International Journal of Pharmacy and Pharmaceutical Sciences

Print ISSN: 2656-0097 | Online ISSN: 0975-1491 Vol 16, Issue 7, 2024

Case Study

ACETAMINOPHEN-INDUCED TOXIC EPIDERMAL NECROLYSIS IN PEDIATRIC PATIENTS-A CASE SERIES

DHARMESH MEVADA, PRATIK CHABHADIYA*, ANIL SINGH

Department of Pharmacology, PDU Govt Medical College, Rajkot, India
***Corresponding author: Pratik Chabhadiya; *Email: pratikchabhadiya35@gmail.com**

Received: 10 Apr 2023, Revised and Accepted: 14 May 2024

ABSTRACT

Acetaminophen is the most widely used over-the-counter medication for treating fever and pain. While adverse reactions to this drug are infrequent, they can occasionally result in severe and potentially fatal events, such as Toxic Epidermal Necrolysis (TEN). Due to the rarity of such reactions, there is a limited amount of information available about toxic epidermal necrolysis caused by acetaminophen. This case series will contribute to the existing knowledge in this area. In our cases, acetaminophen is the most suspected drug for the development of toxic epidermal necrolysis in patients. Causality assessment in all of these adverse drug reaction in context with World Health Organization (WHO) causality assessment scale suggests "Possible." This case series concludes that severe hypersensitivity reactions like TEN caused by acetaminophen use and which can be potentially life-threatening which needs additional treatment.

Keywords: Toxic epidermal necrolysis, Adverse drug reactions, Paracetamol, Acetaminophen

DOI: https://dx.doi.org/10.22159/ijpps.2024v16i7.48175 Journal homepage: https://innovareacademics.in/journals/index.php/ijpps

INTRODUCTION

Acetaminophen is a commonly used pain reliever and fever reducer due to its accessibility and affordability. While it is generally considered to be safe, some individuals may experience adverse reactions such as hives, fixed drug eruptions, swelling, and gastrointestinal issues. However, in extremely rare cases, the use of acetaminophen has been associated with Toxic Epidermal Necrolysis (TEN) [4, 5]. TEN typically begins with a prodrome of flu-like symptoms such as fever, fatigue, joint pain, runny nose, and headache that can last anywhere from 1 to 28 days. This is followed by the development of a rash that appears as a poorly defined, reddish-purple macular eruption with blisters that merge together to form large areas of denuded skin. The blisters can easily rupture, leaving behind a moist and exposed dermis. The rash usually starts on the face and presternal area before spreading to other parts of the body, except for the scalp, which is rarely affected. TEN is a severe condition that can cause significant morbidity and mortality rates, with involvement of mucous membranes, respiratory tract, and gastrointestinal tract. It is most commonly caused by medications such as antibiotics, anticonvulsants, and non-steroidal anti-inflammatory drugs [1-3]. This case series involves patients who was administered acetaminophen as an over-the-counter prescription or prescribed by physician. The findings of this reports will be valuable to physicians in understanding the potential adverse effects of acetaminophen, which are typically rare. However, if adverse drug reactions are detected early and appropriate treatment is administered, it can help reduce the morbidity and mortality associated with such reactions. This case series is approved by institutional ethics committee.

CASE REPORTS

Case 1

On January 3rd, 2022, at 12:30 pm, a 7 y old male patient weighing 19 kg presented with symptoms of toxic epidermal necrolysis after taking Tab. Acetaminophen for fever with chills. The patient was then referred to a government hospital and was admitted to a Pediatric Intensive Care Unit (PICU) isolated ward for further management. On 03/Jan/2022, the patient was treated with Injection Ceftriaxone-950 mg twice a day, Inj Vancomycin 290 mg Intravenous (IV) six hourly, Inj. DNS+5 ml KCL @ 60 ml/hour, Inj. Hydrocortisone 48 mg IV six hourly, Framycetin cream local apply twice a day, Tobramycin and Carboxymethylcellulose (CMC) eye drop in response to the event of toxic epidermal Necrolysis. Dermatologist reference was done. They diagnosed the condition as toxic epidermal necrolysis [with>30% skin detachment] and suspected that reaction was related to Tab. Acetaminophen. On 4th and 5th Jan, treatment was same. Previous medication history:-On Dec 31st, 2021, the patient was administered a single dose of 250 mg Tab. Acetaminophen as an over-the-counter medication for fever with chills. The following day (Jan 1st, 2022), the patient began experiencing itching throughout their body and developed a dusky erythematous macular rash and blisters on their face and presternal area. This gradually spread to involve the trunk and both limbs. The patient had no prior medical or surgical history and no history of drug allergies was reported. On 01/Jan/2022, the patient consulted private hospital with above mentioned complaints. Consultant paediatrician prescribed Tab. Acetaminophen, Mefenamic acid suspension, ORS powder, Calamine lotion, Amoxicillin+Potassium clavulanate syrup, Syrup Multivitamin. lab reports done on 02/Jan/2022 which are given below.

