualizing for each patient [3].

2.1.1 First, the risk / benefit ratio of the allergy study must be considered taking into account the patient's age and comorbidities, the relevance of the drug to be studied in the context of their pathologies and finally the existence of alternative medication.

2.1.2 Secondly, exposure or exposures should be planned taking into account the pathology of the patients and the drugs they may need. Studies of analgesics in a patient with pain versus another asymptomatic patient or an antibiotic in an elderly patient with severe pneumonia versus a healthy child do not require the same amount of depth.

2.1.3 Consider the patient's comorbidities in relation to the risk assumed with the possible adverse effects induced by the administered drug in DPT and a possible allergic response.

2.1.4 Monitor the patient: register skin and mucous coloration, blood pressure and pulse before starting the procedure and before each new administration of the drug. Maintain direct control by nursing and medical supervision at all times. Baseline Spirometry and Peak Flow with periodic Peak Flow and / or spirometry assessments are recommended for asthmatics and NSAID admission after each new exposure. In the cases of a nasal exposure test, this should be controlled with rhinomanometry.

2.1.5 Instruct patient and caregivers about possible early manifestations of anaphylaxis (palmoplantar pruritus, tachycardia, dizziness, cough) or if urticaria, angioedema, dyspnea and other manifestations occur. In this case the monitoring routine of vital signs should be primordial step and
the necessary measures taken to ensure that the patient is treated immediately by the responsible physician.

2.1.6 Have medication and necessary material ready for the treatment of anaphylaxis or the side effects of the administered drug.

2.1.7 Previous requirements must be confirmed:
   a. Signature of Informed Consent.
   b. The patient must never take drugs that may interfere with the provocation.
   c. Suspension of treatment with antihistamines, corticoids, beta-blockers, ACE-inhibitors and antileukotrienes. [2].
   d. Make sure the patient does not suffer from acute disease that may interfere in the evaluation of DPT.

2.2. Placebo / nocebo concept.

With the randomized controlled trial (RCT) is also possible to verify the occurrence of adverse effects, which led to the introduction of the term "nocebo", to denote the harmful effects attributable to placebo. These effects are idiosyncratic and not dose-dependent - and among the psychological mechanisms that contribute to this effect are expectations, conditioning, learning, memory, motivation, reward and anxiety.

Spanish legislation does not explicitly address the use of placebo in clinical practice; Therefore, it does not authorize nor prohibit its use because it conflicts with the current conception of patient autonomy and the practice of shared decisions [9]. It is clear that controlled drug exposure should be blind to the patient so as not to compromise his tolerance. This concept should be included in the terms and accepted by the patient upon receiving the DPT.
2.3. Preparation of drugs.

In oral exposure, opaque capsules are usually used so that the patient cannot identify the drug or the dose taken. Placebo capsules are filled with sucrose or corn starch. In parenteral preparations, commercial preparations are usually used and dilutions are made with physiological saline solutions or distilled water.

Lysine acetylsalicylate is prepared in various pipetting solutions to be deposited in the lower nasal turbinate.

2.3.1. Dose.

Dosage of test preparations and time intervals vary between published studies. This might depend on the type of drug itself, the severity of the adverse reaction under investigation and its mechanisms, the expected time latency between application and reaction. A summary protocol table recommended for drug provocation tests (DPT), under strict hospital surveillance can be found in the in Table 1.

In case a patient is at risk of obtaining a positive test and / or high suspicion of sensitization, the first dose must be equivalent to 10 or 100 times less than the original dose that created the reaction in the first place. If there is low suspicion of reaction or cases where it is sought to confirm tolerance a higher dose of ¼ could be applied. Usually, the therapeutic dose is obtained in the same day and the patient must remain in observation until 1 to 3 hours after the last dose. In the case of non-steroidal anti-inflammatory drugs (NSAIDs), it is recommended to extend the period of surveillance longer [10-12 and table 1].

Regarding the volume of administration, this depends on the chosen guideline. Usually, capsules are used in order to mask the doses in the oral drugs; for the intradermal O.2 ml; for subcutaneous O.2 to O.6 ml and for IM or EV of O.6 ml to 1 ml or continuous perfusion with monitored patient. In intravenous infusions, the fractional
The drug is usually admitted in progressively increasing boluses until the therapeutic dosage is complete.

The dose increases may vary markedly. Dosage increases are usually triplicate or duplicates or when starting with very low doses is multiplied by ten, this depends on the authors and the drugs [10-12 and table 1].

The administration of the defined daily dose is desirable and the expected time latency between application and reaction, DPT may take hours, days or, occasionally, weeks, before completion depending on the type of drug itself, the severity of the ADR under investigation and its mechanisms involved [2,3 and table 1].

2.3.2. Interval between doses.

Usually, 20-to-30-minute intervals are allocated between doses for oral administration and 15 to 20 minutes for parenteral administration [1,2,10-12]. A provocation test consists of administering increasing doses of the suspected drug up to the full therapeutic dose or until symptoms of a drug reaction occurs (Table 1).

2.4. Time interval between reaction and provocation test.

As a general rule, DPT should be performed not earlier than 4 weeks after the episode. A booster effect is recommended in case a reaction happened more than 1 year before, since sometimes the levels of antibodies descend ex. aminopenicillins. Therefore, some authors recommend the repetition of skin test or even a rechallenge 2 to 4 weeks later [2].

