Dear Editor,

Please find enclosed the edited manuscript in word format (file name: **19658-edited**).

Title: Acute dapsone poisoning in 3 year old child- case report with review of literature

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Name of Journal: World Journal of clinical cases

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1) The manuscript has been improved according to the suggestions of reviewers:

Reviewer 1

Needs major revision if to be accepted:

1. Multiple grammatical errors and word choice problems should be addressed by revision, by someone with excellent command of English.

Authors response: Revised article modified for its grammatical errors

2. The patient's methemoglobin levels should be mentioned in the Case Report section, not deferred till Discussion.

Authors response: Yes, it has been included in the case report section

3. The Table needs significant revision. would place the parameters (and units) in the left column, and the numerical results in columns 2 and 3. All non-essential data should be eliminated, only displaying the clinically relevant data.

Authors response: Modified as per the suggestions

Reviewer 2

This is a useful review of Dapsone poisioning and its treatment.

Authors response: nil

Reviewer 3

1. Ascorbic acid (CELIN-1000 mg) was administered: vitamin C can occasionally reduce cyanosis associated with chronic methemoglobinemia but has no role in treatment of acute acquired methemoglobinemia.

Authors response: We agree with the comments.

2. ranitidine: Cimetidine, used as a selective inhibitor of N-hydroxylation, may be effective in increasing patient tolerance to dapsone, chronically lowering the methemoglobin level by more than 25 percent. Since it works slowly, cimetidine is not helpful for the management of acute symptomatic methemoglobinemia arising from the use of dapsone.

Authors response: Accepted the comment

3. The plasma elimination half-life of dapsone is reported to vary from 10 to 80 h and is dose dependent. Renal excretion of unchanged dapsone is limited to approximately 20% of the administered dose.

Authors response: Accepted the comment and incorporated in the revised MS

4. Oxidation of Fe++ to ferric yields MHbA, which does not bind oxygen: In addition, the oxygen affinity of any remaining ferrous hemes in the hemoglobin tetramer is increased. As a result, the oxygen dissociation curve is "left-shifted". The net effect is that patients with acutely increased concentrations of methemoglobin have a functional anemia (ie, the amount of functional hemoglobin is less than the measured level of total hemoglobin). The circulating methemoglobin-containing hemoglobin molecules are unable to deliver oxygen and the remaining oxyhemoglobin has increased oxygen affinity, resulting in impaired oxygen delivery to the tissues.

Authors response: We had mention this in the discussion section 3rd para and also added further

5. In this case, an additional dose of methylene blue was given since the MHbA level was high on 5th day (10.2%): Rebound methemoglobinemia as high as 60 percent may occur up to 18 hours after MB administration, due to prolonged absorption of the implicated agent from topical or enteric sites [Guay J. Methemoglobinemia related to local anesthetics: a summary of 242 episodes. Anesth Analg. 2009;108(3):837]. Accordingly, it is reasonable to perform serial measurements of methemoglobin levels following treatment with methemoglobinemia in order to evaluate the patient for subsequent worsening and the need for additional treatment. This may be especially true for dapsone-induced methemoglobinemia because of its enterohepatic circulation.

Authors response: Accepted the comment and incorporated in the revised MS

6. Use of topical dapsone as treatment for acne vulgaris has also been associated with methemoglobin levels as high as 20 percent. [Swartzentruber GS, Yanta JH, Pizon AF Methemoglobinemia as a complication of topical dapsone. N Engl J Med. 2015 Jan;372(5):491. A simple bedside test is to place one or two drops of the patient's blood on white filter paper. The chocolate brown appearance of methemoglobin does not change with time, whereas deoxygenated hemoglobin appears dark red or violet initially but brightens after exposure to air. Gently blowing supplemental oxygen on the filter paper hastens the reaction with deoxygenated hemoglobin but does not affect the

color of methemoglobin. While clinically important, this bedside test should be confirmed with a laboratory determination of the methemoglobin level. [Haymond S, Cariappa R, Eby CS, Scott Laboratory assessment of oxygenation in methemoglobinemia. Clin Chem. 2005 Feb;51(2):434-44 & Wright RO, Lewander WJ, Woolf AD Methemoglobinemia: etiology, pharmacology, and clinical management. Ann Emerg Med. 1999;34(5):646].

Authors response: We gratefully acknowledge the suggestion. Some part of this included in the revised MS

7. Standard pulse oximeters measure tissue transmission at two wavelengths (660 and 940 nanometers) to determine arterial oxygen saturation as the ratio of oxyhemoglobin to total hemoglobin, and are not reliable when methemoglobin and other hemoglobin derivatives are present. Accordingly, routine pulse oximetry is generally inaccurate for monitoring oxygen saturation in the presence of methemoglobinemia, and should not be used

Authors response: Accepted the comment and incorporated in the revised MS

(2) Language is improved.

(3) References and typesetting were corrected.

Thank you again for publishing our manuscript in the World Journal of clinical cases.

Sincerely,

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