Table 1: Laboratory finding on 02/Jan/2022

CRP	55.3 mg/dl
SGPT	25 units/L
Serum creatinine	0.60 mg/dl
Glomerular filtration rate	213 ml/min
Hb	13 gm%
WBC	14,130 cells/cumm
Platelet count	205000 cells/cumm

On 03/Jan/2022, there was change in treatment at private hospital, which included:-1) I. V. fluid 2) Inj. Cefepime+Tazobactam 3) Inj. linezolid 4) Inj. Pantoprazole 5) Inj. Ondansetron 6) Inj. Acetaminophen 7) Inj. Dexona 8) Inj. levetiracetam. Then at the same day patient was referred to government hospital Rajkot. All previous medication was put on hold by the pediatrician at our government hospital on 03/Jan/2022 and previously mentioned therapeutic management was done. Further management: On Jan 6th, 2022, the patient's treatment was modified by discontinuing Inj. Ceftriaxone and starting Inj. Piptaz 2 gm 8 hourly and levofloxacin 200 mg IV once a day. From Jan 6th onwards, the patient showed signs of improvement. Using the WHO causality algorithm, the association between the drug and the adverse reaction was deemed

Possible. The patient was reviewed 5 d later, and significant healing of skin lesions was observed below the neck and between the shoulder areas on the back. The patient continued to recover and was in a recovering stage on Jan 11th, 2022, as shown in fig. 4.