In delayed reactions (such as exanthema in children), once the immediate tolerance in the allergy department is demonstrated, some authors recommend extra doses at home every 12 hours for at least 2-3 days [6]. In contrast other authors from northern Europe recommend courses of treatment for 7 days, but usually when benzylpenicillins are involved [13].
2.5. Concomitant drugs.

In order to guarantee complete elimination of concomitant drugs and accurately calculate its effects, the drug elimination half time should be multiplied by 5. Any medication or co-medication that might influence the outcome of the DPT result should be completely washed out.

3. Assessment of test results.

A DPT can be considered positive if it reproduces the original symptoms. Sometimes photographs of previous skin reactions can help confirm the diagnosis. General clinical tests such as a complete blood count, eosinophil count and the determination of mediator release (histamine in blood, methylhistamine in urine, eosinophil cationic protein, serum tryptase) can also be helpful.

The predictive value of DPT mainly depends on the type/mechanism of reaction and the drug involved. If the patient finally is labeled as drug allergic, it is essential to provide adequate documentation of those drugs that should not be received again and those that were tolerated in the test. A personalized clinical report should be handed and the allergy warnings specified in the medical history.


Treatment of adverse events that occurred during DPT depends on the type of reaction and its severity. The first action to be taken is to stop further drug tests, followed by adequate general and specific procedures according to the treatment of anaphylactic reactions. Drugs should only be introduced to mitigate this reaction when the symptoms point to a conclusive positive test result.

- Reactions such as urticaria, angioedema and anaphylaxis are treated with antihistamines, corticoids and / or parenteral adrenaline like any other common allergic events.
- Antihistamines and corticosteroids are usually sufficient treatment to fix drug eruptions and monitoring possible associated infections or evolution to other more serious pathologies.

- In drug induced serum sickness, removal of the suspected drug and administration of antihistamines and corticosteroids is usually sufficient. In more severe cases, plasmapheresis may be useful.

- High dose corticosteroids are recommended for the treatment of the Stevens-Johnson Syndrome. The usual daily dose for moderate cases is 80 mg of prednisone and in more severe cases hospitalization, supportive measures and as recommended, 60 mg of EV methylprednisolone for 4-6 h. It is important to reduce the doses gradually over the course of 2-3 weeks, since a sudden withdrawal can cause relapses. Corticosteroids are insufficient to control the process in toxic Epidermal Necrolysis Syndrome and these patients usually require vigilance in a Burn Unit.

- Treatment with corticosteroids is usually enough to accelerate the resolution of the process in other reactions such as drug induced fever, vasculitis or reactions that affect the circulating elements of the blood, even in affected solid organs.

5. Limitations of drug provocation testing.

5.1. Technique.

Although DPT is the gold standard of diagnosis, it has its own limitations. Negative predictive values vary depending on the drugs: beta-lactams between 94-98%, NSAIDs over 96% [11]. A negative exposure does not 100% guarantee a subsequent tolerance of the drug for two main reasons:

- IgE levels lower over time

- Cofactors (food, exercise, viral infections, etc.) can be involved.
5.2. Interpretation by allergy specialist.

Drug provocation test results should be evaluated based on objective parameters; however, subjective symptoms must also be recorded. Clinical presentation as well as the progress of a reaction over time, should be documented and quantitative parameters (e.g., blood pressure, heart rate, oxygen saturation and sometimes peak flow too) should also be measured in each new dose of the drug administered.

In open DPTs, nocebo-like responses might lead to the misinterpretation of subjective symptoms such as a positive DPT results up to a total of 27% of patients [14-17].

The analysis of serum tryptase is an objective marker of true allergic reaction but it is only positive only in 20% of drug exposures [3,18]. However, in case of a serious adverse reaction in the context of a DPT, tryptase test should always be carried out and the window of opportunity for a good diagnostic is within the first 2 hours [19].

5.3. Patient and faculty reluctance.

Recently, the SEAIC has studied the quality of life of patients with drug allergy. Thus, study shows that greatest impact on wellbeing were having suffered an anaphylaxis episode and having developed more than one allergy to different drugs [20].

Bavbek et al. reported that non-atopy, high education level and drug hypersensitivity in elder were associated with nocebo effect during DPTs [21]. A double-blind placebo exposure test may be necessary in adults, especially in those with a history of multiple reactions to drugs from different families [22].

- Although the negative predictive value of the drug-controlled exposure test is high, approximately 1/3 of patients feel reluctant and do not take the drug again despite
5.4. Resensitization.

DPT as inductor of resensitization in patients with negative skin test with a history of penicillin allergy is rare in both pediatric and adult patients, including after repeated doses [5,23-25]. Although, in a usual assessment of drug allergy a routine repeat DPT is not indicated.

6. Benefits of DPT.

Well –defined benefits of DPT include, on the one hand, those derived from excluding allergies and, on the other, access to safe alternatives [12]. The hospital level treatment for wrongly “penicillin allergic” labeled patients is less cost-efficient and more prone to adverse reactions than the ones treated with beta-lactams [3].

When DPT tests are performed and they are negative, anxiety decreases and new exposures are better tolerated [17]. Therefore, it is important to start testing the drug that is the most likely to be tolerated.

