Dipyrone-containing analgesics

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Summary

Analgesics containing dipyrone continue to be available throughout Africa, including South Africa and Zimbabwe. Although an effective analgesic and antipyretic, dipyrone may cause severe side-effects, including agranulocytosis. The mechanism of this hypersensitivity reaction has been well documented, and many reports of agranulocytosis associated with dipyrone use have been published. Use of this drug has been prohibited or restricted in several countries. Dipyrone is known by a variety of official names, which may contribute to confusion in determining whether a particular preparation contains this drug. The prescribing information contained in the Monthly Index of Medical Specialties (MIMS) (South Africa) and the MIMS Desk Reference is inadequate for some of the products available, although the package inserts do provide more detailed information. The continued use of these products is difficult to justify when safer alternatives are available.

Three products containing dipyrone are available in Zimbabwe and South Africa. They are Avafortan, Baralgan, and Buscopan Compositum. These are all combination products containing dipyrone with one or more antispasmodic compounds, and their supply requires a prescription. Many other preparations are available in addition to these in other countries in Africa.

Pharmacology and serious adverse effects of dipyrone

Dipyrone is the methanesulphonate derivative of amidozone (aminopyrine), and has similar pharmacological and toxic properties. Both these drugs are very effective analgesics, antipyretics and anti-inflammatory agents, but are known to cause agranulocytosis. Amidozone is also thought to be carcinogenic, but this appears not to be the case with dipyrone.

In Martindale, The Extra Pharmacopoeia it is stated that the adverse effects of dipyrone are the same as those of amidozone, and that the risk of agranulocytosis is sufficiently great to render amidozone unsuitable for use. The onset of agranulocytosis may be sudden and unpredictable. The use of dipyrone is justified only in serious or life-threatening situations where no alternative antipyretic is available or suitable.

Meyler’s Side Effects of Drugs also states that it is justifiable to expect that dipyrone will have the same adverse reactions as amidozone, and comments that there is much evidence to this effect, although it has been disputed.

The association between certain antipyretic analgesics (including dipyrone, amidozone, and the butazones) and the production of blood dyscrasias has been known since 1934, agranulocytosis being the most common form of drug-induced blood dyscrasia.

The American Medical Association noted in the 1973 edition of its drug evaluations that dipyrone was being misused as a supposedly safer alternative to amidozone in the USA, and suggested that physicians were unaware of its similarity to amidozone because it was marketed under a variety of trade names. They advised that its use should be restricted to reducing fever when safer measures failed and that, because of its potential to cause fatal agranulocytosis and other blood dyscrasias, its use as a general analgesic, anti-arthritic or routine antipyretic could not be condoned. The 1977 edition of the same publication stated that dipyrone had become obsolete in the USA, and in the 1980 edition it is not even mentioned. Dipyrone was withdrawn completely from the US market by the Food and Drug Administration in 1977.

In Sweden, dipyrone was withdrawn from the market in 1973, 1975. In studies conducted before this date, dipyrone had been found to be associated with a five times higher risk of bone marrow damage than the butazones. In two reports of subsequent studies covering 1973-1978, cases of dipyrone-induced agranulocytosis were still reported in Sweden but in these cases the dipyrone had been purchased in other countries.

In the UK, the Committee on Safety of Medicines (CSM) was, between 1963 and 1976, notified of 5 cases (2 fatal) of agranulocytosis associated with dipyrone. Although this is a relatively small number of cases, it should be noted that dipyrone was not marketed in the UK at this time, and that these reports therefore relate to instances where the drug had been obtained in other countries.

A report from Israel in 1979 examined the causes of drug-induced adverse reactions requiring hospital admission. Of 84 single-drug adverse reactions, 4 were associated with dipyrone, compared with 2 for aspirin and 1 for phenacetin. Of these 4 patients, 1 developed agranulocytosis.

