Mechanisms of Clozapine\textsuperscript{†}-Induced Agranulocytosis

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Summary

The aetiology of clozapine-induced agranulocytosis remains unknown. Leading candidates include an immune mechanism that is possibly complement- or drug-dependent and a toxic mechanism. We analysed these mechanisms by culturing the granulocyte precursor stem cell from the bone marrow in the presence of patients' serum, clozapine or clozapine metabolites. Studies with patients' serum failed to identify an immune mechanism. On the basis of our preliminary data, it appears that a toxic mechanism may be responsible, and this is more likely to be due to a metabolite than to clozapine itself. Further studies are required to determine the sensitivity of bone marrow precursors to these clozapine derivatives. For instance, prospective collection of serum will make it possible to evaluate whether high metabolite concentrations develop in sensitive individuals and whether they are responsible for agranulocytosis. If such elevated levels occur, further studies will be required to determine whether prospective monitoring will effectively identify patients at risk and ultimately prevent the onset of agranulocytosis by early discontinuation of the drug.

Clozapine is an effective therapy for treatment-resistant schizophrenia. Its widespread use has been hampered by a high incidence of agranulocytosis. In the US, the annual rate approaches 1.6\% (Baldessarini & Frankenburg 1991), which is higher than that with any other drug causing idiosyncratic agranulocytosis (Coulter & Edwards 1990; Pisciotto 1973). As with other drugs causing blood dyscrasias, the aetiology of the disorder and the presence of risk factors have been difficult to establish. Currently, there are no defined mechanisms of clozapine-induced agranulocytosis. To provide a framework for our recent studies into this disorder, we will review mechanisms of agranulocytosis induced by other drugs and the characteristics of clozapine-induced agranulocytosis, since these may provide clues to the mechanism associated with clozapine use. We will then discuss our recent studies into the mechanism of clozapine-induced agranulocytosis.

1. Mechanisms of Agranulocytosis

There are many mechanisms potentially responsible for drug-induced agranulocytosis. These include the presence of either antigranulocyte or antimyeloid stem cell antibodies, the presence of a toxic metabolite that accumulates in the bloodstream of certain individuals, or a selective idiosyncratic sensitivity of the bone marrow stem cells.
to the drug itself (fig. 1). For instance, penicillins (Murphy et al. 1983), aprindine (Pisciotta & Cronkite 1983), ibuprofen (Mamus et al. 1986) and quinidine (Kelton et al. 1979) have all been associated with antibody-mediated agranulocytosis, in which antibodies, either in the absence or presence of the parent compound, are toxic to myeloid precursors in the bone marrow. Chloramphenicol (Jiminez et al. 1987; Yunis 1980), phenylbutazone (Smith et al. 1977) and penicillin (Nefel et al. 1983) are 3 drugs whose toxic metabolites have been shown to suppress haematopoiesis, as indicated by inhibition of the growth of haematopoietic stem cells of the myeloid lineage in vitro. With these 3 compounds, the metabolites are much more toxic to the bone marrow than the parent compound. However, blood levels of these metabolites in patients affected and unaffected by agranulocytosis have not been shown conclusively to reach the levels at which toxicity is identified in vitro. Less commonly, drugs can elicit a T cell-mediated response in which a cytotoxic T lymphocyte is responsible for agranulocytosis in the absence of the drug or metabolite (Gualde & Malinvaud 1982). In this