A SEAIC multi-center study has confirmed that completing a drug allergy evaluation improves the quality of life of patients who have suffered drug anaphylaxis or more than one allergic drug reaction or a musculoskeletal disease [20].

2. Beta-lactams.

According to different guidelines and following ENDA guidelines of the EAACI [2,5,26] drug provocation test (DPT) is nowadays considered the gold standard for confirming the diagnosis of hypersensitivity reactions (HSR) to Beta-lactams (BLs).

The chemical structure of beta-lactams contributes to the specificity of the immune responses both in immediate and also in delayed reactions. In the Mediterranean countries, the immune response is directed predominantly against the
side chains of aminopenicillins, which differs from some patterns found in Anglo-Saxon countries where more benzyl-penicillins are consumed. In fact, amoxicillin is currently considered the most frequent cause of anaphylaxis among beta-lactams in Spain.

During the last years many studies carried out in both, pediatric [6, 27-29] and adult series [30-33], confirmed the safety and usefulness of the DPT in the diagnosis of BL allergy. A high number of cases can be overdiagnosed if DPT is not carried out because the sensitivity of skin and in vitro tests is not optimal, varying widely among different studies [35-40].

Proposed DPT protocols included in the BLs allergy workup varied widely among different studies in terms of doses, steps, time intervals between each dose administration, incremental doses and days of dosing. For both immediate (IR) and non-immediate reactions (NIR) the EAACI has validated two different algorithms nowadays followed by many groups [41,42]. According to these procedures, after a detailed clinical history, we must perform in vitro test and/or skin test, and after, if negative, we shall consider DPT [41,42]. Nevertheless, in the recent years some studies have claimed the possibility to perform DPTs without previous skin testing in selected cases of mild NIR such as maculopapular exanthema or urticaria, especially in children [6, 43-46], but also in adults with benign reactions [47,48]. From SEAIC, an allergological study consisting of skin tests and in vitro tests prior to exposures is routinely recommended. We should keep in mind that the study of allergy to beta-lactams in Mediterranean areas has highly developed over more than 30 years, unlike other countries that have not studied patients for years and carry older overdiagnosis. Figure 1 shows an algorithm recommended by the SEAIC for studies of immediate reactions in which BL treatment is required.

There is still not consensus about considering DPT in BL allergy in terms of challenge with escalating doses or a unique dose, and the lasting of the procedure, one day or a prolonged DPT. Considering the doses used for the DPT there are different...
dosing approaches that range from some with three steps or less, like for example in mild IR and NIR \([30,49,50]\), to other with additional lower dose steps at the beginning that concern to cases of severe reactions or high-risk patients \([51]\). Nevertheless, as published recently, in mild NIR the possibility of challenge without previous skin test exists without risk \([6,34,43-48,52]\)). Regarding the lasting of the procedure, there is some debate about if DPT performed in just one day would be enough to conclude a diagnosis, especially in NIR. While some groups considered one day as enough \([50,51,53]\), there are other that believe that DPT performed in one single day can be responsible for many false negative results, being necessary to prolong the test during several days to confirm the diagnosis \([10,45,47,54,55]\). The Spanish study for pediatric allergy recommends 2 days \([6]\).

The allergological study of patients labeled with penicillin allergy allows to rule out allergy in our environment in more than 90% of cases and therefore allow this treatment in most patients. Furthermore, many patients have a selective allergy to aminopenicillins, being able to tolerate a wide range of other beta-lactams \([32,35]\).

Currently, when allergy to a beta-lactam is confirmed, it is also crucial to confirm whether there is a therapeutic alternative within the group. It can be considered that the in vivo cross reactivity between penicillins and cephalosporins when the R1 side chain is different is approximately 10% while when it is identical it can be greater than 30% \([32,35,36,55 \text{ and figure 2}]\). The cross reactivity between cephalosporins is also based on the similarity of the chemical structure of the same R1 side chain. It could be very high when there are similar or identic in the side chain. Patients who are allergic to non-monobactam beta-lactams usually tolerate aztreonam although it should be avoided in those patients diagnosed with a ceftazidime allergy that shares the same side chain \([56 \text{ and figure 2}]\).

Recent Spanish guidelines for management of DRESS syndrome recommend controlled re-exposure tests with an alternative ß-lactam (not the culprit) if the benefit.
outweighs or at least equals the risk [57]. The graded challenge exposure test recommended by Romano et al for nonimmediate β-lactam allergic reactions is an initial dose of 1/100 of the therapeutic one. In cases with negative results 3 days to 1 week later, a dose of one tenth is given and, if the result is again negative, a full dose can be given after the same interval as used before [57,58].


According to the classification proposed by Kowalski [59], these acute reactions are first divided into two groups and are then further subdivided by the presence of underlying disease (Table 2).

The diagnosis of NSAIDs hypersensitivity reactions are based on clinical history, physical examination of a patient and, if possible and appropriate, in vitro or in vivo tests, followed by drug challenge procedures.

