Published in final edited form as:

Fundam Clin Pharmacol. 2019 April ; 33(2): 223–224. doi:10.1111/fcp.12449.

EDITORIAL: BETA-LACTAM-INDUCED SEVERE NEUTROPENIA: A DESCRIPTIVE STUDY

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In this issue of *Fundamental and Clinical Pharmacology*, Vial et al analyze reports of solitary, severe neutropenia thought to be caused by sensitivity to beta lactam antibiotics utilizing case reports submitted to the French Pharmacovigilance Database over an entire year and provide a valuable summary of clinical and laboratory findings and response of this condition to treatment. Over the time frame of the study, 62 verified cases were reported, about half of which were identified by a blood count done for some other reason. The median absolute neutrophil count at nadir was 125/ μ l and all but one patient recovered 2 to 56 days after the implicated drug was discontinued. Three patients experienced sepsis, including the single fatality in this group of patients. A review of reported epidemiological studies performed in France and other countries led to an estimate that sensitivity to beta lactam antibiotics might account for 10–25% of all cases of drug-induced neutropenia.

Drug-induced neutropenia is one of many idiosyncratic drug reactions (IDR) that target skin, liver, bone marrow, peripheral blood cells and other organs and which, together, are a major cause of morbidity and mortality in developed countries(1). The range of drugs capable causing IDRs seems almost limitless, although certain agents are far more prone than others to cause this condition. Clinical findings in patients with IDRs and limited laboratory evidence favors the possibility that immune sensitivity underlies most IDRs, including those involving neutropenia(1). With a few exceptions, however(2–4) the pathogenesis of these conditions is poorly understood. Largely for that reason, tools for predicting whether a particular drug is likely to induce an IDR and for identifying persons who may be susceptible are extremely limited, creating serious obstacles for a pharmaceutical industry concerned with the safety of therapeutic agents in development.

Beta lactam antibiotics, the subject of the Vial report, are among drug groups particularly prone to cause IDRs and are well-recognized triggers not only for neutropenia but also for acute immune hemolytic anemia(5, 6) and immune thrombocytopenia(7, 8). As noted for the case of neutropenia in the Vial report, ceftriaxone and piperacillin currently appear to be the most common triggers for the latter two conditions, perhaps in part because they are so widely used. The beta lactam ring structure that defines this class of antibiotics is prone to link spontaneously to free amino groups of proteins(9, 10), in which form the antibiotic structure can be recognized by the immune system, leading to the formation of “hapten-specific” antibodies(11). Early studies of patients who experienced immune hemolysis when treated with massive doses of penicillin provided evidence that this type of antibody can cause of red cell destruction(12) but more recent findings indicate that drug-associated

immune hemolysis and thrombocytopenia is caused by an unusual type of antibody that binds to cell membrane glycoproteins *only when soluble drug is present*(13). Although multiple mechanisms may be involved it is often possible to detect such antibodies by relatively simple assays utilizing hemagglutination(5, 6) or flow cytometry(7, 14).

Clinical criteria such as those used by Vial et al in the present report can be helpful for assessing the likelihood that a drug was responsible for neutropenia but fall short of proof, particularly in patients taking multiple medications, whereas detection of a drug-dependent antibody that targets the affected cell provides powerful evidence for a cause-and-effect relationship. Many of the same drugs known to cause immune thrombocytopenia and hemolytic anemia have been implicated as triggers for neutropenia and it seems likely that similar mechanisms apply in all three types of cytopenia. Unfortunately, convincing descriptions of drug-dependent neutrophil-specific antibodies in patients with drug-associated neutropenia are extremely rare, owing perhaps to the fact that neutrophils adapt poorly to serological assays suitable for red cells and platelets and suggesting that novel approaches are needed. A recent report describes progress in detecting apparently causative antibodies in patients suspected of having drug-induced neutropenia(15). Further work to improve detection of antibodies that are the likely cause of drug-associated neutropenia are needed so that causation can be established with greater certainty in patients suspected of having this condition.

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