

Sodium aurothiomalate and nitritoid reactions: concomitant use of an ACE-inhibitor as a contributing factor

Introduction

Sodium aurothiomalate (Tauredon[®]) is a gold salt with anti-inflammatory activity, which has been approved for the Dutch market on March 6th, 2002. It is indicated: *for rheumatoid arthritis or juvenile chronic arthritis, that is progressive or responds insufficiently to treatment with prostaglandin synthetase-inhibitors or auranofin [1].*

Sodium aurothiomalate is also prescribed to patients who were previously treated with aurothioglucose (Auromyose[®]). Aurothioglucose was withdrawn from the market in 2001. Therefore, sodium aurothiomalate is at this moment the only available parenteral form of gold therapy in the Netherlands.

Common adverse drug reactions of sodium aurothiomalate include: dermatitis, stomatitis, chrysiasis (grey-blue skin pigmentation) and reversible hair loss [1].

A nitritoid reaction is also an adverse drug reaction of gold therapy. The typical symptoms of this vasomotor reaction include facial flushing and dizziness. The name nitritoid reaction refers to the adverse effects of nitrates. Although there is no evidence that gold induced nitritoid reactions are related to nitrates or nitrogenoxide (NO), the vasomotor symptoms resemble the adverse effects of nitrates. Nausea, vomiting and symptoms of hypotension, including syncope, may be experienced. Characteristically, these reactions are transient, occurring within minutes of gold administration. Nitritoid reactions to gold are probably dose dependent. Serious sequels have been reported, including myocardial infarction and stroke [2-4]. Severe nitritoid reactions can resemble anaphylactic shock, but they differ from anaphylactic shock, because only vasomotor symptoms occur and no allergic symptoms, such as skin rash, angioedema or bronchospasm.

Reports

Until August 2004 Lareb received 4 reports of symptoms interpreted as a nitritoid reaction associated with the use of gold sodium aurothiomalate. In all cases the symptoms occurred within several minutes after injection of gold sodium aurothiomalate. In several cases, the reaction was in first instance interpreted and treated as an anaphylactic shock, leading to immediate and permanent discontinuation of gold treatment.

Cases A and C were reported by health professionals, case D was reported by the Marketing Authorisation Holder (MAH) and case B was reported by a health professional as well as by the MAH. It is remarkable that in all reported cases an ACE-inhibitor was used as concomitant medication at the time of the event. In case D the vasomotor reaction did not occur before the use of enalaprilate was started and did not reoccur after enalaprilate was discontinued.

Table 1. reports of nitritoid reactions associated with the use of sodium aurothiomalate.

Patient, Sex, age	dose schedule	Reported symptoms	Concomitant medication	Previous use of aurothioglucose	Time to onset, outcome
A F, 63	50 mg, 1 x in 10 weeks	unwell, collapse, hypotension	<i>lisinopril</i> , piroxicam	yes, since 1987	several months, recovered
B F, 61	50 mg, 1 x in 4 weeks	scarlet red, tachycardia, hypotension, dizziness, nausea and sweating	<i>enalaprilate</i> , hydrochlorothiazide	yes, since 7 years	16 months, recovered
C M, 73	100 mg, frequency unknown	unwell, red face, dizziness	<i>ramipril</i> , prednisone, azathioprine, omeprazole, pravastatin, diclofenac, acetylsalicylic acid and ferrous sulfate	unknown	2.5 years, not reported
D F, 69	50 mg, 1 x in 2 weeks	vasomotor reaction (red face, weak)	<i>enalapril</i> , metformin, glibenclamide, prednisolone, and calcium with vitamin D suppletion	unknown	unknown, recovered

Other sources of information

Literature

Information from the literature indicates that nitritoid reactions associated with parenteral gold are in almost all cases associated with sodium aurothiomalate. Nitritoid reactions during treatment with aurothioglucose are described very rarely. The incidence of nitritoid reactions during therapy with sodium aurothiomalate is roughly 5 %. [5, 6]

The idea that concomitant use of an ACE-inhibitor is a contributing factor for a nitritoid reaction after a gold injection is also mentioned in the literature. Several patients developed a nitritoid reaction to parenteral gold just after adding an ACE-inhibitor to the therapy [2, 7, 8].

Databases

The database of the WHO did not reveal any information on nitritoid reactions to gold therapy, because nitritoid crisis or vasomotor reaction does not exist in WHO adverse reaction terminology. Apart from a single case of flushing related to sodium aurothiomalate, no reports with an indication for nitritoid reactions could be found in the WHO database.

Mechanism

The mechanism behind gold induced nitritoid reactions is unknown, but the fact that in almost all cases the reaction is related to the aurothiomalate form indicates that the vehicle could be the responsible agent. ACE-inhibitors prevent bradykinin degradation, resulting in high bradykinin levels. One of the effects of bradykinin is vasodilatation. This might explain the contributing vasomotor effects of ACE-inhibitors [2, 5, 7].

