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Anaphylactic reactions on the combination of paracetamol, propyphenazone and caffeine (Saridon®)

Introduction

Saridon®, a combination of paracetamol, propyphenazone and caffeine, has been approved on 20-01-1983. It is indicated for: *headache, toothache, nerve pain, lumbago, muscular pain, menstrual pain and fever and pain with influenza and viral rhinitis; fever and pain after vaccination* [1]. The SPC mentions as contraindications: known hypersensitivity to paracetamol, propyphenazone or other pyrazolone derivatives, or caffeine. In section 4.8 is stated that anaphylactic reactions were reported very rarely (<0,01%) [1]. Propyphenazone (chemical name: 4-Isopropyl-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one) is a classic NSAID that belongs to the group of pyrazolone derivatives. It is related to antipyrine (phenazone) and is also known as isopropyl-antipyrine.
The combination of paracetamol, propyphenazone and caffeine is available as an OTC product by various marketing authorization holders (table 1).
This report discusses a concerning reporting rate of anaphylactic reactions after use of Saridon®.

Table 1: Products available in the Netherlands and active substances composition.

Drug	Paracetamol (mg)	Proyphenazone (mg)	Caffeine (mg)
Saridon®	250	150	50
Sanalgin®	250	250	46
Hoofdpijnpoeders Daro®	250	150	50
Para-don®	250	150	50
Proyphenazon comp.	250	150	50

Reports

Up to June 8, 2004, a total of 20 adverse reactions to Saridon® have been reported to Lareb. Lareb interpreted 16 of these reports to be allergic reactions. Table 2 gives an overview of the reactions as reported (table 2).

Table 2 allergic reactions to Saridon®, as mentioned by the reporter

Reported as	Number
anaphylactic reaction	10
pruritus, lip swelling, dyspnoea	1
generalized exanthema within one hour	1
immediate allergic reaction	1
facial edema within hours	1
urticaria and convulsions within hours after first use, with a history of diclophenac hypersensitivity	1
dyspnoea after first use	1
Total	16

There were another 8 reactions reported to the non-Saridon® drugs as stated in table 1, of which 6 were interpreted as allergic reactions (table 3).

Table 3 allergic reactions to non-Sardinon® propyphenazone products, as mentioned by the reporter

Reported as	Number
anaphylactic reaction	4
laryngeal edema	1
acute life-threatening stridor with urticaria	1
total	6

A search in the Lareb database for anaphylactic reaction to paracetamol only resulted in 6 reports out of a total of 114 reports on paracetamol.
No reports of caffeine and anaphylaxis have been received.
Table 4 gives an overview of the reports on the different active substances:

Table 4 reports of anaphylaxis associated with the use of propyphenazone combinations, paracetamol or caffeine

Drug	Reported as anaphylaxis by reporter	Interpreted as anaphylaxis by Lareb	Total number of allergic reaction / anaphylactic	Total number of reports on this drug
Saridon	10	6	16	20
Other propy-phenazone drugs	4	2	6	8
Paracetamol	6	0	6	114
Caffeine	0	0	0	1

Other sources of information

Literature

Meyler states that severe hypersensitivity reactions to propyphenazone as well as to phenazone have been reported. There are no indications that propyphenazone has a lower incidence of adverse reactions than phenazone, since neither compound has been widely studied alone. A case report is mentioned in which urticaria and angioedema were seen after use of propyphenazone, a skin test was negative, but a provocation test resulted in anaphylaxis [2].

Van der Klauw *et al.* described anaphylactic reactions that were reported to the Drug Safety Unit of the Dutch Inspectorate for Health Care (now the Netherlands Pharmacovigilance Centre Lareb) in the years 1974 to 1994. Of the 936 reports, 39 were associated with the use of (propy)phenazone or propyphenazone/phenacetine [3].

Perl describes a case of anaphylaxis after use of a phenazone containing drug, with a history of positive rechallenge [4]. Another case report concerning the same substance is presented by Limb [5].

Maucher *et al.* describe a diagnostic skin patch test in which 30% of patients who had had an anaphylactic reaction to a pyrazolone derivative showed an immediate urticarial reaction [6].

Databases

The WHO database contains reports coded as anaphylactic shock or anaphylactoid reaction. Since from the Lareb reports this distinction can not always be made, these two reactions were combined in table 5 which shows the reporting odd ratio's for the three components of saridon®.

Table 5: ROR for anaphylactic/oid reactions on Saridon components in the WHO database

	Anaphylactic shock and Anaphylactoid reaction
Propyphenazone	18.2 (10.6 – 31.3)
Paracetamol	1.4 (1.2 – 1.6)
Caffeine	0.8 (0.1 – 5.7) anaphylactoid reaction only

Mechanism

Anaphylactic reactions are caused by an immunologic mechanism, in which immunoglobulin E is involved. It can also be caused by massive aspecific mediator release (mainly histamine) by mastcells. In case of anaphylactic reactions to NSAID's the latter mechanism is supposed to be involved, and is then more accurately called anaphylactoid reaction. Inhibition of COX-1 may play a role [7,8]. Clinically there is no difference between an anaphylactic and anaphylactoid reaction.

Discussion and conclusion

There is no information available of the incidence of anaphylactic reactions to propyphenazone, there are only few case reports in literature. The SPC states an incidence of less than 0.01%. However, the high fraction of reports with an allergic reaction on Saridon® and comparable drugs in the Lareb database, suggests the actual incidence to be higher. This leads to concern, since Saridon® is available as OTC medication.

References
1. Dutch SPC Saridon®. (version date 21-1-2004) http://www.cbg-meb.nl/IB-teksten/03780.PDF.
2. Dukes MNG, Aronson JK. Meyler's side effects of drugs. 14 ed. Elsevier Amsterdam; 2000; 9, p. 292
3. van der Klauw MM, Wilson JP, Stricker BCh. drug-associated anaphylaxis: 20 years of reporting in the netherlands (1974-1994) and review of the literature. Clin Exp Allergy 1996;26(12):1355-63.
4. Perl S. anaphylaxis after dichloralphenazone treatment. Br Med J 1977;2(6096):1187-8.
5. Limb DG. anaphylaxis after dichloralphenazone treatment. Br Med J 1977;2(6100):1480
6. Maucher MM, Fuchs A. kontakturtikaria im epikutantest bei pyrazolonallergie. Hautartzt 1983;34(8):383-6.
7. Bochner BS, Lichtenstein L.W. Anaphylaxis. N Eng J Med 1991;324:1785-90.
8. Berkes E. anaphylactic and anaphylactoid reactions to aspirin and other NSAIDs. Clin Rev Allergy Immunol 2003;24(2):137-48.