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A RARE CASE OF DIOSMIN AND HESPERIDIN INDUCED CHEST TIGHTNESS AND DYSPNEA

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ABSTRACT

Diosmin and hesperidin are medicines derived from flavonoids present naturally in the citrus fruits. It is given as a combination drug therapy for internal hemorrhoids. These drugs are considered safe when it is used up to 3 months. Serious reactions including respiratory adverse drug reactions (ADRs) are very rare with the use of these drugs. There are no case reports of presentation of diosmin and hesperidin induced chest tightness and dyspnea. A 65-years-old female patient admitted to hospital presented with diosmin and hesperidin induced chest tightness and dyspnea. Evaluating the presented ADRs confirmed to diosmin & hesperidin use and were stopped after clinical pharmacy opinion. No rechallenge was done considering the seriousness of ADRs. This case report will help in establishing a safety message among the patients and clinicians as they must be made aware of possible respiratory ADRs caused by these drugs.

Keywords: Diosmin, Hesperidin, Dyspnea, chest tightness, Adverse Drug Reactions (ADRs)

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INTRODUCTION

Diosmin and Hesperidin are naturally acquired products derived from the flavonoids, present naturally in the citrus fruits. The drugs are considered safe when used for a short period of time up to a span of 3 months.[1][2][3] They increase lymphatic drainage & protects from inflammation. Combination therapy is indicated in the treatment of internal haemorrhoids.[4][5][6][7][8] Pharmacological properties of Diosmin and Hesperidin are anti-inflammatory, antioxidant and antiulcer effects. ADRs associated with these drugs use on respiratory system are very rare and can cause dyspnea, epistaxis, bronchospasm, cough, laryngeal edema, pharyngeal edema, respiratory distress, asthma, dysphonia, asphyxia, oropharyngeal pain, pulmonary embolism, suffocation feeling, upper respiratory tract irritation and wheezing.[1][3][5] Hesperidin may be of irritating nature to mucous membranes and the upper respiratory tract as well. Clinical Pharmacy reported ADRs and literature reviews are increasing in India and beneficial for other healthcare professionals as well.[9][10][11][12] There are no case reports of these drugs causing serious respiratory ADRs.[1][13]

CASE REPORT

A 65-years-old female patient was admitted to the surgery department at the hospital with presenting complaints of swelling of right leg for one month and occasional shortness of breath and fever for the last 10 days. She is a known case of varicose vein with thrombophlebitis. She did not have any respiratory disorders or history of any chest pain or giddiness. The patient was not a smoker or an alcoholic. Medication history showed that she was receiving tablet Diosmin (900 mg) + Hesperidin (100 mg) since past 18 days. On examination, vitals were as follows: *BP* = 130/76 mm of Hg, *pulse* = 84 bpm, *Arterial gas analysis* = normal with pCO_2 =35.9, pO_2 = 81.8; *CVS:* S1+ S2 heard, no murmurs heard; *CNS:* no focal neurological deficit; *Abdomen:* soft, tender; *Leg:* mild tenderness noted in the leg with diffuse swelling of right limb along with pitting oedema. Laboratory reports showed: HIV = non-reactive; HCV = non-reactive; HbsAg = non-reactive; Urea = 20 mg/dL; Creatinine = 0.8 mg/dL; Electrolytes: $Na^+/K^+/Cl^-$ = 140 / 4.5 / 104 mEq/L; Hb = 13.7 g/dL; Total WBC Count = 6,600 cells per microliter (mcL); Differential Count: N/L/E/M/B = 76.8/19.3/4.9/3.7/0.3 %; Platelets Count: 3.13 × 10^9/L; and PT-INR = 1.07. The case was diagnosed as 'right limb varicose vein with superficial varicosities'. The care plan was to treat the patient with antibiotics, nebulization of bronchodilators and surgery (if needed). Patient was started on intravenous (IV) Cefoperazone + Tazobactam (1.125 gm), BID; IV Esomeprazole (40 mg), OD; IV Acetaminophen (1 gm), BID; IV Amikacin (500 mg), BID; PO Diosmin (900 mg) + Hesperidin (100 mg), OD; with oxygen inhalation (2 litres/minute for 16 hours).

After two days of continuing of the treatment, chest tightness and dyspnea was observed. She was started on Nebulization (Neb.) Salbutamol (2.5 mg) and Ipratropium (500 mcg), TID; Neb Formoterol (6 mcg), Budesonide (200 mcg) TID; PO Acetylcysteine (600 mg), BID; PO Acebrophylline (200 mg), OD; and Inhaler Formoterol (6 mcg) with Budesonide (200 mcg), 2 puffs, OD. She was referred to pulmonology department of hospital for opinion suspecting possible Pulmonary Arterial Hypertension (PAH) and clinical pharmacy opinion for suspected drug induced 'chest tightness and dyspnea' due to the use of Diosmin and Hesperidin. PAH was not diagnosed by pulmonologist. The patient's medication history was noted and evaluated to confirm if the reactions were drug induced. Ascertaining that this was unlikely with other drugs or diseases; these reactions were confirmed to be Adverse Drug Reactions (ADRs) of Diosmin + Hesperidin. The causative drugs Diosmin and Hesperidin were dechallenged after clinical pharmacy opinion. No rechallenge was done considering the seriousness of the ADRs. Pulmonary function tests were normal within few days. Patient's condition was significantly improved with symptomatic treatment following which she was discharged on medical advice.