Prescription data

It was assumed that when a nitritoid reaction occurs it forced the patient to stop therapy. Therefore, Lareb asked the 'Geneesmiddelen Informatie Project' (GIP; College voor Zorgverzekeringen, Diemen) for a dedicated query on prescription data of 7 million people in 2003 to see how many patients who stopped gold therapy were prescribed an ACE-inhibitor concomitantly. In 150 patients sodium aurothiomalate was used during the first half of 2003 and discontinued in the second half of 2003. Of these patients, 14 (9%) patients used an ACE-inhibitor at the time of last sodium aurothiomalate prescription.

Figure 1 shows overall prescription of aurothioglucose and sodium aurothiomalate.

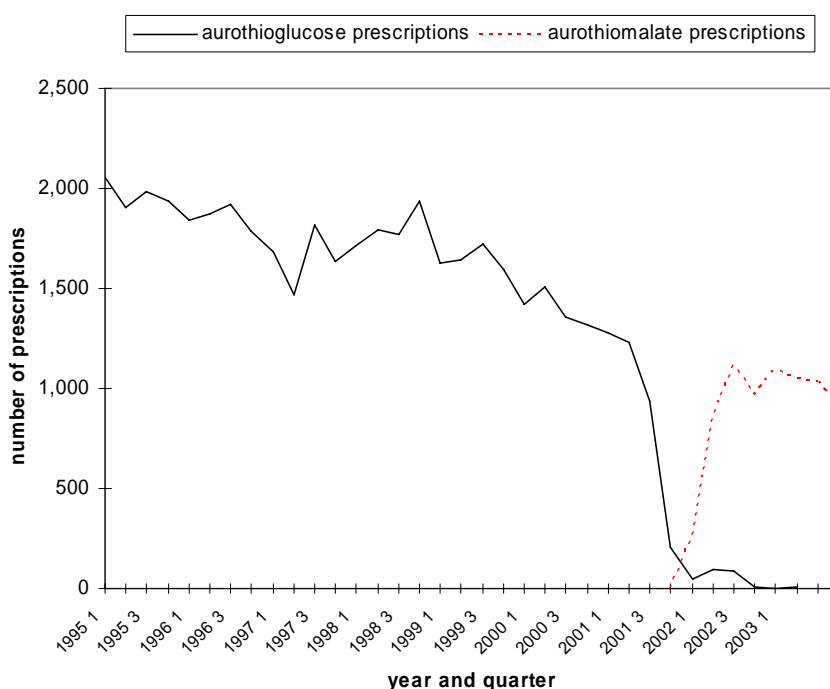


Figure 1. Total number of prescriptions and all reports per prescriptions per quarter since 1995 (Source: GIP College voor Zorgverzekeringen, Diemen).

Conclusion

The Lareb reports and literature data stress that the concomitant use of an ACE-inhibitor seems a contributing factor for developing nitritoid reactions to parenteral gold. Prescription data do, due to low numbers, not support nor reject this. This implies that patients do not have to be deprived from effective gold therapy when discontinuation of the concomitant ACE-inhibitor leads to non-recurrence of the nitritoid reaction after re-administration of parenteral gold. This information is currently not yet implemented in the Summary of Product Characteristics.

References

1. Dutch SPC Tauredon. (version date 19-2-2004) <http://www.cbg-meb.nl/IB-teksten/27387-27388.pdf>.
2. Arthur AB, Klinkhoff A, Teufel A. Nitritoid reactions: case reports, review, and recommendations for management. *J Rheumatol* 2001;28(10):2209-12.
3. Prupas HM. Stroke-like syndrome after gold sodium thiomalate induced vasomotor reaction. *J Rheumatol* 1984;11(2):235-6.
4. Harris BK. Myocardial infarction after a gold-induced nitritoid reaction. *Arthritis Rheum* 1977;20(8):1561
5. Choulis N.H., Dukes M.N.G. Dukes MNG, Aronson JK, editors. *Meyler's side effects of drugs*. 14 ed. Amsterdam: Elsevier; 2000; 22, Metals p. 690-5.
6. Evans TI, Small RE, Redford TW, Han J, Moxley G. Tumor necrosis factor microsatellite markers TNFa5b5 and TNFa6b5 influence adverse reactions to parenteral gold in Caucasians. *J Rheumatol* 1999;26(11):2303-9.
7. Ching DW, McClintock AD. Nitritoid reaction in a patient on ACE inhibitor and Myocrisin treatments. *Aust N Z J Med* 1997;27(3):343
8. Healey LA, Backes MB. Nitritoid reactions and angiotension-converting-enzyme inhibitors. *N Engl J Med* 1989;321(11):763