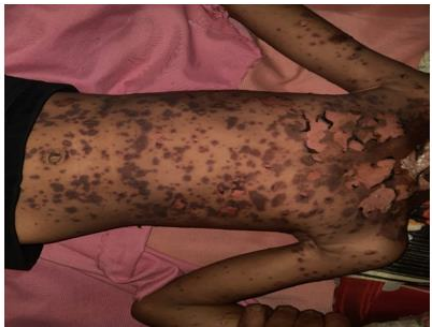

Fig. 1

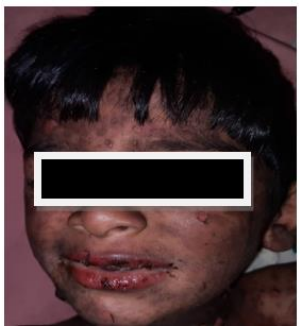

Fig. 2

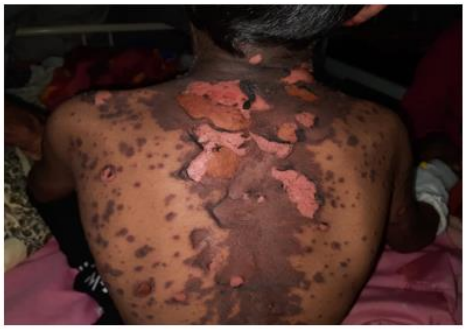

Fig. 3

Fig. 1-3: Initial presentation of patient on 03/Jan/2022

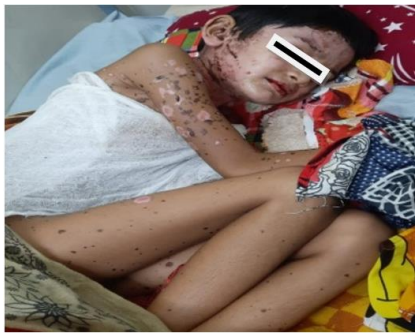

Fig. 4: Recovering stage [on 11/Jan/2022]: After treatment

CASE 2

This initial spontaneous case report was received on 03/Nov/2022 from the physician regarding a 5-month-old female patient who developed toxic epidermal necrolysis while on treatment with Syrup Paracetamol, Syrup Azithromycin, Syrup Simethicone, Syrup Fixed Drug Combination of [Ambroxol+Terbutaline+Guaifenesin] for Fever and Cough. No any past medical history or drug history found. On 01/Nov/2022, the patient was started on treatment with Syrup Paracetamol 120 mg, Syrup Azithromycin 100 mg, Syrup Simethicone 12 mg, Syrup FDC of [Ambroxol 15 mg+Terbutaline 1.25 mg+Guaifenesin 50 mg] twice a day. On 03/Nov/2022, the patient has developed peeling of skin started from face and ear, then involved rest of body and fluid filled lesion over legs. The patient was advised to stop the medication by the physician on 03/Nov/2022. On 03/Nov/2022, the patient was treated with IV Hydrocortisone, Ointment Clotrimazole and Framycetin and liquid Glycerin in response to the event of TEN. TEN was resolved on 16/Nov/2022. The dermatologist suspected that the adverse event toxic epidermal necrolysis was possibly related to the Syrup Paracetamol and Syrup Azithromycin as per WHO causality assessment scale. No additional information was available at the time of this report.

CASE 3

This initial spontaneous case report was received on 23/April/2022 from the physician regarding a 16 yold male patient who developed toxic epidermal necrolysis while on treatment with Tablet Paracetamol, Tablet Nimesulide, Tablet Cefpodoxime+Clavulinicacid. No any past medical history or drug history found. On 23/04/2022, the patient was started on treatment with Tab. Paracetamol 500 mg, Tab. Nimesulide 100 mg, Fixed Drug Combination of Tab. Cefpodoxime [100 mg]+Clavulanic acid[62.5 mg]for fever and upper respiratory tract infection. On 23/04/2022, the patient has developed multiple bilateral symmetrical vesicles and few target lesions seen over chest, back, abdomen, trunk and both extremities and also oral ulceration. The patient was advised to stop the medication by the physician on 24/04/2022. On 24/Apr/2022, the patient was treated with IV Hydrocortisone, Ointment Clotrimazole and Framycetin and liquid Glycerin in response to the event of TEN. Toxic epidermal necrolysis was resolved on 14/May/2022. The dermatologist suspected that the adverse event toxic epidermal necrolysis was possibly related to the Tablet Paracetamol, Tablet Nimesulideand tablet Cefpodoxime+Clavulinic acid as per WHO causality assessment scale. No additional information was available at the time of this report. As per shown in table 2 below, adverse drug reaction is analyzed for their causality, severity and preventability assessment using WHO and Naranjo causality assessment scale, Modified hartwig and seigle's severity assessment scale and Schumock and Thorton preventability scale.

Table 2: Adverse drug reaction analysis based on different assessment scales

	WHO causality assessment scale	Naranjo causality assessment Scale [16]	Modified hartwig and seigle's severity assessment Scale [17]	Schumock and thorton preventability scale [18]
Case 1	Possible	Possible	Level 5	Definitely preventable
Case 2	Possible	Possible	Level 5	Definitely preventable
Case 3	Possible	Possible	Level 5	Definitely preventable

DISCUSSION

TEN is a rare but serious skin condition that causes widespread blistering and detachment of the skin. It is usually associated with medications and has an incidence of 0.4 to 1.2 million patient-years globally, with mortality rates ranging from 30% to 50%. To be diagnosed with TEN, a patient must have skin detachment of more than 30% of their total body surface area (excluding the buttocks). Hypersensitivity reactions to medications are the most common cause of TEN mentioned below: Some drugs carry a high risk of inducing TEN, and their use should be carefully evaluated and suspected promptly if symptoms appear. These drugs include Allopurinol, Carbamazepine, Cotrimoxazole (and other anti-infective sulfonamides and sulfasalazine), lamotrigine, Nevirapine, Non-steroidal Anti-inflammatory Drugs (NSAIDs) (oxicam type; e. g., meloxicam, para-aminophenol derivative e. g., acetaminophen), Phenobarbital, and Phenytoin. Drugs with a moderate risk for inducing TEN include Cephalosporin, macrolides, quinolones, tetracycline, and NSAIDs of the acetic acid type (such as diclofenac). Drugs without increased risk for TEN:-B-blockers, Angiotensin

