Coffee Colored Serum, Adverse Reaction of Eltrombopag

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Abstract

Serum index and macroscopic characteristics of samples can give valuable information and should be interpreted as a result. Following centrifugation of the sample, on gross inspection it was observed that the serum had a brown color. After ruling out the main causes that can cause a brown coloration, such as intravascular hemolysis or high concentrations of methemoglobin, it was noted that the patient was receiving a high-dose of Eltrombopag therapy. Eltrombopag is a non-peptide thrombopoietin receptor agonist approved for the treatment of severe aplastic anemia (SAA). The drug in solution has a brown color and at high concentrations it is capable of changing the color of the serum and may have different effects in different assays of laboratory. This article describes the case of a patient with brown serum due to the consumption of high doses of Eltrombopag that started to cause cutaneous hyperpigmentation.

Introduction

A fundamental aim in the daily routine of a clinical laboratory in relation to patient safety is to communicate precise and accurate analytical results. Otherwise, serious errors in clinical interpretation would be made. Serum index results are very useful for monitoring the degree of potential interference due to lipemia, hemolysis and jaundice. Nevertheless, in some cases the clinical laboratory must go further and be able to detect certain hidden pathologies using these indices, such as dyslipidemia, hemolysis in vivo, liver disease [1,2] or, as in the present case, adverse drug effects. Endogenous and exogenous constituents in the sample matrix can affect laboratory tests. Some of these potentially interfering factors can be recognized in the pre-analytical phase by colorimetric appearance, turbidity and viscosity, whereas others are detected only by direct analysis. The following case is a description of a patient who presents brown serum due to the consumption of high doses of Eltrombopag that began to cause hyperpigmentation of the skin.

Clinical-diagnostic case

We report a 78-year-old man diagnosed with severe aplastic anemia (SAA) on treatment with cyclosporine 125 mg/12h + eltrombopag 150 mg/24h + allopurinol 300 mg/24h. During the follow-up carried out by the Haematology service, a blood test including a complete blood count and basic biochemistry was obtained. After processing the sample, the hemolysis index was normal, however we detected a high rate of jaundice and lipemia index (Table 1). Due to this result, the hepatic study was included by adding bilirubin determination and the ions were re-analysed by direct potentiometry to correct the negative interference produced in the lipemic samples by indirect potentiometry. After carrying out the corresponding analysis, no increase in total bilirubin was observed in accordance with the patient's jaundiced index. Furthermore, the serum showed a dark brown colour and not a cloudy appearance like a serum with a high lipaemic index would have (Figure 1).

The possible causes of abnormal plasma coloration according to literature could be related with the presence of high levels of metalbumin, myoglobin or methemoglobin. Hemolytic anemia, rhabdomyolysis and exposure to exogenous oxidizing agents could cause the rise of these proteins respectively [3].

To rule out these pathologies, we sequentially added lactate dehydrogenase plus haptoglobin for the assessment of intravascular hemolysis and creatine kinase for the study of rhabdomyolysis. Furthermore, we measured methemoglobin evaluating co-oximetry after requesting a new heparinized sample and rejecting the previous possibilities. The methodology used for the determination of all parameters was the Abbott Alinity assay, except for methemoglobin, which was determined by the radiometer ABL 90. The results shown in Table 1 rule out any of the aforementioned diagnoses.

The next step was checking if any of the drugs the patient was taking could cause abnormal coloration of the serum. According to the eltrombopag data sheet, hyperpigmentation is a reported adverse effect, although infrequently (≥1/1000 to <1/100) [4].

There have been a few small-case reports of patients on treatment with high doses of eltrombopag causing brown discoloration of serum.

One article, described a 52-year-old woman with aplastic anemia who after increasing the dose of eltrombopag to 150 mg/24h, showed a "Reddish-brown serum" [5]. Another one, reported a series of three acute myeloid leukemia patients with eltrombopag doses of 200-300 mg/24h who presented a "brown serum" [6]. The last article related to our topic, described a patient with "brown serum" who was treated with an eltrombopag dose of 150 mg/24h [7].

