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COMMENTARY

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Metamizole (dipyrone)-induced agranulocytosis: Does the risk vary according to ethnicity?

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Summary

What is known and objective: Based on spontaneous reports from Spain, it is claimed that the British, Irish and Scandinavians are at a greater risk of dipyrone-induced agranulocytosis. This report examines the evidence.

Comment: Although interethnic differences in drug response are well known, there are no reliable epidemiologic data to support the above claim. Available information on chlorpromazine suggests variable ethnic sensitivities to drug-induced agranulocytosis. Agranulocytosis induced by at least four drugs has been associated with variant HLA alleles. Preliminary evidence also suggests that the presence of specific variant HLA alleles may sensitize individuals to dipyrone-induced agranulocytosis. There are historical reasons to suspect that the three populations referred to may share some key genetic features, including the potentially culprit variant HLA alleles, that predispose them to dipyrone-induced agranulocytosis.

What is new and conclusion: The possibility that the British, Irish and Scandinavians show higher susceptibility than other populations to dipyrone-induced agranulocytosis cannot be ruled out. If this complication is linked to specific HLA allele(s), populations with higher frequency of variant HLA allele(s) may be at a greater risk. If confirmed, screening for the risk allele may be useful in reducing the risk of dipyrone-induced agranulocytosis.

KEYWORDS

agranulocytosis, antithyroid drugs, chlorpromazine, clozapine, dipyrone, ethnicity, HLA alleles, levamisole, metamizole, sulfasalazine

1 | WHAT IS KNOWN AND OBJECTIVE

"Britons die after taking Spanish painkiller" read the headline of a news item in The Sunday Times, a popular UK newspaper, on 5 August 2018.[1] The painkiller, referred to as metamizole (also known as dipyrone) and sold in Spain under the brand name Nolotil®, is available as capsules containing 575 mg of the drug. I had been approached a couple of days earlier by the newspaper to comment on what was known about the toxicity of the drug in different populations and whether Britons might be more susceptible to the toxicity of the drug. This commentary addresses this and related issues.

The news item reported that metamizole-induced "blood poisoning" (agranulocytosis) and associated serious consequences, including fatalities, had affected more than 100 tourists and expatriates. Agranulocytosis is typically defined by most investigators as a neutrophil count of no greater than 0.5×10^9/L. Three expatriate populations, the British, the Irish and the Scandinavians, were singled out for their apparently greater susceptibility compared to the Spanish. Reportedly, the bulk of the cases from about 2002 to 2018, collated by a local medical and legal translator after an appeal on the social media, were British. Having been alerted to this, the (local) Hospital Marina Salud de Denia issued an advice to prescribe alternative

drugs to British and Scandinavian patients. The medicines regulator in Spain, the Spanish Agency of Medicines and Medical Devices, confirmed that it had launched an investigation and was gathering evidence. Boehringer Ingelheim, the manufacturer of Nolotil®, emphasized that it should be available only on prescription and that there was no scientific evidence on specific populations being at greater risk.

Interestingly, almost a decade earlier, Mérida Rodrigo et al[2] had reported a retrospective analysis of all the patients discharged from Hospital Costa del Sol (Marbella, Spain) with a main diagnosis of dipyrone-related agranulocytosis from January 1998 to December 2003. Of the 13 cases identified, five were British. These investigators estimated the event rate to be about 2.5-fold higher in the local British population, compared to the overall population, and concluded that the use of dipyrone must be avoided in the British population.

Interethnic differences in drug response have been known for long. The objectives of this commentary are (a) to examine the evidence for the claim of ethnic variability in sensitivity to dipyrone-induced agranulocytosis and (b) to review available key evidence and suggest further investigations.

2 | COMMENT

The above reports, helpful as they are in raising concern regarding a serious but well-known side effect of a commonly used analgesic, provide a compelling signal for further investigation of claims of interethnic differences in response to dipyrone. Although interethnic differences in drug response have been known for a long time, the current claim relating to dipyrone-induced agranulocytosis is based on anecdotal evidence from spontaneous reports with little reliable epidemiologic data to support it. Whereas spontaneous reports are very helpful in generating a signal or a hypothesis, they are notoriously misleading for actual risk attribution, let alone identify any interethnic differences. Firstly, reports gathered following an appeal on social media are particularly prone to a whole range of biases, depending on the construction and the targeting of the appeal. Secondly, it seems likely that expatriates suffering unexpected serious events while on holidays may generate or attract greater attention than does the native population with similar events. Finally, not all known cases are reported, particularly in the native population. Dipyrone-induced agranulocytosis, like a number of other adverse drug reactions, is reported to be approximately twice as frequent in females compared to the males.[3,4] However, the absence of robust quantitative data on drug usage in most studies makes it difficult to validate any claimed difference in gender-specific susceptibility. In the 161 reports analysed by Stammschulte et al[5], about two-thirds of the affected patients were females but this was consistent with the gender distribution of dipyrone prescriptions in Germany. This observation underscores the need for reliable data on usage ("denominator") as well as on actual number of cases ("numerator") to enable estimation of incident risk. This is not to diminish the potential significance of the reported apparent increased susceptibility of the three populations to dipyrone-induced agranulocytosis. They may indeed be at a greater risk, but only a well-designed study can provide the necessary confirmation. However, comparing two populations for their relative risks of a serious toxicity presents methodological and ethical challenges when the event rate is low and the duration of treatment to the onset of the event varies widely. Combining data from 158 patients with dipyrone-induced agranulocytosis from two studies,[5,6] the interval to onset of agranulocytosis was 1-2 days in 33 (21%), 3-21 days in 91 (58%) and more than 21 days in 34 (21%). These data suggest that potentially two different mechanisms may underpin the complication.