Converting Enzyme (ACE) inhibitors, Calcium channel blockers, Thiazide diuretics (with sulfonamide structure), Sulfonylurea Antidiabetics (with sulfonamide structure), Insulin, NSAIDs (propionic acid type; e. g., ibuprofen) etc. Apart from drugs, viral infections [cytomegalovirus, dengue] and mycoplasma pneumonia infection were also reported as potential causes [6-8]. Clinical manifestations of TEN: Initially, this disease may present as a fever, flu-like symptoms, and sore throat, making early diagnosis difficult. However, characteristic skin lesions typically appear next. These lesions are typically poorly defined and coalescing, with red macules that have purpuric or necrotic centers. The lesions may be accompanied by intense pain and erythema and typically begin on the face and thorax, spreading to other areas symmetrically while sparing the scalp, palms, and soles. As the disease progresses, vesicles and bullae may develop, and the skin may begin to slough. Two important clinical signs of TEN include the nikolsky sign, which is the dislodgement of intact superficial epidermis with gentle lateral pressure, indicating a cleavage plane at the dermo-epidermal junction, and the bulla spread sign, which is the lateral spread of bullae upon pressure application [4]. TEN can affect the mucous membranes in up to 90% of patients, resulting in erosions and crusts that can appear before or after skin lesions. The condition often affects the oral mucosa and vermilion border, causing painful haemorrhagic erosions with a greyish-white membrane. This can make it difficult for patients to open their mouth, leading to undernutrition and dehydration. Eye involvement is also common, occurring in 80% of cases and causing purulent conjunctivitis, corneal ulcers, anterior uveitis, or panophthalmitis. However, the eye manifestations usually recover completely. Females are more likely to experience urogenital lesions, such as vaginal ulcers and erosions, vulval bullae, or vaginal synechiae. The acute phase of TEN typically lasts for 8-12 days and is characterized by fever, epidermal sloughing, and large areas of denuded skin, mucosal erosions, and ulcers. This is usually followed by a phase of re-epithelialization and healing. Diagnosis of TEN is primarily based on clinical observation. Blood tests may reveal anaemia and lymphopenia, as well as reduced serum albumin, and elevated liver enzymes, urea, and creatinine, which can indicate impending multiorgan failure. Metabolic abnormalities such as dyselectrolytemia and elevated blood glucose levels are also common. Although serum markers such as soluble FasL, soluble Cluster of differentiation (CD)40L, High Mobility Group Box (HMGB)-1, granulysin, and Interleukin (IL)-15 have been studied, their usefulness in the diagnosis and management of TEN require further validation in larger studies [5, 13]. The patient in our case-1 exhibited similar symptoms, including widespread lesions and extensive detachment of the epidermis (more than 30%) as shown in the fig. number 1, 2, and 3. The timeline of events is detailed in the case report, and the suspected cause was determined to be Tab. Acetaminophen. Treatment at our hospital involved intravenous antibiotics (cephalosporin, vancomycin) and systemic steroids, with Tab. Acetaminophen being discontinued from the treatment regimen. Acetaminophen, also known as paracetamol, is commonly used in both prescription and over-the-counter medications to alleviate pain and reduce fever. It is available in single-ingredient and combination drug products. Acetaminophen may rarely cause serious skin reactions. Serious skin reactions can occur even if you have taken acetaminophen in the past without any problems. Acetaminophen is primarily metabolized in the liver through glucuronidation, sulfation, and a minor oxidation pathway. When acetaminophen is metabolized by Cytochrome P (CYP) isozymes, it produces a reactive metabolite called NAPQI [n-acetyl para-amino benzo quinone imine], which is detoxified by the glutathione pathway. At high doses, the sulfation pathway becomes saturated, leading to an increased amount of the drug being eliminated unchanged and oxidized to NAPQI. Excessive NAPQI can deplete GSH stores and cause protein adducts to form, primarily targeting mitochondrial proteins and ion channels, resulting in energy loss, ion misbalance, and cell death. Although toxic epidermal necrolysis is a rare adverse drug reaction caused by acetaminophen, it has been reported in 0.49% of cases. Meanwhile, the National Institute for Health and Care Excellence (NICE) guidelines for pediatric fever management do not recommend using antipyretic agents solely to reduce body temperature in children with fever [9-11, 15]. Despite ongoing investigation, the mechanism behind this reaction is not yet fully understood. Two main theories have been proposed: the pharmacologic interaction of the drug with the immune system (known as the p-i concept), and the pro-hapten concept. According to the pro-hapten concept, drugs are broken down into metabolites that bind to cellular peptides, creating an immunogenic molecule that can activate the immune system. On the other hand, the p-i concept suggests that a drug can stimulate the immune system by binding directly to the major histocompatibility complex (MHC) I and the T-cell receptor (TCR) without forming a covalent bond, like how the drug would bind to its intended target [5, 6, 11, 12]. The activation of T-cell mediated immunity and CD8+lymphocytes can result in the immune system targeting the body's own keratinocytes, leading to their apoptosis. CD8+cytotoxic T cells and natural killer (NK) cells are responsible for inducing this apoptosis. Additionally, CD4+ cells have been implicated in the development of apoptosis. Caproni and colleagues examined cellular infiltrate in skin samples from patients with toxic epidermal necrolysis and found a strong presence of cells staining for CD40 ligand (CD40L) in the dermis, with some of these CD40L cells infiltrating the epidermis. CD40L is a molecule expressed on the surface of activated CD4+cells and is an important co-stimulator of macrophages, dendritic cells, B cells, and epithelial cells, leading to the release of cytokines such as tumor necrosis factor-alpha (TNF-α), nitric oxide (NO), interleukin 8 (IL-8), and cell adhesion molecules. Caproni and colleagues also noted elevated levels of soluble CD40L (sCD40L) in the sera of patients with TEN, suggesting that sCD40L could be used as a potential biomarker for TEN [12, 13]. Thus, despite the central role of CD8+cells, CD4+cells and cells of the innate immune system (CD3, CD56+, NK cells, dendritic cells, mast cells, CD14, CD16, monocytes, granulocytes) also play a role in TEN. Research suggests that granulysin plays a major role in inducing keratinocyte apoptosis in TEN. Granulysin is a component of cytotoxic granules found in CD8+, NK, and NK/T cells and is involved in killing tumor cells and bacteria. Upon activation of NK cells, granulysin is released and can cause ionic instability and mitochondrial damage in target cells, leading to apoptosis. Another important molecule involved in inducing apoptosis is FasL. FasL is a transmembrane protein from the TNF family that is expressed on the surface of cytotoxic T cells, NK cells, immune-privileged cells, and keratinocytes. When cytotoxic T cells are activated, FasL is expressed on their surface and binds to its receptor on target cells, activating intracellular caspases and leading to the destruction of the target cell. FasL can also be cleaved from the cell membrane, producing a soluble form that can still bind to the Fas receptor and trigger apoptosis. The Fas-FasL pathway has been shown to be important in the development of TEN [5, 13].

