

A case of 'anaphylactic-like' reaction during LDL apheresis: a pathophysiological hypothesis on white wine containing metabisulphite

Dear Editor,

This report regards a 60-year-old man who has been treated for 8 years for heterozygous familial hypercholesterolemia associated with lipoprotein (a) hyperlipoproteinemia in aggressive coronary and polydissectual atherosclerotic disease. This patient presented two consecutive episodes of systemic malaise likely to be due to the interaction between low-density lipoprotein (LDL) apheresis procedure and intake of crafted or home-made white wine.

His first cardiovascular event, an acute myocardial infarction, occurred at the age of 51. He was treated with percutaneous coronary artery revascularisation procedure/stenting on anterior descending artery and on the bifurcation between circumflex artery and second marginal branch of the left coronary artery. Subsequently, his atherosclerotic disease progressed and he had persistent angina of effort due to progressive coronary atherosclerosis at the second marginal branch, which required a new percutaneous stent placement. At this time, atherosclerotic plaque was noted on both carotid arteries and ectasia seen in the abdominal aorta.

When he first came to our attention, a probable diagnosis of heterozygous familial hypercholesterolemia was made using the Simon Broome Register criteria (Scientific Steering Committee on behalf of the Simon Broome Register Group, 1991). He was placed on intensive lipid lowering therapy with LDL apheresis [Schwartz *et al.*, 2013; heparin-mediated LDL precipitation (HELP), Plasma Futura, B. Braun, Melsungen, Germany] every 2 weeks treating 4000 mL of plasma per session, in addition to lipid-lowering therapy. His baseline pre-apheresis lipid profile after titration on maximally tolerable lipid-lowering therapy (Atorvastatin 40 mg) was a total cholesterol of 191 mg dL⁻¹, high-density lipoprotein 60 mg dL⁻¹, triglycerides 111 mg dL⁻¹, LDL 128 mg dL⁻¹ and Lp(a) 141 mg dL⁻¹. Other drugs taken at this time were aspirin 100 mg once a day (OD), atenolol 50 mg OD and ramipril 5 mg OD.

During the following 8 years, the patient did suffer another acute cardiac event. He had regular treadmill tests, which were always negative, and carotid artery Doppler examination, which remained unchanged (intimal medial thickness less than 1 mm with a 30% stenosis at the bulb bilaterally). The ectasia of

abdominal aorta was stable (Ø30 mm). His lipid profile control remained adequate and he was physically active.

In this case, LDL apheresis is appropriate, due to heterozygous familial hypercholesterolemia with lipoprotein (a) hyperlipoproteinemia and progressive coronary disease (Schwartz *et al.*, 2013). The patient was regularly treated without any relevant problem with the exception of fatigue on the day of treatment. Unexpectedly, the patient presented with two consecutive episodes of systemic malaise characterised by sweating, paresthesias of the lips and flushing. In the second episode, these symptoms were followed by bradycardia and presyncopal episode. Both episodes occurred after more than 2 h treatment, respectively at 3100 and 2900 mL of plasma treated value. These episodes were cured with fluid administration and bolus of 500 mg intravenous methylprednisolone. His blood pressure, which was normal before the start of LDL apheresis, was low but responsive to administration of fluids. The symptoms, however, were so grave to require the discontinuation of LDL apheresis procedures.

LDL apheresis is generally well tolerated, but may cause fatigue in patients treated with dextran sulphate procedure and in those taking angiotensin-converting enzyme inhibitors (and here apheresis is expressly contraindicated by the manufacturer), due to reduced bradykinin catabolism (Owen & Brecher, 1994).

Upon revaluation of the possible concomitant causes of these unexpected episodes, which occurred in absence of technical problems and without drug therapy changes, we noted, our patient discontinued ramipril 48 h before the second treatment, without effect on the onset of symptoms. However, we noted changes in his lifestyle: at dinner, the patient drank two or three glasses of white wine that he had produced. The following apheresis was performed without any prior drinking wine and he did not report any reaction. Furthermore, no problems occurred in the subsequent nine apheresis performed so far with this setting.

The symptoms pointed out in our patient are likely to be due to the use of metabisulphite which has a long history as a preservative in the food industry. Metabisulphite is highly appreciated in winemaking for its ability to control bacteria and apiculate yeast, without damaging *Saccharomyces cerevisiae* cells, the main agent of the winemaking process (Andorrà *et al.*, 2008). However, metabisulphite is a chemical compound belonging to the sulphite class and it decomposes with the yield of sulphur dioxide (SO₂). Despite its common use, SO₂ and its derivatives show some adverse effects: about 1% of people in the United States are sulphite hypersensitive, according

Correspondence: Francesco Sbrana, MD, Fondazione Toscana Gabriele Monasterio, via Moruzzi, 1, 56124 Pisa, Italy.
Tel.: +39 050 3152705; fax: +39 050 3153030; e-mail: francesco.sbrana@ftgm.it

to Food and Drug Administration estimation. Exposure to sulphite-containing compounds induced adverse clinical effects in sensitive individuals, ranging from dermatitis, urticarial, hypotension and diarrhoea to life-threatening anaphylactic and asthmatic reactions (Mahmoud *et al.*, 2015). Usually, symptoms of sulphite intolerance can occur within 15–30 min following oral exposure. In our patient, who had introduced white wine craft produced more than 12 h before the symptoms onset, we can assume that sulphur dioxide compounds were stored linked to proteins, as haemoglobin (Berzofsky *et al.*, 1972). These compounds modify their molecular forms at different pH values with subsequent effects on biocidal activity against yeast and human cell cultures (Corte *et al.*, 2012).