Drug provocation test (DPT)

Depending on the route of NSAID administration, nasal, bronchial and oral DPT can be used. The oral provocation test is considered as the gold standard for diagnosis hypersensitivity reactions to this drug and it is indicated to confirm or exclude the diagnosis when there is no other test available and to find an alternative NSAID once the diagnosis is confirmed [60]. These tests should be performed in a single blind placebo in a controlled manner and in some cases it is necessary a double blind procedure. Other medications are withheld before testing, according to international guidelines [61].

Nasal lysine-aspirin challenge is recommended particularly for patients with symptoms of the upper respiratory tract and severe asthma. This test may also be performed in an outpatient clinic [61-65]. The sensitivity of this test is 73% and the
specificity 94% [64,65].

Bronchial provocation test (BPT) is indicated in patients with bronchial symptoms with NSAIDs [66,67]. The specificity of the BPT is 100% with a sensitivity of 62%, although it is less dangerous and time consuming that oral DPT [67].

Oral provocation test (OPT) is the only available test for diagnosing patients with non-immunological reactions with skin symptoms [59,60].

Different protocols exist, with different drugs, time interval and total cumulative dose and the most often recommended be those described [60,68] in Table 3.

One week interval is needed if various NSAIDs are studied by OPT. In cases with respiratory symptoms it is not usually performed with strong COX-1 inhibitory activity, due to the possibility of severe bronchospasm [60].

**DIAGNOSTIC ALGORITHM**

In figure 3 a practical diagnostic algorithm is proposed that helps determine the type of NSAID hypersensitivity and allows for choosing proper patient management. In most cases of NSAID hypersensitivity, however, information acquired from history is not sufficient to confirm the diagnosis, thus further steps including oral provocation challenges may be necessary to perform.

An acute type of reaction can be suspected if the reaction started to develop within hours (up to 24 hours, but usually 1-2 hours) after drug intake. The next step depends on the symptoms that are referred by the patient.

a) Patients developing respiratory symptoms. It begins with an NPT or BPT with LSA if it is possible to carry out in the Allergy Department. A positive response will confirm the diagnosis of NERD. The patient is prompted to avoid all NSAIDs with
strong COX-1 inhibitory activity. The tolerance to alternative analgesic: paracetamol (acetaminophen), selective COX-2 inhibitors and preferential COX-2 inhibitors, such as meloxicam should be tested. If there no response, this drugs can be recommended.

b) Patients developing cutaneous symptoms. Up to one third of patients with chronic urticarial experience exacerbations when are exposed to NSAIDs that inhibit COX-1, but not to COX-2 inhibitors. \([69,70]\).

The NECD can be achieved by the clinical history. Tolerance to alternative analgesic should be verified.

In patients with urticaria and/or angioedema without underlying chronic urticaria two possibilities exist:

- First, if the patient reports reactions with more than 2 NSAIDs from non-related chemical groups, then he is diagnosed by the clinical history as a multiple hypersensitivity to NSAIDs, (NIUA). \([59,60]\). In this cases tolerance to alternative analgesic should be assessed.

- Second, if patients reacted with less than 2 NSAIDs from non-related chemical groups an OPT with ASA or potent COX-1 inhibitor (if ASA is involved) should be carry out. If positive response, as NIUA should be diagnosed, and oral challenge to alternative analgesic should be verified.

If patient tolerate ASA administration, a OPT with the culprit drug should be performed and if positive, the diagnosis is acute selective reaction (SNIUAA). The decision of administered the culprit drug in this group of patients depends on the type of reactions, being contraindicated in patients with anaphylaxis.

If tolerance exist to ASA and the culprit NSAID, the patient should be diagnosed non allergic.
4. Macrolide, Quinolone and Aminoglycoside antibiotics.

MACROLIDES

Macrolides are amongst the safest antibiotics accounting for very few drug hypersensitivity cases reported [71]. Skin tests with different suspicious macrolide antibiotics under study have usually yielded negative results except a few reports in immediate or delayed reactions as fixed drug eruptions. History alone leads to an over-estimation of macrolide hypersensitivity and skin / laboratory tests that seem to not be useful in identifying these patients. Oral challenge tests are considered to be the gold standard to establish or exclude drug hypersensitivity [72]. According to a low frequency of hypersensitivity it is recommended that a graded challenge is performed in the context of a low likelihood of drug allergy [72,73]. Several studies about cross reactivity in this drug group have suggested that the overall risk is low given the differences in size of the lactone ring [74]. Findings also observed with macrolides immunosuppressants [75]. In conclusion, when an allergic reaction to a macrolide is detected, an exposure to an alternative macrolide is recommended to confirm its tolerance [76,77].

QUINOLONES

There is considerable cross-reactivity among quinolones, but no predictive pattern has been established [78]. Sensitization to one quinolone does not predict sensitization to another member of the group. Furthermore, as skin tests provide little information, it is necessary to carry out challenge tests to confirm sensitivity or tolerability [79]. However, it is considered advisable to perform skin tests with several quinolones to guide the diagnostic study before the TPO [80]. Basophil activation test or specific IgE to quinolones are also recommended if they are available [81]. Among quinolones, levofloxacin is usually the safest quinolone alternative [78].
AMINOGLYCOSIDES

Aminoglycosides rarely cause drug allergic reactions, including IgE-mediated systemic reactions, in fact the most frequent reactions are delayed by neomycin [5]. In cases of previous reaction to an aminoglycoside, controlled administration of an alternative aminoglycoside from another group is recommended. Cross-reactivity between gentamicin, tobramycin and neomycin has been described and by other way between streptomycin and kanamycin has also been reported [75].