The cases highlight the importance of being aware of the potential for severe hypersensitivity reactions to occur with acetaminophen, even though it is generally considered to be a safe drug when used appropriately. Clinicians need to carefully consider a patient's medical history and any previous adverse reactions before prescribing acetaminophen or any other medication. Patient education is also important in helping to prevent adverse reactions, as patients need to be aware of the risks associated with taking medication and the importance of seeking medical attention if they experience any unusual symptoms or reactions.

CONCLUSION

Toxic epidermal necrolysis, a life-threatening condition typically caused by drugs, may also be triggered by over-the-counter medication like acetaminophen, as seen in these cases. It is crucial for clinicians to remain vigilant about hypersensitivity reactions and to prioritize supportive care in treatment. Corticosteroids and antibiotics are often used as therapy, but a risk assessment must be conducted to prevent further tissue damage. Drug-induced activation of CD8+cells, FasL, granulysin, and other immune components play a significant role in the development of TEN. Further research into these molecules may lead to new treatment and prognostic options, ultimately reducing the morbidity and mortality associated with this condition.

ACKNOWLEDGEMENT

We are thankful to IPC-Pharmacovigilance program of India.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

DECLARATION OF PATIENT CONSENT

The authors certify that they have obtained all appropriate patient consents. The patient's guardians had given their consent for their child's images and other clinical information to be reported in the journal. They understand that their names and initials will not be published and due efforts will be made to conceal their identity.

AUTHORS CONTRIBUTIONS

Patient information, consent and other case details were collected from hospital by Mr. Dharmesh and Dr. Pratik. Data analysis and interpretation, manuscript writing and other adhoc work was completed by Dr. Pratik and Dr. Anil.

