DRUG INFORMATION CENTER

PHARMA INFO-LINE

Novalgin® to use or not to use!

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Dipyrone or metamezol (Analgin® and Novalgin®) is the sodium sulfonate of aminophenazone that is widely used as analgesic, antipyretic and antiinflammatory drug. In many countries its use is considered justified only in severe pain where no alternative is available or suitable. Dipyrone has been given orally, intramuscularly, intravenously and rectally as suppository [1].

Dipyrone has been banned at 1974, because of its controversial association with agranulocytosis. The balance between the benefit and harm associated with this drug is particularly important for developing countries as dipyrone may be the first-line analgesic, where other drugs may not be readily available [2].

In fact; there are many case reports for dipyrone - induced agranulocytosis that have been early reported as well as many reviews that have addressed the association between agranulocytosis and dipyrone [3, 4]. However till now there is no agreed upon incidence rate from all population – based case – control studies that had been performed. Because drug-induced agranulocytosis is rare, unpredictable and independent of the dose, some underlying individual genetic or other risk factors are probably mandatory for these reactions to occur [5].

The risks of agranulocytosis and aplastic anemia in relation to analgesic drug use were extensively evaluated in the **The International Agranulocytosis and Aplastic Anemia Study (IAAA study)** [6], which was a population-based case-control study conducted in Europe and Israel.

Analgesic use in the week before the onset of illness was compared between 221 cases of agranulocytosis and 1425 hospital controls. Among analgesics, dipyrone was associated with the highest rate ratio estimate for agranulocytosis (= 23.7) however indomethacin, and butazones (phenylbutazone and oxyphenbutazone) were also associated with agranulocytosis in rate ratio of 8.7 and 3.8 respectively. The study at the end suggested that the risk for agranulocytosis is as low as 1.1 cases per million users[6]. This study had been a subject for criticism; the vastly varying risks in different countries that ranged from 0.9 in Budapest and up to 33.3 in Barcelona, methodological issues aside, and different incidences could be related to several factors that confounded the analysis; consumption and frequency of use of dipyrone differs from country to country, and some populations may have increased genetic susceptibility to agranulocytosis[7].

A Swedish study 2002 [4], described the pattern of blood dyscrasias associated with dipyrone, identified possible risk factors and calculated the incidence of agranulocytosis associated with

Article summary:

- Agranulocytosis is defined as an absolute neutrophil count of less than 500 / μl .

- Estimated incidence 1-10 cases / million /year.

- Fatality from agranulocytosis may range from 6-10%.

- 70% of agranulocytosis are associated with drug use.

- The rate ratio for dipyrone induced agranulocytosis is not established yet.

- Many variables are responsible for dipyrone induced agranulocytosis.

dipyrone. The authors reviewed all spontaneous reports of serious blood dyscrasias that were associated with dipyrone in Sweden and the reported incidence of agranulocytosis was estimated from total prescription sales of dipyrone. Sixty six cases were identified till the end of 1999, 52 of which were agranulocytosis. The authors found the reported incidence of agranulocytosis with dipyrone in Sweden to be estimated at least 1 case / 1439 prescriptions, with 92% of the cases of blood dyscrasias occurred during the first 2 months of treatment. This high prevalence may indicate that there is high incidence in naïve population since the drug was a prescription - only and its use was highly restricted in Sweden at the time of the study [4].

Despite rigor definition of agranulocytosis by Hedenmalm and Spigset's , collection of data, and attribution, the Swedish data are based on a small number of events. If these were reflected in populations in which dipyrone is commonly used, such as in Spain or Brazil, there would be an overwhelmed agranulocytosis reports every year [2]. ***However this is not the case according to recent studies in these countries.***

Dipyrone is available in Latin American countries and in which it has been widely sold over the counter, therefore association between agranulocytosis and dipyrone can be addressed properly in these countries.

The Latin study [8]; *Incidence of aplastic anemia and agranulocytosis in Latin America,* which has the goals of estimating the incidence of aplastic anemia and agranulocytosis in Latin American countries and identifying the risk factors for these diseases including the use of dipyrone. The study was planned to have two phases: an initial phase ("pilot phase") and the main phase. The pilot study began in April 2002 and was completed in April 2003, while the main phase is planned to end in August 2006. Initial report from the pilot study on the incidence of agranulocytosis and aplastic anemia in Brazil was published at 2005[8], whereas sixteen patients with agranulocytosis were identified. The patients had a median age of 31 years; 32.2% were male and 81.2% were white, the incidence of agranulocytosis was estimated to be 0.5 cases per million individuals per year, ranging from 0.0 to 1.1 cases per million per year between different regions. The authors concluded that agranulocytosis is a rare disease in Brazil, and there was considerable variability in its incidences between different regions [8].

The data that will be available at the conclusion of the LATIN Study will enable definition of the frequency of agranulocytosis in Brazil and other Latin American countries, as well as to what extent dipyrone is associated with its onset. This information is essential for defining health policies regarding dipyrone in these countries [9].

In addition, Luisa Ibanez et al (2005) in Spain have assessed association of agranulocytosis with metamizol (dipyrone) in a large database for the surveillance of blood dyscrasias. They included all laboratory units of hematology in a defined area (3.3– 4.1 million inhabitants) that contributed to the ascertainment of all cases of agranulocytosis meeting strict diagnostic criteria. These cases of patients with agranulocytosis and sex-, age-, hospital- and date - matched controls were interviewed using a structured questionnaire about previous drug exposures, and relative risks were calculated for several categories of exposure to metamizol. However, compared with the cases from Sweden study, the duration of use of metamizol by exposed cases was substantially shorter. After a total follow-up of 78.73 million persons /years, the author found 273 community cases of agranulocytosis of which 96 were excluded for various reasons and 177 were included in the case-control analysis and were compared with 586 matched controls. Thirty cases of agranulocytosis (16.9%) and nine controls (1.5%) had been exposed to metamizol during the week before the index day. After adjusting for confounding, the relative risk was 25.8 and the attributable incidence was only 0.56 (0.4– 0.8) cases per million inhabitants and per year. The risk disappeared after more than 10 days since the last dose of metamizol, and it increased with duration of use. Those with agranulocytosis exposed to metamizol had taken the drug for longer periods than the exposed controls. The author concluded that in the study condition **agranulocytosis attributable to metamizol is rare** [10].