In LDL apheresis, performed with a selective elimination of LDLs and fibrinogen by heparin precipitation at acid pH systems, plasma obtained by filtration of whole blood is continuously mixed with an equal volume of an acetate buffer (pH 4.85) containing heparin. After removal of the precipitated heparin complex by filtration, excessive heparin is adsorbed to a specially developed filter, and the clear plasma filtrate is subjected to bicarbonate dialysis/ultrafiltration to restore physiologic pH and remove excessive fluids (Seidel *et al.*, 1988). The 'restored' plasma that joins the whole blood, however, in our patients is maintained at a pH of 6.85. This pH level could modify the sulphur dioxide compounds linked to protein. Furthermore, sulphite species enhance carbon monoxide (CO) release from CO-releasing molecules (McLean *et al.*, 2012) as haemoglobin and have an impact on physiological buffering systems of the human organism useful to mitigate the slight pH variations secondary to LDL apheresis treatment. The pathophysiological pattern described could explain the symptoms presented by our patient.

During LDL apheresis, a case of reaction secondary to herbal remedy was described (Adamski *et al.*, 2010), but

'anaphylactic-like' reaction, that may be linked to metabisulphite, has not been previously linked with LDL apheresis. Nowadays, the increasing production of wine at home may lead to an increased risk of interactions between drugs or therapeutic procedures (as LDL apheresis) with potentially serious consequences, and is an example of an interaction with a medical therapy with over-the-counter medications or herbal products and food additives. Therefore, further examples of such interactions could be very useful to identify interaction and to develop future safer procedures. This case shows how a careful medical history can help to understand unexplained or unexpected reactions during LDL apheresis.

ACKNOWLEDGMENTS

F. S. designed and performed the research and wrote the paper; G. C. and B. D. P. designed and performed the research; F. B., M. P. and R. L. reviewed the literature; L. S. wrote the paper; T. S. designed the research.

CONFLICT OF INTEREST

The authors have no competing interests.

F. Sbrana,¹ G. Cardinali,^{2,3} B. Dal Pino,¹ F. Bigazzi,¹ L. Sabatino,⁴ M. Pianelli,¹ R. Luciani,¹ T. Sampietro¹

¹Fondazione Toscana Gabriele Monasterio, Pisa, Italy

²Department of Pharmaceutical Sciences – Microbiology,

University of Perugia, Perugia, Italy ³CEMIN, Centre of

Excellence on Nanostructured Innovative Materials,

Department of Chemistry, Biology and Biotechnology,

University of Perugia, Perugia, Italy ⁴CNR Institute of Clinical

Physiology Pisa, Italy

REFERENCES

- Adamski, J., Jamensky, L., Ross, J., Siegel, D.L. & Sachais, B.S. (2010) Anaphylactoid-like reactions in a patient with HyperLp(a)lipidemia undergoing LDL apheresis with dextran sulfate adsorption and herbal therapy with the spice turmeric. *Journal of Clinical Apheresis*, **25**, 354–357.
- Andorrà, I., Landi, S., Mas, A., Guillaumon, J.M. & Esteve-Zarzoso, B. (2008) Effect of oenological practices on microbial populations using culture-independent techniques. *Food Microbiology*, **25**, 849–856.
- Berzofsky, J.A., Peisach, J. & Horecker, B.L. (1972) Sulfheme proteins. IV. The stoichiometry of sulfur incorporation and the isolation of sulfhemin, the prosthetic group of sulfmyoglobin. *Journal of Biological Chemistry*, **247**, 3783–3791.
- Corte, L., Roscini, L., Zadra, C., Antonielli, L., Tancini, B., Magini, A., Emiliani, C. & Cardinali, G. (2012) Effect of pH on potassium metabisulphite biocidal activity against yeast and human cell cultures. *Food Chemistry*, **134**, 1327–1336.
- Mahmoud, A.A.T., Hassan, G.M., Sadek Hassan, A.M., Mohammed Abdel Latif, A.K. & Ramadane, M.F. (2015) Demonstrating adverse effects of a common food additive (sodium sulfite) on biochemical, cytological and histopathological parameters in tissues of albino Wistar rats. *European Journal of Integrative Medicine*, **7**, 234–242.
- McLean, S., Mann, B.E. & Poole, R.K. (2012) Sulfite species enhance carbon monoxide release from CO-releasing molecules: implications for the deoxymyoglobin assay of activity. *Analytical Biochemistry*, **427**, 36–40.
- Owen, H.G. & Brecher, M.E. (1994) Atypical reactions associated with use of angiotensin-converting enzyme inhibitors and apheresis. *Transfusion*, **34**, 891–894.
- Schwartz, J., Winters, J.L., Padmanabhan, A. *et al.* (2013) Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: the sixth special issue. *Journal of Clinical Apheresis*, **28**, 145–284.
- Scientific Steering Committee on behalf of the Simon Broome Register Group (1991) Risk of fatal coronary heart disease in familial hypercholesterolaemia. *British Medical Journal*, **303**, 893–896.
- Seidel, D., Armstrong, V.W., Schuff-Werner, P. & Eisenhauer, T. (1988) Removal of low-density lipoproteins (LDL) and fibrinogen by precipitation with heparin at low pH: clinical application and experience. *Journal of Clinical Apheresis*, **4**, 78–81.