Ibáñez et al[6] suggested that geographical disparities in risk could be partly explained by differences in patterns of dipyrone use in terms of dose, duration and concomitant medications. One study reported that additional risk factors were identified in 24 (36%) of the 66 patients studied,[3] whereas another reported off-label use in 25% of the 161 cases reported.[5] Therefore, from a public health perspective, there is a danger that inadequate documentation of an association of a toxicity with a specific ethnic population may deprive a large subset of that population of a beneficial medication and/or expose that population to an equally unsafe alternative. Current concerns surrounding the use of opioid analgesics are all too familiar.[7,8]

Therefore, it seems an opportune moment to summarize what little is known about the possible mechanism(s) underpinning dipyrone-induced agranulocytosis and interethnic differences in susceptibility to agranulocytosis induced by drugs.

Dipyrone (noramidopyrine methanesulfonate) has been available in Germany since 1922. It was subsequently introduced as an analgesic, antipyretic, antispasmodic or anti-inflammatory agent to the market in most countries, including the UK, United States and Sweden, under no fewer than 60 brand names (https://www.drugs.com/international/metamizole.html), often in combination with other drugs such as dextropropoxyphene, diazepam, paracetamol or scopolamine. Dipyrone is water-soluble and available in oral and parenteral forms. After oral administration, it is rapidly hydrolysed to 4-methylaminoantipyrine (MAA) which is further metabolized to a number of metabolites.[9] The half-life of MAA is 2.6-3.5 hours.[10] The concentration-time course of CSF concentrations of MAA is consistent with its plasma concentrations and the analgesic effect of dipyrone.[11] One of the metabolites of MAA is further metabolized by acetylation, but no significant difference was found between rapid and slow acetylators in MAA kinetics.[12] Population pharmacokinetic analysis showed considerable interindividual variability, and age was a significant predictor of the drug's disposition.[13]

The potential of dipyrone to induce agranulocytosis has been known since at least 1946.[14] Since then, there have been numerous literature reports of this potentially fatal complication. For example, one 2015 report summarized data on 1417 international and 77 Swiss spontaneous reports of this association.[4] As far as the present author is aware, there is no information on dipyrone-related myelotoxic moiety. Earlier studies on the incidence of dipyrone-induced agranulocytosis show wide geographical variation,[15] for example, ranging

from one case per 1439 prescriptions in Sweden[3] to one case per 133 000-466 000 treatments in Greece.[16] All dipyrone-containing products in Sweden were withdrawn in March of 1974 only to be re-introduced in September 1995 and to be suspended once again in April 1999 with different computations and estimates of risk at each time point.[3] Studies over the last few years from Spain, Switzerland, Germany, Poland and Latin America have reported on the rarity of this serious complication of dipyrone therapy.[4,6,17-20] For example, in 2005, Ibáñez et al[6] reported that the frequency of dipyrone-induced agranulocytosis in Barcelona area was <1 case per million per year. The fatality rates vary widely, for example, from 0%[6] to 24%.[5]

Following the availability of nonsteroidal anti-inflammatory drugs (NSAIDs) as analgesics, dipyrone was removed from many markets including the UK, United States and Sweden in mid-1970s because of the risks of agranulocytosis.[2] Notwithstanding, it is still available, with or without a prescription, in a number of countries, including Spain and some other European countries, in the Far East and in South America.[5] Apart from its efficacy, one particular advantage of dipyrone compared to NSAIDs is its apparent lack of any teratogenic adverse effects.[21-24] It is particularly suitable for those in whom NSAIDs are contraindicated or pose a greater risk.[25] It has remained a popular analgesic not only because it is effective but also is generally safer than NSAIDs and opioids[26] and cheap. For example, the risk of agranulocytosis and pseudo-allergic effect prompted German authorities in 1986 to restrict the indications for dipyrone, but following a transient decrease, its use increased from <20 million defined daily doses in 1990 to >140 million in 2012, the corresponding number of spontaneous reports of agranulocytosis being 10 in 1990 and >50 in 2012.[5] Dipyrone was removed from the market in India in 2013, only to be re-introduced in 2014 subject to specific warning and indications. A 2016 survey of anaesthesiologists in German-speaking countries reported that dipyrone is the preferred nonopioid analgesic for the treatment of acute and chronic pain.[27]