DISCUSSION

The combination of Diosmin and Hesperidin increases the lymphatic drainage & protect from inflammation and combined therapy is mainly indicated in the treatment of internal haemorrhoids.[4][5] It acts by improving vascular

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tone, reducing the inflammatory reactions and capillary permeability, inhibition of prostaglandin synthesis and thromboxane synthesis also inhibits the activation, migration and endothelial adhesion of leukocytes, decreases the neutrophil activation and hence provides protection against microcirculatory damage.[6][7][8] Inflammatory reactions upon the drug can be mainly triggered by the biological and chemical mediators like arachidonic acid derivatives (leukotrienes, thromboxane & prostaglandins) free radicals and vasoactive amines.[1][3][4]

There were few reports by FDA and WHO for dyspnea in patients who had received these drugs. There was no information on usage of these drugs in pregnancy & nursing or about hypersensitivity with the use of this combination.[1][3] Based upon the patient's medical history, ADRs and analysis with WHO Probability Scale, Naranjo's Scale and Karch & Lasagna's Scale, chest tightness and dyspnea presented by the patient can be attributed to Diosmin and Hesperidin.[14][15][16][17]

CONCLUSION

Diosmin and Hesperidin use is usually considered safe. However, ADRs due to the use of these drugs may not be ruled out. Patients and clinicians must be made aware of the possible respiratory ADRs and caution must be taken.

CONFLICT OF INTEREST

None.

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REFERENCES

1. U.S. Food and Drug Administration, United States, 2017. Daflon-Diosmin. https://www.fda.gov/ohrms/dockets/dockets/95s0316/95s-0316-rpt0325-04-Tab-C-vol257.pdf (accessed 17.02.2018).
2. [dataset] Therapeutic Research Faculty, publishers of Natural Medicines Comprehensive Database, United States, 2017. Diosmin and Hesperidin. http://naturaldatabase.therapeuticresearch.com (accessed 17.02.2018).
3. [dataset] VigiBase®, the World Health Organization's (the "WHO") global database for ADRs, Uppsala Monitoring Centre, Sweden, 2017. Diosmin and Hesperidin. http://www.vigiaccess.org/ (accessed 17.02.2018).
4. Thanapongsathorn W, Vajrabukka T. Dis Colon Rectum 1992; 35:1085.
5. Douglas M. Haemorrhoids and Varicose Veins: A Review of Treatment Options. Alternative Medicine Review 2001; 126.
6. Giannini I, Amato A, Basso L. Flavonoids mixture (Diosmin, Troxerutin, Hesperidin) in the treatment of acute haemorrhoidal disease: a prospective, randomized, triple-blind, controlled trial. Tech Coloproctol 2015; 19:339.
7. Diana G, Catanzaro M, Ferrara A, Ferrari P. Activity of purified Diosmin in the treatment of haemorrhoids 2000; 151(5):341-344.
8. M Cospite. Double-Blind, Placebo-Controlled Evaluation of Clinical Activity and Safety of Daflon 500 mg in the Treatment of Acute Haemorrhoids. Angiology 1994; 45:566-573.
9. Mishra A, Manideep R, Adepu R, Mothi S, Swamy V. Induced Stevens-Johnson Syndrome in a Human Immunodeficiency Virus Patient: A Case Report. Asian J Pharm Clin Res 2016; 9(1):1-2.
10. Mishra A, Kumar AP, Undela K, Dileep KP. Severe upper gastrointestinal bleeding with gastric ulcer and anaemia secondary to prolonged use of aspirin and clopidogrel – A case report. Int J of Allied Med Sci and Clin Res 2016; 4(4):727-730.

11. Mishra A, Shamshavali K, Sanathan S, Rao S, Talal B, Sravanthi R. Challenges in the Diagnosis and Treatment of Melioidosis: A Review. European Journal of Pharmaceutical and Medical Research 2017; 4(03):226-232.

12. Mishra A. An important drug of last resort for multidrug-resistant (MDR) pathogens and the first glycylcycline antibiotic-tigecycline. International Journal of Pharmaceutical Research and Bio-Science 2017; 6(2):133-140.

13. Hesperidin. Safety Data Sheet, Cayman, 2015. https://www.caymanchem.com/msdss/18646m (accessed 19.02.2018).

14. The use of the WHO–UMC system for standardised case causality assessment. Accessed from: http://www.WHO-UMC.org/graphics/4409 (accessed 20.02.2018).

15. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. 1981. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 30: 239–245.

16. Karch FE, Lasagna L, 1976. Evaluating adverse drug reactions, Adverse Drug Reaction Bulletin. 59:204-207.

17. Tallarida RJ et al. A scale for assessing the severity of diseases and adverse drug reactions: Application to drug benefit and risk. Clinical Pharmacology and Therapeutics 1979; 25(4):381-390.

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