5. Other antimicrobial and tuberculostatic drugs.

TUBERCULOSTATICS

Challenge tests with those drugs are usually performed orally route, except for gentamicin and tobramycin that are only available by injection or topical route. According to the severity of the previous reactions, any positive tests or multiple pathologies associated, it is recommended to start with an alternative drug of the group at 1/10 therapeutic dose [72,78,82]. Challenge test with gentamicin and tobramicin follow the same rules as those oral administrated.

In Spain, some adverse reactions (paresthesia) attributed to penicillins in the 70s and 80s occurred it being administered together with streptomycin. It is interesting in these cases to confirm tolerance to penicillin (rule out allergy) but nothing should be done with streptomycin because it is not currently in use.

Rifampicin and pyrazinamide are the most frequently involved drugs in this group [83-87].

Skin tests (prick and intradermal) with tuberculostatic agents are not very useful, although there are cases with positive intradermal test [87,88-90]. In non-immediate reactions (NIR) these intradermal tests with delayed readings and epicutaneous tests are helpful [91-94].
Concerning in vitro tests, IgE antibodies in IR and Lymphoblastic transformation test (TTL) in NIR can be positive and can help diagnosis [88,95].

Drug provocation protocols have been published with rifampicin, isoniazid, pyrazinamide and ethambutol and desensitization have also been described [85,96-99].

SULFAMIDES
Skin tests are useful in IR to confirm the diagnosis and to look for alternative drugs. In non-immediate reactions, epicutaneous tests do not seem to be useful [100], except in some fixed drug eruptions (FDE) [101].

Sometimes IgE against sulfamethoxazole is positive in IR [102,103].

There is cross-reactivity between antimicrobial sulfonamides [101], but it is not clear yet between anti-microbial and non-anti-microbial sulfonamides [104-106], except with sulfasalazine that has cross-reactivity with anti-microbial sulfamides [107].

TETRACICLINES
Doxycycline may have the best overall safety profile regarding the potential for allergic reaction compared to minocycline and tetracycline [108].

Tetracycline cross reactivity due to dermatological manifestations can be variable. Some studies show cross-reactivity between the tetracycline class in FDE but other studies do not [109-111].

GLUCOPEPTIDES
Leaving aside the red man syndrome which is considered an infusion-related reaction, in hypersensitivity reactions, skin tests are helpful for diagnostic and to look for alternative drugs.
Allergic reactions to vancomycin and teicoplamin have been reported where skin tests were positive [112-114]. Cross reactivity is variable [115-120]. Some vancomycin challenge protocols have been published [121].

**NITROIMIDAZOLES**

Some authors consider skin and in vitro test to be useful while others do not [122, 123].

The cross reactivity of imidazoles is variable [124, 125].

**LINCOSAMIDS**

Clindamycin skin tests have limited diagnostic potential [126]. Sometimes, positive patch tests are found [127-129]. No cross-reactivity studies or desensitization protocols, have been reported by PubMed.

**LEPROSTATIC SULPHONS**

There has been reports of dapsone hypersensitivity cases, although, no cross-reactivity studies or desensitization protocols have been found by PubMed [130-133].

**ANTIPARASITICS**

Skin tests (prick and ID) with antimalarials are of little use, however, patch tests are useful in non-immediate allergy [134-139]. There is some report of IR and NIR to paramomycin [140-141].

Hypersensitivity reactions to praziquantel, benzimidazole, albendazole and pentamidine, have been described but no cross-reactivity or desensitization protocols studies have been found by Pub Med [142-151].

**6. Corticosteroids.**

Corticosteroids are anti-inflammatory medications used widely to treat allergic inflammation. Although the endocrine and gastrointestinal side effects
of corticosteroids have been described, the occurrence of immediate hypersensitivity reactions and delayed contact dermatitis due to corticosteroids remains under-recognized. Hypersensitivity reactions can occur due to a corticosteroid itself, or due to the additives and vehicles present in corticosteroid preparations.

Skin testing and DPT can help us to confirm the suspected culprit agent in IR and therefore help us identify an alternative tolerated corticosteroid. Regarding the reading of the skin prick and intradermal tests, we have to perform an immediate reading (after 20-30 minutes) and a non-immediate one (after 24, 48 and/or 72 hours).

Patch testing and DPT can aid to identify the culprit agents in contact dermatitis and NIR. Cross-reactivity patterns found in contact dermatitis studies are not applicable to immediate hypersensitivity reactions [152-156]. See tables in references from Dooms-Goossens research group [157,158]. Sensitization in contact dermatitis exhibits cross-reactivity patterns based on corticosteroid structure. A DPT should be performed in case of non-severe cutaneous reactions with negative skin tests results in order to find an alternative corticosteroid [159]. It is recommended a succinate-free alternative [160,161]. There are several clinical reports explaining cross-reactivity and the two main groups are: budesonide with group B and group D members and methylprednisolone with hydrocortisone or prednisolone [161-163].

In the rare cases where a safe alternative cannot be identified, if corticosteroids are needed, desensitization can be performed, as it is described in methylprednisolone and hydrocortisone [164-166].