Finally **Frank Andersohn, et al 2007**[11]**;** recently reviewed published case reports of patients with non-chemotherapy drug–induced agranulocytosis and identified all drugs that are definitely or probably related to agranulocytosis. The authors after causality assessments of 980 reported cases of agranulocytosis found that;

- Associations were definite in 56 (6%).
- Probable in 436 (44%).
- Possible in 481 (49%).
- Unlikely in 7 (1%).

In this review also the authors assigned a level of evidence to each reported drug:

- Level 1 evidence had to have at least 1 definite case report.
- Level 2 evidence had to have at least 1 probable report but no definite report.
- Level 3 evidence had to have at least 1 possible report but no definite or probable case report.

A total of 125 drugs were definitely or probably related to agranulocytosis. Thirty six drugs had level of evidence 1, and Dipyrone was one of the drugs for which more than 10 reports were available. Carbimazole, clozapine, dapsone, methimazole, penicillin G, procainamide, propylthiouracil, rituximab, sulfasalazine, and ticlopidine were also included and accounted for more than 50% of definite or probable reports. The onset of agranulocytosis was 2 days after dipyrone use [11].

Conclusion:

Dipyrone is used as a cheap analgesic with great power to reduce pain and treat pyrexia, therefore it is the first line for treating pain and fever in Egypt as well as many other countries in the world such as Latin America and Spain. It has been reported to induce agranulocytosis, however rarely. The incidence rate from all population – based case – control studies varies a lot, as many factors such as genetics, consumption, and other risk factors have affected the results.

Studies from countries that have not banned the drug would be eligible for generalization and can represent the Egyptian situation; therefore the still ongoing Latin study will be the right example for this incidence rate and the real association between dipyrone and agranulocytosis. In all previous studies from countries that did not ban the drug; the incidence ranged from 0.5- 4.1 / million individuals / year, in addition, it is not the only drug that can induce this serious adverse effect.

Weighing advantages against the risk we can conclude that;

While we wait for the results from the Latin study, which will be published in the near future, The drug should be a prescription only (not an OTC as it is now), physician should prescribe it if only other treatments fail, and pharmacists should inform patients who are using Novalgin® on symptoms for agranulocytosis such as unexplained sore throat, mouth and anal ulcers, fever, vague body-ache and decreased immunity (prone to bacterial infections).

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Vitamin D and calcium supplementation reduces cancer risk

In a recent randomized trial that was done by Lappe et al [1], calcium and vitamin D supplementation significantly reduced all-cancer risk in postmenopausal women. The study was a 4-year, population-based, double-blind, randomized, placebo-controlled trial that included 1179 community-dwelling, postmenopausal women.

Participants were randomized into 3 groups;

- First group received 1400-1500 mg every day of supplemental calcium
- Second group received 1400-1500 mg of supplemental calcium + 1100 IU vitamin D3
- The third group was the control group (placebo)

The results showed that the incidence of cancer was lower in the women who received calcium + vitamin D than in the placebo group and the relative risk was (RR = 0.402), both calcium supplementation and 25-OHD levels were independent risk factors of cancer. The authors concluded that improving calcium and vitamin D nutritional status substantially reduces all cancer risk in postmenopausal women.

It is worthy to mention that this combination (calcium and vitamin D) is used in the elderly, and for post-menopausal women for the prevention of osteoporosis. Calcium may be used alone or with other therapies at any age if calcium intake is lower than the recommended level. All patients with osteoporosis should be on daily calcium and vitamin D supplements.[2]

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No Association found between patients receiving isotretinoin for acne and the development of depression.

Acne is an inflammation of the pilosebaceous units of certain body areas (face, trunk, and rarely buttocks) that occurs most frequently in adolescence. Acne is very common, affecting approximately 85% of young people, at puberty 10 - 17 years in females, 14 to 19 in males; however, may appear first at 25 years or older, and it is more severe in males than in females[1]. Oral isotretinoin is indicated for moderate and severe, recalcitrant, nodular acne. The patient must have been resistant to other acne therapies, including systemic antibiotics, before being treated with isotretinoin due to its adverse hepatic effect [1].

There has been concern that the use of isotretinoin to treat acne may lead to depression. To date, research has not conclusively determined if this concern is warranted when contemplating the use of isotretinoin. *Jordan Cohen et al* (2007)[2] investigated the impact of isotretinoin use for patients with acne on mood status; whether there is a relationship between isotretinoin and depression. The study was a prospective, controlled, cohort design that was conducted in a community dermatology clinic. The exposed cohort consisted of consenting patients who were initiating isotretinoin treatment for acne. Patients were either treated with isotretinoin therapy (study group) (N=100) or by oral (N=41) or topical acne therapy (control group) (N=59). Depression was assessed both at baseline and after 2 months of prescribed use of isotretinoin or a control medication (topical or oral antibiotics). The authors found no correlation between isotretinoin use and the development of depression, based on the 2 scales that were used either the Centre for Epidemiologic Studies Depression scale (Fisher's exact test, P=0.497) or Zung Depression Status Inventory (ANOVA; F=1.4, P=0.2). Finally the authors concluded that isotretinoin does not appear to be associated with the development of depression[2].

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