SUPPLEMENTARY MATERIAL

Methods_SuppInfo

Drug causality algorithms

The Naranjo causality algorithm was used to determine the probability of adverse drug reaction, it is a method to assess whether there is a causal relationship between an identified untoward clinical event and a drug using a questionnaire to assign probability scores (total score ≤0: doubtful, 1-4: possible, 5-8 probable and ≥9: definite)[1].

In the two hepatitis cases, we use the updated RUCAM (Roussel Uclaf Causality Assessment Method), a tool to quantitatively assess causality in cases of suspected drug induced liver injury (DILI) and herb induced liver injury (HILI)[2]. Total score and resulting causality grading are ≤0, excluded; 1-2, unlikely; 3-5, possible; 6-8, probable; ≥9, highly probable

Skin testing

Skin tests were carried out at least 4 weeks after the adverse reaction. Skin prick test (SPT) and intradermal test (IDT) (only skin prick test in ibuprofen cases) were performed with delayed reading at 24 h. Skin prick test were performed using ibuprofen 40 mg/ml and metamizol 200 mg/ml. Intradermal test was realized with metamizole 1mg/ml and 10 mg/ml.

Epicutaneous test, they were performed using ibuprofen at 5% with petrolatum and metamizole at 30% with petrolatum. Reading was recorded at 48 and 96 hours.

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Drug provocation test (DPT)

DPT was performed with increasing doses of metamizol or ibuprofen over 2 days until one tablet of ibuprofen 400 mg or metamizol 575 mg were tolerated. Subsequently, patients continued to take the treatment at home at a dose of 1 tablet every 24 hours for 3 days, thus confirming good tolerance.

Lymphocyte transformation test

The LTT was performed using different concentrations of the drug/drugs involved. Mononuclear cells were separated over a density gradient (Histopaque-1077, Sigma-Aldrich) from fresh peripheral blood and were incubated for 6 days at 10^6 cells/ml with various drug concentrations in triplicate. Drugs were assayed at four concentrations from 0.1 to 100 µg/ml, Phytohemagglutinin (5 µg/ml) was used as a positive control. For the final 18 hours of the incubation period, proliferation was determined by the addition of [^{3}H] thymidine (0.5 µCi/well). Proliferative responses were calculated as stimulation index (SI), defined as the ratio between the mean values of counts per minute in cultures with drug and those obtained without drug[3].

Receiver Characteristic Operating curve analysis

ROC curve analysis was performed to calculate the optimal threshold value of stimulation index for LTT for ibuprofen and metamizole. As a gold standard, we used the post-episode drug re-exposure and the causality algorithm score in cases in which re-exposure data were not available. Three scores were assessed independently: >4, >5 and >6. The optimal cutoff value of LTT for ibuprofen and metamizole would correspond to the greatest sum for specificity and sensitivity values. (Table S2)

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References

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