7. Antifungal drugs.

Available antifungals employed to treat systemic micosis can be classified in two main gropus against the wall (caspofungin) and against cytoplasmic membrane (amphotericin B, bifonazole, clomidazole, clotrimazole, croconazole, econazole,
fenticonazole, ketoconazole, isoconazole, miconazole, neticonazole, oxiconazole, sertaconazole, sulconazole, tioconazole and anti-parasitics).

As a Fixed Drug Eruption is the most frequent reported symptom, patch tests have to be performed not only with the culprit drug to confirm the diagnosis, but also, with other family members to discard cross-reactivity before the DPT [167-173]. Cross-reactivity is not well described in the antifungal group, and there are several clinical reports with different results between members of the same family [167-174].

In the rare cases in which a safe alternative cannot be identified, when antifungals are needed, desensitization can be performed, as it is described in amphotericin B and voriconazole [175, 176].

8. Heparins, anticoagulant drugs, Insulin and antidiabetic drugs.

HEPARINS and ANTICOAGULANT DRUGS

This anticoagulant group includes heparins, hirudins and cumarins [177]. Heparins and hirudins may cause different types of allergic reactions: cell- mediated type IV reactions, followed by, less frequently, antibody-mediated type II reactions and very rarely type I reactions [178,179].

Two situations can unfold depending on the result of the allergological tests obtained.

1. In the case on ADR is highly suspected with SPT or patch test positive to heparin or hirudin under study, a challenge test to an alternative heparin with negative test can be carried out.

2. In the case that SPT or Patch test were negative to all heparin tested there are two possibilities:

2.1. An heparinoid, synthetic pentasaccharide (Fondaparinux) or an hirudin is recommended, If the allergic reaction was induced by a UFH (Unfractionated Heparin)
or LMWH (Low molecular weight or fractionated heparin) because the likelihood of cross-reactivity among UFH and LMWH is very high [180-183].

2.2. Another anticoagulant from any group can be tested if the anticoagulant involved in the ADR was an heparinoid, fondaparinux or an hirudin,

In the case of low suspicion of allergy by medical history with positive allergic tests, the attitude is the same as in the previous case. However, with negative allergic tests a provocation test with the suspected heparin can be done. It is not recommended a DPT in cutaneous necrosis cases or antibody-mediated reactions.

Drug administration guidelines vary according to the type of reaction [184-187]:

In the type I reactions 1/10, 3/10 and 6/10 of the total heparin dose should be administrated, leaving 30 minutes among administrations. The total dose dispensed must be adapted to the needs of the patient and the pathology to be treated. The route of administration can be subcutaneous (SC), preferably in abdominal area, or intravenous (IV), depending on the heparin class. It is especially important to perform the test using the same route of administration in which the patient presented the reaction. There are published cases of allergy to a subcutaneously administered drug, which nevertheless tolerate the intravenous route [188].

In the NIR, 1/10 of the SC dose can be injected and, after waiting if there are no reactions in the following 7 days, the rest of the 9/10 dose could be administered. The challenge is considered negative 7 days after this second DPT. In an emergency, it can be administered intravenously in a slow regimen. The most widely used protocol is the one proposed by Gaigl: 2,500 IU of heparin on the first day, followed by 5,000 IU on the second day and 7,500 IU every 6 hours for three days [188].
INSULIN AND ORAL ANTIDIABETICS.

Allergic reactions to insulin treatment is rare and a prevalence of 0.1-2% is estimated [189,190]. Type I, type III (localized Arthus reaction) and type IV reactions have been reported. The insulin molecule, NPH (neutral protamine Hagedorn) or different additives (zinc, cresol, glycerol) can act as allergens [191-193].

A provocation test is indicated when there is suspicion that the allergic reaction is due to the NPH molecule or an additive, and another class of insulin without them is available.

DPT to demonstrate allergy or tolerance can also be performed in cases in which the SPT is negative and the determination of IgE and IgG are as well negative.

The only option is desensitization in cases of life-threatening anaphylaxis and also in cases of allergy to insulin itself because DPT is not recommended [194].

In case of IR, the procedure should follow as previously: 1/10 of the total dose, followed by 3/10 and finally 6/10, keeping 30 minutes between doses. If a NIR occurred (generalized or local) a single dose can be inoculated, and the reading can be carried out in following days. This insulin could be administered if no reaction is observed in the subsequent 5 to 7 days. Just like heparin, there are demonstrated allergy cases involving SC insulin and posterior IV tolerance [195].

In addition to the usual controls that are carried out in any drug challenge, serial controls of blood glucose should be performed.

9. Biological and cytostatic drugs.

Only a few series about DPT in regard to antineoplastic and biological agents (BA) have been reported [196-203].

A risk assessment based on the initial reaction severity, comorbidities and the indication from the referring physician is mandatory before DPT [196-198, 200].
Patients with severe HSR, positive skin tests/specific IgE and/or comorbidities should be excluded. β–adrenergic blocking agents and ACE inhibitors should be discontinued 24 hours prior to the DPT. It should be performed in the medical intensive care unit consisting in administering the desired full dose of the culprit drug according to the manufacturer’s instructions including infusion rates for standard regimens [196-198, 200]. In Madrigal-Burgaleta et al. study, 229 DPT out of the 341 performed were negative (67%), therefore these patients received the scheduled treatments with the standard regimens. In contrast, 112 were positive (33%), of which seventeen DPT were severe HSR (15%). Forty three percent (48/112) were mild and 42% (47/112) were moderate reactions according to Brown’s classification. Authors conclude that DPT is a vital diagnostic tool that helps to exclude HSR and avoid unnecessary desensitization [198].

