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Beta-lactam allergies: Assessment of the risk of cross-reactivity with cephalosporins and carbapenems in penicillin-allergic patients

Summary of the systematic review with meta-analyses

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Beta-lactam allergies: Assessment of the risk of cross-reactivity with cephalosporins and carbapenems in penicillin-allergic patients

Summary of the systematic review with meta-analyses

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The complete systematic reviews *Beta-lactam allergies: Assessment of the risk of cross-reactivity with cephalosporins and carbapenems in penicillin-allergic patients* are available on request.

SUMMARY

Introduction

In general, beta-lactams (BLs), especially penicillins, are the most commonly used antibiotics, but they are also the leading cause of drug allergies. Fearing cross-reactivity, physicians refrain from prescribing another BL, such as a cephalosporin or a carbepenem, to penicillin-allergic patients. This can have significant consequences, both for the patients and the health-care system (e.g., exposure to broad-spectrum antibiotics, an increased risk of bacterial resistance and adverse effects, and increased health-care costs). To help health professionals to better assess the risk of cross-reactivity with cephalosporins and carbapenems in penicillin-allergic patients, INESSS conducted two systematic reviews, each with a meta-analysis (with aggregate and individual data for the cephalosporins and with aggregate data only for the carbapenems). A better knowledge of the risk of cross-reactivity between BLs would improve the management of penicillin-allergic patients and reduce the health consequences and the costs associated with the use of broader-spectrum antibiotics. This project stems from a need identified by clinicians during the updating of the optimal use guidelines for antibiotic therapy.

Methods

We conducted two systematic reviews with meta-analysis to assess the absolute risk of cross-reactivity between BLs. The first one looked at cross-reactivity between penicillins and cephalosporins, the second one between penicillins and carbapenems. The data search was performed in three databases, MEDLINE (PubMed), Embase (OvidSP) and Cochrane, and was limited to studies published in French or English between 1980 and 2016. In addition, the lists of references in the selected articles were examined for other relevant publications. Two reviewers independently evaluated the quality of the studies selected for the two systematic reviews and extracted and validated the data. The meta-analysis concerning the penicillins and cephalosporins was performed using individual and aggregate data, and the one concerning the penicillins and carbapenems was performed using aggregate data only. The absolute risk of cross-reactivity was calculated for each cephalosporin and carbapenem identified in the selected articles. In addition, the analyses were performed according to the generation of cephalosporins and the degree of similarity in structural (R1 side chains) and physicochemical properties between the penicillins and cephalosporins. The results were stratified according to the type of penicillin allergy (types I and IV). Both meta-analyses used a random effects logistic regression model to take intra- and interstudy variability into account, using r-meta library. Interstudy heterogeneity was evaluated using Cochran's Q test, the I^2 statistic and forest plots. Publication bias was evaluated using funnel plots and Egger's test (when possible). All the results were summarized in the form of an analytical narrative synthesis, tables and graphs.

Results

Based on the discussions with the advisory committee's experts, an absolute risk of cross-reactivity ≥ 5% was considered high. The results of the meta-analysis concerning the cephalosporins showed that cephalexin, cefadroxil, cefamandole and cefalotin had reached this cutoff, unlike the others (cefatrizine, cefuroxime, ceftazidime, ceftriaxone, ceftibuten, cefixime and cefotaxime). Cefaclor, cefazolin and cefpodoxime also had a low risk of cross-reactivity.

These results should, however, be interpreted with caution, given the wide confidence intervals. A meta-analysis could not be performed for cefepime, cefradine or cephaloridine because only one study had investigated each of these drugs.

These results can be explained by the structural and physicochemical properties of the drugs. Cross-reactivity appears to occur more often when the cephalosporins and penicillins have a high degree of similarity (up to 15.6% of cross-reactions), but appears to be very low ($\leq$ 2.0%) when BLs have structural and physicochemical differences.

In the case of the carbapenems, the risk of cross-reactivity in penicillin-allergic patients seems to be low ($\leq$ 1%) for the three examined drugs (imipenem, meropenem and ertapenem).

Conclusions

Based on the combined data from the studies used for the two systematic reviews with meta-analysis, the risk of cross-reactivity to a cephalosporin in a penicillin-allergic patient is higher if both BLs have similar structures and physicochemical properties. It would therefore be inadvisable to administer such drugs to penicillin-allergic patients. On the other hand, the risk is low for carbapenems and cephalosporins with different structural and physicochemical properties. The occurrence of cross-reactivity seems to be independent of the type of penicillin allergy (type I or IV). However, one should take into consideration certain methodological limitations of the two meta-analyses due to publication bias evaluation, which was often not possible, heterogeneity, or the fact that the selected studies were mainly from Europe with participants recruited from specialized centres, which may have influenced the external validity of the results.