Interethnic differences in drug response are well known, and therefore, regulatory authorities require subset analysis of safety and efficacy data by demographic variables such as age, gender and ethnicity/race.[28] Although there are many examples, BiDil® (a fixed-dose combination of 20 mg of isosorbide dinitrate and 37.5 mg of hydralazine hydrochloride) illustrates this well. Based on the results of randomized trials, it was controversially approved in June 2005 for use in the treatment of heart failure as an adjunct to standard therapy in self-identified Black patients.[29] BiDil® represents the first medicine to be approved for a specific ethnic group.

It is worth recalling that agranulocytosis following treatment with chlorpromazine is a rare complication that has been reported typically in white Caucasian patients only.[30-33] Lambo[34] reported as long ago as 1957 that African patients treated with even higher doses of chlorpromazine for long periods failed to show any of the reactions such as agranulocytosis or jaundice. Lambo[34] also noted that observations among the Chinese and the African patients also indicate that the chlorpromazine jaundice is largely confined to European and American patients. Histological features of jaundice and agranulocytosis induced by chlorpromazine are highly suggestive of an immune-mediated hypersensitivity reaction.

HLA alleles have been associated with hypersensitivity reactions, particularly skin reactions, to a number of drugs.[35] They are also associated with agranulocytosis induced by drugs such as levamisole,[36,37] clozapine,[38,39] antithyroid drugs[40-43] and sulfasalazine.[44] Interestingly, with regard to antithyroid drugs, the main variant alleles implicated were *HLA-B*38:02* and *HLA-DRB1*08:03* in Chinese patients[40] but *HLA-B*27:05* in white Europeans.[45]

Various mechanisms have been proposed for drug-induced immune neutropaenia generally.[46,47] Dipyrone is also believed to induce agranulocytosis via an immune mechanism[48-50] although dipyrone has not been studied rigorously and the mechanism has not been well characterized. Vlahov et al[51] reported on nine cases of drug-induced agranulocytosis identified in the period from 1982 to 1987 among the population of Sofia. Of these, five were associated with dipyrone, and in these five cases, there was a higher frequency of *HLA A24-B7* haplotype compared to the nonexposed patients and the reference group. The HLA-DQwl antigen and dipyrone-related agranulocytosis were associated in all the five cases in contrast to the patients not exposed to dipyrone and the controls. Although these findings require confirmation by other independent groups, the study does provide tentative evidence that these HLA genotypes may be associated with dipyrone-induced agranulocytosis.

The prevalence of various HLA alleles varies widely in different populations. Although the British, Irish and Scandinavian populations are now culturally distinct and geographically separate from each other, there are historical reasons dating back to centuries to suggest that some of their key genetic features overlap.[52-56] The inevitable question is whether the three populations also share parts of their HLA allelic profile and, therefore, the high risk of dipyrone-induced agranulocytosis; one study has already reported a high incidence of this complication in Sweden at one case per 1439 prescriptions.[3] Provided specific HLA allele(s) can be identified to be associated, with sufficient specificity and sensitivity, with dipyrone-induced agranulocytosis, it may be worth investigating whether the prevalence of these HLA alleles is higher in the British, Irish and Scandinavians compared to the Spanish. This information may clarify whether HLA-based immune factors could account for the reported difference in risk or indicate whether other lines of investigations are necessary. Other additional mechanisms such as direct toxicity and/or metabolic activation cannot be ruled out.

3 | WHAT IS NEW AND CONCLUSION

There is tentative evidence that agranulocytosis from dipyrone may be immune-mediated and that specific HLA alleles may confer the risk. Although there is no reliable epidemiologic evidence to show that this complication is more frequent in the British, Irish and Scandinavians, data on chlorpromazine-induced agranulocytosis suggest that this possibility cannot be excluded. Investigations of

the HLA allelic profile of cases with dipyrone-induced agranulocytosis and various populations may help to clarify whether immune factors could account for the apparent increased sensitivity of these three populations. If an association is confirmed, screening for the risk allele may be useful in preventing dipyrone-induced agranulocytosis in populations in which the frequency of the risk allele is high without having to remove an effective, popular and cheap drug from the market.

4 | COMPLIANCE WITH ETHICAL STANDARDS

This is a commentary on data in the public domain, and the author declares compliance with all ethical standards.

CONFLICT OF INTEREST

Rashmi R. Shah has no conflict of interests that are relevant to the content of this commentary and has not received any financial support for writing it. He was formerly a Senior Clinical Assessor at the Medicines and Healthcare products Regulatory Agency (MHRA), London, UK, and now provides expert consultancy services to a number of pharmaceutical companies.

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