In regard to taxanes, Picard et al. reported a study that included 49 DPT in patients with mild/moderate IR and NIR showing negative cutaneous tests. The decision on performing DPT was based on the severity of the initial reactions, skin test results and each patient’s comorbidities (FEV1 values, coronary heart disease) need of treatment administration and patient’s consent [204]. DPT consisted in administering the culprit drug diluted in 250 mL of normal saline starting at 10 mL/h and progressively increasing up to 160 mL/h without an adverse reaction and, therefore, all patients tolerated at least for 1 infusion. In 2013, the protocol was modified using 3-step every 15 minutes, with approximately 10-fold increments for each step in infusion rates until the final manufacturer recommendation dose was achieved. This change was made to ensure that the procedure could register any HSR that might appear with a regular infusion [204]. Two patients (4%) had a mild IR and one (2%) had a delayed one. Premedication with antihistamines, H2 blockers, antileukotrienes and/or acetylsalicylic acid can be used in DPT although the authors are unclear.
Recently, Pagani et al. reported a multicentric study that enrolled 84 patients with IR due to taxanes [203]. Sixteen patients without any alternative treatment, negative skin tests and mild reactions that involved the skin or a single organ (usually back pain), underwent graded challenges successfully. The offending drug was administered at 10 mL/h for the first hour and if tolerated, the rest of the drug was administered according to the manufacturer's instructions [203].

In patients with mild BA reactions, negative skin tests and normal tryptase levels obtained during IR, DPT can be performed [201-202]. The offending drug can be administered in 2 steps, 1/10 of the total dose and if tolerated administer the rest can be administered until the target dose is achieved [201-202].

**SPECIFIC CONSIDERATIONS**

DPT with antineoplastic and biological drugs differs from testing in other drugs in many aspects:

1. The timing of performing DPT is essential since it must happen together with the next scheduled treatment. For this reason, multidisciplinary collaboration is needed between allergists, referring physicians, nurses, and clinical pharmacologists.

2. Following the manufacturer's recommendations of the infusion rate a premedication is mandatory for these drugs. In contrast, many DPTs with antineoplastic and with BA should be performed with a different or additional premedication for challenge test [196-198, 200, 203].

3. Concerning premedications, its involvement in the HRS must be also ruled out before the procedure, as can happen with other concomitant drugs [196,198-200].
4. Regarding the target dose, it must be prescribed by the referring physician based on previous laboratory findings and then pharmacists have to prepare it according to manufacturer/institutional safety recommendations.

5. The safety of the procedure requires of allergists with experience on these drugs, specially-trained nurses, one on one nursing and it must be accomplished in Intensive Care/Desensitization Units [196-198, 200, 203, 204].

An algorithm designed to illustrate the recommended protocol for DPT with antineoplastic and biological agents (BA) can be found in figure 4.


In the absence of standardized controlled provocation test protocols for the group of drugs indicated, we have developed a unified "graded challenge" proposal for these substances, belonging to different pharmacological groups. The protocol recommended for drug provocation tests (DPT), always under strict hospital surveillance is previously indicated in table 1.

Related to a series of fatal anaphylactic/anaphylactoid reactions that occurred in 2013 after parenterally administered iron preparations, the EMEA published a series of recommendations for successive re-exposures. These recommendations are an exception to the usual indications for re-exposures and / or desensitizations because the products are not indicated for patients with known serious hypersensitivity to other parenteral iron products [205].

The risk is enhanced in patients with known allergies including drug allergies, patients with a history of severe asthma, eczema or other atopic allergies. There is also an increased risk of hypersensitivity reactions to parenteral iron complexes in patients with
immune or inflammatory conditions (e.g., systemic lupus erythematosus, rheumatoid arthritis).

11. Conclusions.

The first step of a diagnosis begins with the detailed clinical history of the patients. Skin tests are only useful in some drugs and in most of the cases the diagnosis can only be confirmed by provocation testing. Although cross-reactivity is usually present, provocation testing is able to diagnose confirm and contribute to find an alternative tolerable drug. Individual patient management taking into account comorbidities normally enables for a solution to be found in most patients. Finally, in the majority of urgent or life-threatening cases, we can resort to desensitization or cautious administration of drugs, always under extremely thorough supervision.

FINANCIAL SOURCES STATEMENT

The preparation of this document has not had any funding.

CONFLICT OF INTEREST

The authors have not conflicts of interests to declare.
References


77.- Chia FL, Thong BY. Macrolide allergy: which tests are really useful? Allergol Immunopathol (Madr). 2011;58:11-23.


104.- Wulf NR, Matuszewski KA. Sulfonamide cross-reactivity: is there evidence to support broad cross-allergenicity? Am J Health Syst Pharm. 2013;70:1483-94.