A case of severe agranulocytosis caused by amidozone (in an English teacher in Mozambique) was reported as late as 1980, even though this drug had officially been withdrawn by the manufacturers. A few weeks later a similar report of dipyrone-induced agranulocytosis was published. In both these cases it was noted that the same drug had been taken a few months earlier, with no apparent adverse effects.

There has been disagreement on the actual incidence of agranulocytosis associated with dipyrone use. Earlier estimates of an incidence approaching 1% have been disputed in later prospective studies, although the method of calculation in these later studies has also been questioned.

Apart from the potential to cause agranulocytosis and other blood dyscrasias, dipyrone has also been reported to cause anaphylaxis after parenteral use.

Clinical features and mechanism of dipyrone-induced agranulocytosis

In 1964 it was suggested that agranulocytosis associated with dipyrone was due to an immunological mechanism. Agranulocytosis can develop in patients who have been taking...
amidopyrine or dipyrone regularly for a few days or many months, or even occasionally for a period of weeks or years. The agranulocytosis develops suddenly, perhaps after the administration of only one dose. A chill with fever and malaise develops shortly after the drug is taken; this is followed by a fall in the leucocyte count and disappearance of granulocytes within 6-24 hours. Granulocytes begin to reappear in the blood 5-10 days after withdrawal of the drug, the clinical picture depending on whether infection occurs during the period of agranulocytosis. Dominant clinical features may include injection of the oropharynx with oedema and ulceration, but non-infective symptoms such as skin rash may be present.

Dipyrone-induced agranulocytosis has been described as a type II hypersensitivity reaction involving the binding of antigen to a target cell, and the subsequent reaction of antibodies with the cell surface antigen causing cellular destruction.

In patients sensitized by previous use of dipyrone, or in those who have recovered from an earlier episode of dipyrone-induced agranulocytosis, cell destruction in the peripheral blood may start acutely even following a low dose of the drug. Antibodies may be directed against both peripheral cells and the precursor cells of the bone marrow. Maturational arrest of granulocytes at the level of the bone marrow stem cells has been reported.

**Regulatory decisions about dipyrone**

Dipyrone use has been prohibited in several countries, including Denmark, Sweden, the UK and the USA. Its use has been restricted to conditions in other countries, including Egypt, France, Germany, Israel, Italy and Japan.

**Confusion over nomenclature**

Much confusion, and subsequent difficulty in identifying products containing dipyrone, may have arisen from the variety of official names used for dipyrone. 'Mortindale' lists several additional names for dipyrone, including amidopyrine-sulfonate sodium, analginum, metamizol, methamphetamine, novamidazofen, sodium noramidopyrine methanesulphonate, and sulpyrine. Prescribers, even those aware of the serious side-effects of dipyrone, may be unaware that metamizol is simply another name for dipyrone.

**Prescribing information**

Dipyrone-containing products continue to be available throughout most of Africa, and prescribing information is accordingly included in *MIMS* (Africa), *MIMS* (South Africa) and the *MIMS* Desk Reference (MDR). Information for the individual products is also provided in the form of package inserts. The content of package inserts is determined by the manufacturer, although in Zimbabwe and South Africa the drug regulatory authorities have a degree of control over the content, requiring the manufacturer to include adequate data on adverse effects and to omit non-approved indications. Unfortunately, package inserts may not be readily available to the prescribing doctor unless he has supplies of the drug itself; and it is also difficult to maintain an easily usable collection of package inserts, as lack of uniformity in their size and shape makes efficient filing an almost impossible task.

A recent survey of doctors conducted in South Africa found that *MIMS* and the MDR were used more frequently than package inserts by the majority of respondents. The information content of the *MIMS* publications is therefore of paramount importance if doctors are to be well informed about the drugs they are using.

*MIMS* (Africa) would appear to be superior to *MIMS* (South Africa) in alerting the potential prescriber to the dangers of dipyrone. All entries for these products in *MIMS* (Africa) warn of agranulocytosis, and advise that they should be used only where no alternative analgesic is suitable. This publication also lists more contraindications than its South African counterpart for the three drugs available in Zimbabwe and South Africa.

