Pyrazoione-induced agranulocytosis: an epidemiological evaluation

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1. INTRODUCTION

Hundreds of drugs have been alleged to cause agranulocytosis. Specifically with regard to pyrazolones, a causal relationship has been demonstrated by rechallenge, and by transfusion studies. However, the magnitude of the risk of agranulocytosis associated with pyrazolones remained uncertain, and the quality of the available information has not improved appreciably over the past 50 years. It consists of series of case reports, letters to the editor and notes to agencies monitoring adverse reactions. Most cases have involved multiple drug exposures, and attribution to a specific drug has usually been based on informal ad hoc judgments as to which one was responsible, since no specific diagnostic procedure is available and intentional rechallenge is ethically unacceptable. Such ad hoc judgments are often biased in implicating drugs already under suspicion. In addition the inaccurate documentation of the temporal relationship between drug exposure and the event give rise to serious problems of misclassification.

Side-effects of Anti-inflammatory Drugs. Rainsford, KD and Velo, GP (eds)
II. ASSESSMENT OF PREVIOUS CASE REPORTS

These problems characterize the series of cases published amongst others by Pretty et al\(^1\), Palva and Mustala\(^2\), Kantero et al\(^3\), and Heimpel and Abt\(^4\). In none of these publications was an attempt made to measure drug exposure in a control group, and it is likely that multiple sources of bias were present. For these reasons many of the inferences drawn in these studies are of questionable validity.

Shinar et al\(^5\), in a retrospective study of hospital records in Jerusalem over 12 years found notes that dipyrone, a commonly used analgesic-antipyretic in Israel, was taken within 1 month preceding the diagnosis by 11 cases out of a total of 48 cases. It is, however, impossible to interpret these findings without obtaining standardized information on dipyrone use from a properly selected control group. As a matter of fact, during the years 1969-76, 21\% of all patients who were admitted to a medical department in the same hospital gave an unsolicited positive history of having taken dipyrone during the month before admission\(^6\).

Agranulocytosis most commonly presents with fever and infection with subsequent hospitalization and diagnosis. It is therefore essential that drug histories be carefully timed to determine whether exposure to any specific drug took place before the onset of the first symptom of agranulocytosis. Otherwise drugs (e.g. antibiotics and analgesic-antipyretics) given for the treatment of early symptoms may wrongly be implicated as causes.

Aspirin, paracetamol and phenacetin have all appeared in the drug histories of agranulocytosis patients described in the above-cited papers, although they were not usually judged to be causal. However, they could have been, and indeed some investigators have implicated these drugs. For example, Jouet et al\(^7\) suggested that paracetamol may account for as much as 10\% of all cases of agranulocytosis.

Taking into account all the complexities mentioned it is not surprising that this field has been difficult to study and that reliable data have been either lacking, or, where available, incomplete or conflicting. At present it is difficult to compare quantitatively the risks associated with various analgesic drugs. This led to the present situation in which there are conflicting judgments and regulations about the use of analgesic drugs. The one estimate of the incidence of pyrazolone-induced agranulocytosis which is constantly cited in textbooks and by regulatory agencies is that of Huguley\(^8\) which in turn is mainly based on calculations made by Discombe\(^9\). It is regrettable that the rates reported by them of 0.79\% to 0.86\% are still cited as if these studies were reasonably valid. Huguley and Discombe based their calculations on earlier reports, the first two of which\(^10,11\) were prompted by the primary identification of small clusters of cases, followed by secondary attempts to quantify the denominators. In a third report\(^12\) some cases of neutropenia, none of which were considered by the investigators to be clinical agranulocytosis, were observed among patients treated for rheumatoid arthritis with a combination of aminopyrine and phenylbutazone. Without giving details Discombe reclassified two patients as cases of agranulocytosis.