FIGURE LEGENDS:

**Figure 1.** Algorithm for betalactam allergy diagnosis when immediate beta-lactam treatment is necessary.

Modified from M.J. Torres Jaén et al Tratado de Alergología 2016
Figure 2. Beta-Lactam structures and rates of cross-reactivity.
**Figure 3.** Clinical history of hypersensitivity acute reactions to NSAIDs (<24h). Abbreviations: COX, cyclooxygenase; NSAID, nonsteroidal anti-inflammatory drug; OPT: Oral provocation test; BPT: Bronchial provocation test; NTP: Nasal provocation test; NERD: NSAID-exacerbated respiratory disease; NECD: NSAID-exacerbated cutaneous disease; NIUA: NSAID-induced urticaria/angioedema.
Figure 4. Proposed algorithm for DPT with antineoplastic and biological agents (BA). *Adapted from Brown’s classification (Brown, 2004).

Abbreviations: SCAR: severe cutaneous adverse reactions, IDT: intradermal test; SBP: systolic blood pressure, Sp O2: peripheral oxygen saturation, §: according to the manufacturer’s recommendations.
Table 1. General protocol recommended for drug provocation tests (DPT), under strict hospital surveillance.

<table>
<thead>
<tr>
<th>Route</th>
<th>Immediate IgE-mediated reactions</th>
<th>Non-immediate Drug Reaction without systemic involvement (e.g. delayed rash or exanthemas) (*)</th>
</tr>
</thead>
</table>
|                                    | Low likelihood of drug allergy                                         | High likelihood of drug allergy                                                                  | Administer 10% of the dose within 30 min, then in 30 minutes administer the remainder of the dose (90%) 

8,9. |
| IV administration                  | Administer 10% of the dose within 30 min, then in 30 minutes administer the remainder of the dose (90%) 

8,9. | Administer, successively, the doses of 1% - 10% - 50% and 100% of the daily dose of the drug. Doses should be administered over 30 minutes and the patient will be kept under observation for 30 minutes, before the next dose 

1,10,11. |
| Oral, subcutaneous or intramuscular administration | Administer 25% of the total daily dose of the drug, observation 60 minutes and then administer the remaining dose (75%) 

8,9. | Administer, in incremental doses: 1% - 10% - 50% - 100% of the usual daily dose, at an interval about 30 minutes 

1,10,11. |
|                                                    | Administer 25% of the total daily dose of the drug, observation 60 minutes and then administer the remaining dose (75%) 

8,9. |

(*) If the DPT is negative, a full-course of drug treatment should be extended for 2 to 10 days, or for at least as long as it took the patients to develop their anamnestic reaction.
Table 2. Classification of Hypersensitivity Acute Reactions Induced by Nonsteroidal Anti-inflammatory Drugs (NSAIDs)


<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Clinical Manifestation</th>
<th>Underlying Disease</th>
<th>Cross-reactivity</th>
<th>Putative Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAID-exacerbated respiratory disease (NERD)</td>
<td>Bronchial obstruction, dyspnea and/or rhinorrhea or nasal congestion/</td>
<td>Asthma and/or rhinosinusitis</td>
<td>Cross-reactive</td>
<td>COX-1 inhibition</td>
</tr>
<tr>
<td>NSAID-exacerbated cutaneous disease (NECD)</td>
<td>Wheals and/or angioedema</td>
<td>Chronic urticaria</td>
<td>Cross-reactive</td>
<td>COX-1 inhibition</td>
</tr>
<tr>
<td>NSAID-induced urticaria/angioedema (NIUA)</td>
<td>Wheals and/or angioedema</td>
<td>No</td>
<td>Cross-reactive</td>
<td>Unknown, probably COX-1 inhibition</td>
</tr>
<tr>
<td>Single NSAID–induced urticaria/angioedema or anaphylaxis (SNIUAA)</td>
<td>Wheals/angioedema/anaphylaxis</td>
<td>No</td>
<td>Non cross-reactive (selective)</td>
<td>IgE-mediated</td>
</tr>
</tbody>
</table>

Abbreviations: COX, cyclooxygenase; NSAID, nonsteroidal anti-inflammatory drug;
Table 3. Interval of administration and dose of the drugs used in the oral drug provocation test.

<table>
<thead>
<tr>
<th>DRUGS</th>
<th>DOSE (MG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etoricoxib</td>
<td>60 - 90 *</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>100 - 200*</td>
</tr>
<tr>
<td>Paracetamol (Acetaminophen)</td>
<td>100 - 250 - 500 - 1000*</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>7,5 - 15**</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>500 - 1.000**</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>25 - 50**</td>
</tr>
<tr>
<td>Metamizole (dipyrone)</td>
<td>1ˢᵗ day: 50 – 100 - 250**</td>
</tr>
<tr>
<td></td>
<td>2ⁿᵈ day : 575***</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>1ˢᵗ day: 50 – 100 - 200 - 400**</td>
</tr>
<tr>
<td></td>
<td>2ⁿᵈ day : 600***</td>
</tr>
<tr>
<td>Acetylsalicylic Acid</td>
<td>1ˢᵗ day:50 - 100***</td>
</tr>
<tr>
<td></td>
<td>2ⁿᵈ day : 250 - 500***</td>
</tr>
</tbody>
</table>

Administration interval of each dose (min):
* 60 minutes ** 120 minutes, *** 180 minutes