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Case Study

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Stevens–Johnson Syndrome/Toxic Epidermal Necrolysis Associated with Paracetamol in a Patient with Diabetes Mellitus

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Abstract: Paracetamol is an over-the-counter medication widely used for the management of fever and pain, resulting in a continuous increase in its consumption. