The Lymphocyte Transformation Test in Delayed Hypersensitivity Reactions Induced by Ibuprofen and/or Metamizole

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Single nonsteroidal anti-inflammatory drug (NSAID)–induced delayed hypersensitivity reactions (SNIDHRs) are immunologically mediated hypersensitivity reactions to NSAIDs [1,2]. They develop more than 24 hours after exposure [1] and comprise a variety of entities ranging from mild reactions (eg, maculopapular exanthema) to potentially life-threatening reactions (eg, Stevens-Johnson syndrome/toxic epidermal necrolysis [SJS/TEN]) and organ-specific reactions (eg, hepatitis or nephritis) [2].

Oral challenge test with the culprit drug is the gold standard in the diagnosis of NSAID hypersensitivity, although it is not risk-free and is contraindicated in severe reactions [1]. Data on the sensitivity and usefulness of the lymphocyte transformation test (LTT) in these reactions are scarce [3].

Our objective was to analyze the usefulness of the LTT in the diagnosis of SNIDHRs.

We performed a retrospective, cross-sectional, descriptive study in patients with delayed adverse reactions to metamizole and/or ibuprofen managed in a tertiary hospital (La Paz University Hospital, Madrid, Spain) between 2015 and 2020. The study was conducted according to the Declaration of Helsinki and approved by the local ethics committee (PI-4962). Clinical histories were reviewed to determine the results of allergy studies, which included skin testing (prick and intradermal with delayed reading and/or patch tests), assessment of drug re-exposure, and LTT (see Methods_Supple.). Skin testing was not performed in cases of organ-specific reactions. Causality algorithms were used to determine the probability of adverse drug reaction (Naranjo causality algorithm and updated RUCAM for the hepatitis cases) [4,5].

LTT was also performed in nonallergic controls exposed to ibuprofen (n=15) and metamizole (n=8).

Receiver operating characteristics (ROC) curve analysis was performed to calculate the optimal cut-off value for a positive stimulation index (SI), the gold standard being re-exposure to the suspected NSAIDs or a causality algorithm score >5 in cases when re-exposure was not performed (see Methods_Suppl).

The study population comprised 40 cases with DHRs to metamizole and/or ibuprofen (25 female; mean [SD] age, 44.4 [21.4] years) (Table S1). The mean interval between administration and reaction was 6.4 (6.85) days. In 67.5% of the cases, other drugs were involved in addition to the NSAID. The reactions reported and drugs involved are shown in Table S1.

The reactions consisted of exanthema (19), delayed urticaria (1), erythema multiforme major (3), acute generalized exanthematous pustulosis (2), possible drug rash with eosinophilia and systemic symptoms (1), SJS (1), agranulocytosis (5), immune thrombocytopenic purpura (1), exacerbation of eosinophilic gastroenteritis (1), interstitial nephritis (2), hepatitis (2), exanthema plus hepatitis (1), and exanthema plus eosinophilia (1).

The NSAIDs involved in the delayed reactions were ibuprofen (n=19) and metamizole (n=15). Some patients also experienced a single reaction after the intake of both drugs simultaneously, as follows: ibuprofen and metamizole (n=2), ibuprofen and naproxen (n=2), ibuprofen and acetylsalicylic acid (n=1), and metamizole and dexketoprofen (n=1).

There were no statistically significant differences in the type and severity of symptoms between reactions to ibuprofen and metamizole.

The causality algorithm scored the NSAID implicated as possible in 13/40 and as probable in 27/40.

The results of the positive skin tests are shown in Table S2. Two out of 12 had positive results in the intradermal test with metamizole. There were no positive skin test results for ibuprofen or positive patch test results for ibuprofen or metamizole.

The LTT was performed with the suspected NSAIDs and concomitant drugs (Table S1). The mean time between the reaction and the LTT was 5.2 (3.93) months.

The SI cut-off for ibuprofen and metamizole was 1.95, as determined by ROC curve analysis (sensitivity, 92%; specificity, 88%) (Table S3). The LTT result was positive in 16/46 with the NSAID involved. The LTT result was negative in exposed controls.

Of the 40 patients, 19 (47.5%) presented exclusively cutaneous reactions (18 maculopapular rashes and 1 delayed urticaria). In this group, 4 cases had a positive LTT result, and no re-exposure was performed owing to the high suspicion that it was truly responsible for the reaction. A negative LTT result was recorded in 15 patients, of whom 9 underwent re-exposure with good tolerance. The LTT was not performed in 2 cases owing to a positive intradermal skin test result and to circumstances such as loss to follow-up or use of alternative medication (retrospective study) in the remaining 4. These results are shown in the corresponding column of Table S1 (NSAID involved and tolerated in the re-exposure).

The pathogenic mechanism underlying SNIDHR involves stimulation of drug-specific T cells [1]. LTT detects T-cell proliferation after drug exposure in vitro [6].

We report the largest series to date of DHRs to ibuprofen and metamizole assessed using LTT.

Causality algorithms have previously been used as a standard to ensure a correct diagnosis of drug causality in delayed hypersensitivity reactions [7,8]. We used causality algorithms in cases in which drug tolerance results were not available to assess the diagnostic performance of LTT (they had to reach a score of at least 5 to be considered true positive). Confirmation of another drug as the culprit (cases with positive skin tests or positive re-exposure tests) also helped us to rule out the NSAID as being responsible for the reaction.

Patch testing and delayed reading of intradermal skin tests have low sensitivity and are more reliable with pyrazolones [1], as corroborated in our study (Table S2).

Our study is limited by its low sample size and the fact that drug re-exposure was not performed in all patients owing to the presence of severe reactions in some and loss to follow-up in others (retrospective study). Our study is also limited because the technique requires a specialized laboratory and skilled personnel. However the ENDA/EAACI Drug Allergy Interest Group position paper indicates that it might be advisable to perform LTT before in vivo tests in severe reactions with a suspected T-cell mechanism [9].

The LTT with ibuprofen and metamizole is highly sensitive and specific, making it a useful tool in the diagnosis of delayed hypersensitivity reactions to these drugs.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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