

## **DIPYRONE (NOVALGIN, METAMIZOLE): BANNED AND UNBANNED: THE DILEMMA OF A COMMONLY PRESCRIBED AND OVER THE COUNTER ANALGESIC**

Dear Editor,

Pain Management has recently and increasingly acquired importance as a clinical field of its own right.<sup>1</sup> This has been followed by an increasing number of new generation analgesics targeted against better defined pain pathways and modulators.<sup>2</sup> However in developing countries, such new analgesics are often not available and may not be cost effective. Dipyron (Novalgin) is a readily available, relatively cheap and highly efficacious analgesic that is widely prescribed in Africa, Europe and South America.<sup>3</sup> This drug first went under the hammer as being "unacceptably toxic" in 1974 after the International Agranulocytosis and Aplastic Anemia Study (IAAS)<sup>4</sup> but significant methodological flaws in the study led to widespread criticism and the drug was reluctantly unbanned in 1995 but as a 'prescription only' medication.<sup>3</sup> Further studies led to more controversies regarding its association with agranulocytosis and it was again withdrawn from the market in 1999.<sup>3</sup> Given the above, the dilemma is should we follow suit and ban a useful and cheap analgesic? Is dipyron really risky? What is the transposability of studies in non Negroid to Negroid population?

One answer to the risk evaluation of dipyron related agranulocytosis (DRA) in our environment will be to conduct a well designed research but the scarcity of research funds, the difficulty of defending a proposal for sponsorship of such studies (to possibly discredit and not to promote a drug) coupled with the unavoidable inclusion of subjective data in analgesic studies make such a study a logistical nightmare. However a review of the available studies may suggest a position.

It is absolute risk that is important when determining the adverse effects of drugs.<sup>3</sup> The worst case scenario of the risk of DRA as defined by the IAAS was stated a 9 cases per million per year<sup>4</sup> while the Swedish study suggested 1 case per 1431 prescriptions.<sup>5</sup> Given that both are correct, these studies strongly suggest that genetic differences in drug response may be an important factor among others. Most of the studies use different definition of agranulocytosis and doses were between 0.5 to 6g daily and onset of symptoms in adverse reaction was from day 15.<sup>4,5</sup> These do not reflect current practices (dipyron is mostly given as maximum daily oral dose

of 3g-two 500mg tablets t.i.d- and rarely for more than 7 days in continuous prescription doses). Moreover recent studies have failed to clearly support such a risk.<sup>6,7</sup> Reversibility of adverse effects has undeniable clinical points and DRA is traditionally described as 'irreversible'. It may be reassuring that all the cases of DRA in Hedenmalm and Spigset's study responded to rapid drug withdrawal, antibiotics and colony stimulating factors.<sup>5</sup>

The critical assessment of cost benefit is particularly important in developing countries where therapeutic options are often limited. While there is little argument that dipyron causes agranulocytosis, the risk is still unsettled and sufficiently so that it remains in use in Brazil and most part of Europe.<sup>3</sup> It may be important to note that dipyron and acetaminophen (Paracetamol) are the only analgesics in the market that are effective inhibitors of the recently discovered cyclooxygenase three (COX - 3) enzyme and that while DRA is of insufficiently defined risk, the absolute risk of hepatotoxicity with acetaminophen in doses above 4g is clearly defined.<sup>8</sup> The COX-3 issue may yet 'unban' dipyron again. It may be safe to take the position that there is insufficient evidence that dipyron significantly increase the absolute risk of agranulocytosis in Africans, that 'on face value' dipyron is cost effective in these regions and thus continue the prescription of the efficacious analgesic.

### **References**

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