In *MIMS* (South Africa), only the entry for Avafortan warns of agranulocytosis, although the entry for Buscopan Compositum refers the reader to the MDR, where the entry for this drug gives extensive coverage of adverse effects including agranulocytosis. The entry for Baralgan leaves a lot to be desired. It simply states that Baralgan rarely causes allergic reactions, and there is no referral to the MDR for additional information. The entry in the MDR does however include rare allergic reactions and agranulocytosis as toxic effects of Baralgan. It is interesting to note that for Baralgan dipyrone is referred to as metamizol in the South African publications but as dipyrone in *MIMS* (Africa). For the other two products only the name dipyrone is used, so the use of the name metamizol is unlikely to reflect a geographical difference in preferred nomenclature.

**Conclusions**

There would appear to be a need for greater awareness of the potential of dipyrone to cause severe and life-threatening agranulocytosis. Products containing amidopyrine have practically disappeared from use in Africa (with the exception of Rheopyrine, a combination of phenylbutazone and amidopyrine which is still marketed by Medimpex in some countries), but dipyrone, the similar toxic effects of which have been proved beyond reasonable doubt, continues to be used throughout most of Africa, and in the case of Baralgan is recommended as a general analgesic in southern Africa.

Agranulocytosis is a serious complication of drug therapy, and must surely have a worse prognosis in areas where laboratory facilities for diagnosis, and medical facilities for adequate treatment, are overstretched. In many other countries it has been decided that the risks associated with dipyrone outweigh its usefulness as an analgesic or antipyretic, especially as safer drugs are available. It is time to think again about the desirability of having such products available in southern Africa.

**REFERENCES**

Quantifying the risks of radiation exposure

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Summary
The considerations leading to the recommendation of dose-equivalent limits by the International Commission for Radiological Protection are outlined. The dose-equivalent limits are based on radiation risk factors estimated from effects of radiation observed over many decades. These limits are designed to ensure that radiation exposure does not entail a greater risk than that experienced by the general public in everyday life. The risk factors should, however, not be used to assess the risk to patients from diagnostic procedures.


The commissioning of the Koeberg nuclear power station during 1984 has created in the public an awareness of and interest in the risks due to radiation exposure. Concern has been expressed about the level of knowledge possessed by medical practitioners of the risks due to radiation exposure. 1 Recently the Atomic Energy Corporation (AEC) of South Africa issued document NKKS 10/82 in which revised dose-equivalent* limits for radiation workers were laid down. These latest dose-equivalent limits were based on the recommenda-

*For radiation protection purposes, the radiation received by tissue is quantified in terms of the dose equivalent, its SI unit is the sievert (Sv). 1 Sv = 100 rem.

The International Commission for Radiological Protection (ICRP) 2-3

It is thus appropriate to review briefly the present state of knowledge of risks from radiation, as compiled by the ICRP, and to outline the considerations leading to the laying down of dose-equivalent limits for radiation workers and the general public.

International Commission for Radiological Protection (ICRP)

The ICRP was established in 1928 as the International X-ray and Radium Protection Commission by the Second International Congress of Radiology held in Stockholm, Sweden. It assumed its present name in 1950, and functions under the auspices of the International Congress of Radiology. The Commission consists of a Chairman and not more than 12 members. The selection of members is made by the ICRP from nominations submitted to it by the national delegations to the International Congress of Radiology and by the ICRP itself. The selections are subject to approval by the International Executive Committee of the Congress. Members of the ICRP are chosen on the basis of their recognized activity in the fields of medical radiology, radiation protection, physics, health physics, biology, genetics, biochemistry and biophysics with regard to an appropriate balance of expertise rather than to nationality. Not less than 3 but not more than 5 members are changed at any one Congress.

The ICRP may invite individuals to give special technical advice, and may also establish such committees as it deems necessary to perform its functions. Much of the work is performed by ad hoc task groups, by means of which the Commission has been able to call on the services of a large number of individuals who are not members of a committee.

The Commission has regularly published reports and recommendations. These are now available in the form of a review