CONFLICT OF INTERESTS

The Author(s) declares that there is no conflict of interest.

REFERENCES

1. Kasper DL, Fauci AS, Hauser SL, longo DL, Jameson JL, loscalzo J. Harrison's principles of internal medicine. 19th ed. New York: McGraw-Hill Education; 2016.
2. Pereira FA, Mudgil AV, Rosmarin DM. Toxic epidermal necrolysis. J Am Acad Dermatol. 2007 Feb;56(2):181-200. doi: 10.1016/j.jaad.2006.04.048, PMID 17224365.
3. Mockenhaupt M. The current understanding of Stevens-Johnson syndrome and toxic epidermal necrolysis. Expert Rev Clin Immunol. 2011;7(6):803-14. doi: 10.1586/eci.11.66, PMID 22014021.
4. Parida JR, Tripathy SR. Stevens-Johnson syndrome/toxic epidermal necrolysis spectrum for the rheumatologist. Indian J Rheumatol. 2019;14(5):67. doi: 10.4103/0973-3698.272155.
5. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: Part I. Introduction, history, classification, clinical features, systemic manifestations, etiology, and immunopathogenesis. J Am Acad Dermatol. 2013;69(2):173.e1-13. doi: 10.1016/j.jaad.2013.05.003, PMID 23866878.
6. Bygum A, Gregersen JW, Buus SK. Acetaminophen-induced toxic epidermal necrolysis in a child. Pediatr Dermatol. 2004 May-Jun;21(3):236-8. doi: 10.1111/j.0736-8046.2004.21309.x, PMID 15165202.
7. lonjou C, Borot N, Sekula P, Ledger N, Thomas L, Halevy S. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. Pharmacogenet Genomics. 2008;18(2):99-107. doi: 10.1097/FPC.0b013e3282f3ef9c, PMID 18192896.
8. George N, Johnson P, Thomas J, Mariya A. Drug induced-Stevens Johnson syndrome: a case report. JPPCM. 2016;2(4):144-5. doi: 10.5530/jppcm.2016.4.7.
9. Halevi A, Ben Amitai D, Garty BZ. Toxic epidermal necrolysis associated with acetaminophen ingestion. Ann Pharmacother. 2000 Jan;34(1):32-4. doi: 10.1345/aph.19064, PMID 10669183.
10. Watanabe H, Kamiyama T, Sasaki S, Kobayashi K, Fukuda K, Miyake Y. Toxic epidermal necrolysis caused by acetaminophen featuring almost 100% skin detachment: acetaminophen is associated with a risk of severe cutaneous adverse reactions. J Dermatol. 2016 Mar;43(3):321-4. doi: 10.1111/1346-8138.13073, PMID 26362011.
11. Labib A, Milroy C. Toxic epidermal necrolysis. In: Treasure Island, (FL): StatPearls Publishing; 2023 May 8. p. 2024. PMID 34662044.
12. Paul C, Wolkenstein P, Adle H, Wechsler J, Garchon HJ, Revuz J. Apoptosis as a mechanism of keratinocyte death in toxic epidermal necrolysis. Br J Dermatol. 1996 Apr;134(4):710-4. doi: 10.1111/j.1365-2133.1996.tb06976.x, PMID 8733377.
13. Caproni M, Torchia D, Schincaglia E, Volpi W, Frezzolini A, Schena D. The CD40/CD40 ligand system is expressed in the cutaneous lesions of erythema multiforme and Stevens-Johnson syndrome/toxic epidermal necrolysis spectrum. Br J Dermatol. 2006;154(2):319-24. doi: 10.1111/j.1365-2133.2005.07023.x, PMID 16433803.
14. Recommendations. Fever in under 5s: assessment and initial management | Guidance | NICE. Available from: https://www.nice.org.uk/guidance/ng143/chapter/recommendations.
15. Hodgman MJ, Garrard AR. A review of acetaminophen poisoning. Crit Care Clin. 2012;28(4):499-516. doi: 10.1016/j.ccc.2012.07.006, PMID 22998987.
16. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-45. doi: 10.1038/clpt.1981.154, PMID 7249508.
17. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm. 1992;49(9):2229-32. doi: 10.1093/ajhp/49.9.2229, PMID 1524068.
18. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hosp Pharm. 1992 Jun 1;27(6):538. PMID 10118597.