The Lymphocyte Transformation Test in delayed hypersensitivity reactions induced by ibuprofen and/or metamizole

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

Oral challenge test with the culprit drug is the gold standard in the diagnosis of NSAID hypersensitivity, however 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 SNIDHR.

A retrospective, cross-sectional, descriptive study was conducted in patients with delayed adverse reactions to metamizole and/or ibuprofen studied 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 institutional ethical committee (PI-4962). Clinical histories were reviewed with the corresponding allergy study that included skin testing (prick and intradermal with delayed reading and/or

epicutaneous tests), assessment of drug re-exposure and LTT (See Methods_Supple.). Skin testing was not performed in cases of specific organ reactions. Causality algorithms were used to determine the probability of adverse drug reaction (It was applied Naranjo causality algorithm and for the hepatitis cases updated RUCAM) [4,5].

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

Receiver operating characteristics (ROC) curve analysis was performed to calculate the optimal cutoff value for Stimulation Index (SI) positivity ; the gold standard was the re-exposure to the suspected NSAIDs or causality algorithm score >5 in cases when re-exposure was not performed (See Methods_Suppl).

Forty cases with delayed hypersensitivity reactions to metamizole and/or ibuprofen (25 female; mean age 44.4 ± 21.4 years) were included (Table S1). The mean interval between the drug administration and the reaction was 6.4 (± 6.85) days. In the 67.5 % of the cases, other drugs were involved in addition to the NSAID. Reported reactions and involved drugs can be observed in Table S1.

Reactions consisted of 19 exanthema, 1 delayed urticaria, 3 erythema multiforme major, 2 acute generalized exanthematous pustulosis (AGEP), 1 possible Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), 1 SJS, 5 agranulocytosis, 1 immune thrombocytopenic purpura, 1 exacerbation of eosinophilic gastroenteritis, 2 interstitial nephritis, 2 hepatitis, 1 exanthema plus hepatitis and 1 exanthema plus eosinophilia.

NSAIDs involved in the delayed reactions were ibuprofen (n=19) and metamizole (n=15); there were also patients that had one single reaction after the intake of both drugs at the same time: ibuprofen and metamizole (n=2), ibuprofen and naproxen (n=2), ibuprofen and acetyl-salicylic acid (ASA) (n=1) and metamizole and dexketoprofen (n=1).

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

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 of the supplementary material. Two out of 12 were positive in the intradermal test with metamizole. There were no positive skin tests to ibuprofen, neither epicutaneous tests to ibuprofen or metamizole.

LTT was performed with suspected NSAIDs and concomitant drugs (Table S1). Mean time between the reaction and the LTT performance was 5.2 ($\pm$3.93) months.

The cutoff for stimulation index (SI) for ibuprofen and metamizole was 1.95 as determined by ROC curve analysis (sensitivity=92%, specificity=88%) (Table S3). LTT were positive in 16/46 with the NSAID involved. LTT were 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 for high suspicions of being truly responsible for the reaction; 15 had negative LTT and re-exposure was performed in 9 with good tolerance, in 2 it was not performed due to a positive intradermal skin test and in the remaining 4 it was not performed due to different circumstances like loss of follow up or use of alternative medication (retrospective study). These results are shown in Table S1 in the NSAID involved tolerated in re-exposure column.

The pathomechanism of SNIDHRs involves the stimulation of drug-specific T cells and represents a delayed type hypersensitivity [1]. LTT detects T-cell proliferation after drug exposure in an in vitro setting [6].

Our report shows the largest series of delayed hypersensitivity reactions to ibuprofen and metamizole studied by LTT published so far.

Causality algorithms have been previously used as a standard for a correct diagnosis of drug causality in delayed hypersensitivity reactions [7, 8]. We have used causality algorithms as a standard in cases in which drug tolerance information was not available to assess the diagnostic performance of LTT (they should at least reach a score of >=5 to be considered as true positives). The confirmation of another involved drug as the culprit drug (cases with positive skin tests or re-exposure positive tests) helped us also to discard the NSAID as responsible for the reaction.

Epicutaneous test and delayed reading of intradermal skin test have a low sensitivity and are more reliable with pyrazolones [1]. This has been corroborated in our study. (Table S2).

Our study has limitations such as the low sample size and that drug re-exposure has not been performed in all patients due to the presence of severe reactions or loss of following in others (retrospective study). Other limitation is that this 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].

LTT to ibuprofen and to metamizol has shown a high sensitivity and specificity proving to be a useful tool in the diagnosis of delayed hypersensitivity reactions to these drugs.

Funding

Conflicts of interest

The authors declare that they have no conflicts of interest.

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