Discussion

Severe aplastic anemia (SAA) is a bone marrow hypoplasia/aplasia in association with pancytopenia [8]. According to the classification of disease severity and assessment of medical fitness, the Haematology service selected the best treatment approach for the patient. Some guidelines recommend in selected patients a combination of immunosuppressive therapy such as eltrombopag plus cyclosporine [4]. Eltrombopag is a non-peptide thrombopoietin receptor agonist approved for the treatment of SAA, idiopathic thrombocytopenic purpura and chronic hepatitis C associated thrombocytopenia [9]. In SAA we can reach the higher doses of eltrombopag (150 mg/24h) comparing to the other aproved uses [4], which could lead to a major exposure to the drug and a major number and more severe adverse reactions. All the aforementioned cases had doses greater than or equal to 150 mg/24h [5-7]. After detecting this abnormal color of the serum in our patient, he was called for a more exhaustive clinical review. The patient presented a slight cutaneous hyperpigmentation and a yellow sclera of the eye. The cause of the hyperpigmentation is not fully understood. Cases have been described in patients taking similar doses (150 mg/day) [9, 10], this may be of concern to the patient, but there are currently no known adverse clinical sequelae from tissue or plasma pigmentation from the use of eltrombopag [10]. Moreover, the effect is reversible after the drug withdrawal [8]. A differential diagnosis to take into account in patients with hyperpigmentation or a yellow hue is serious liver failure. This is important because the drug is hepatotoxic [11] since it is metabolized and eliminated mainly in the liver [12]. Thereby, we must monitor transaminases and bilirubin for any sign of liver damage in patients taking eltrombopag. This is not an easy task, because as we have described previously, it has the potential to give a brown hue which interferes with some laboratory tests. The interferences found in the spectrophotometric methods are dependent on the technology used. Positive interference in spectrophotometric measurements of total bilirubin has been detected in some laboratories [13-14], which is a serious analytical error because we could lead to a misdiagnosis of liver damage. A study carried out in 2016 evaluated possible interferences of eltrombopag using the Roche Cobas 6000 technology, finding changes greater than 10% in parameters associated with the lipid profile. On the other hand, no interferences were found in the determination of bilirubin or transaminases [15]. Laboratory professionals must know how their determinations are affected so an erroneous diagnosis is not reached. We found out that our patient had total bilirubin measurement of 20,5 umol/L (diazo method, Abbott Alinity) but discordant icterus index (icterus index=3.4, corresponding to 51-85 umol/L of total bilirubin). The unlikely nature of these results led us to investigate the possibility of an analytic interference.

The sample was sent to a reference laboratory that determined total bilirubin using high performance liquid chromatography (HPLC). The result was similar to our laboratory (total bilirubin = 17 umol/L). We can conclude that the measurement of total bilirubin in patients treated with eltrombopag is not affected by the Abbott Alinity assay. The adverse reactions described were reported to the Spanish Pharmacovigilance System through the spontaneous reporting system for adverse drug reactions.

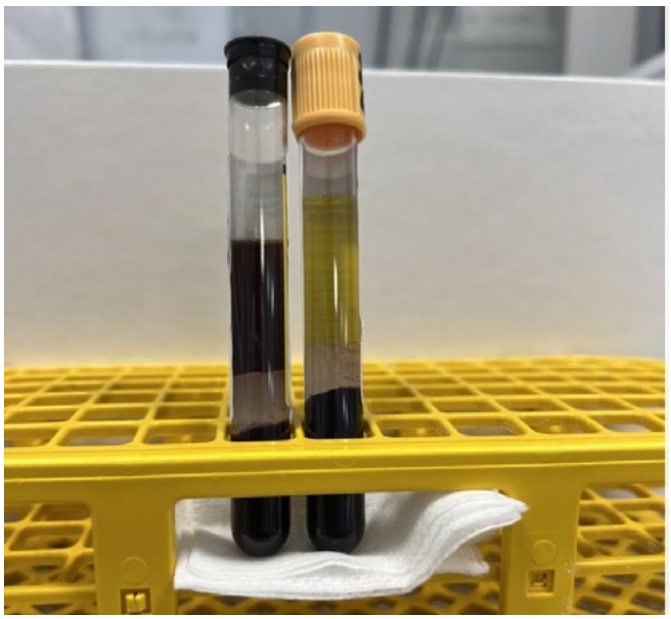

Figure 1: The brown serum on the left belongs to the patient on treatment with eltrombopag and the serum on the right to a control patient without treatment to show different coloration.

Table 1: Results of serial analyses performed in our laboratory

Laboratory test	02/05/23	08/05/23	Reference values
Total bilirubin (umol/L)	20.5	18.8	0.0-20.5
Direct bilirubin (umol/L)	10.2	8.5	0.0-8.5
Indirect bilirubin (umol/L)	10.3	10.3	0.0-11.9
Glumatic oxaloacetic transaminase (U/L)	16	20	5-34
Glumatic pyruvic transaminase (U/L)	12	13	0-45
Lactate dehydrogenase (U/L)	191	184	125-220
Haptoglobin (umol/L)	30	28	2-30
Creatine kinase (U/L)	160	170	30-200
Methemoglobin (%)	0.7	0.6	0.0-1.5

Learning points

• Our objective with this article is to present the importance of serum index. They are normally used as an alert system for possible analytical errors, but they can also contribute to the detection of hidden liver diseases, unstudied dyslipidemias or, as the case may be, adverse pharmacological effects.

• The most common causes of a brown colored serum are the presence of metalbumin, myoglobin, and methemoglobin and should be ruled out first.

• Interferences in the laboratory are usually method dependent and it is the laboratory professional who must know how they interfere with their results.

• Remember that whenever we are faced with a possible pharmacological adverse effect, it must be notified.

Author Contributions:

All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors' Disclosures or Potential Conflicts of Interest

No authors declared any potential conflicts of interest.

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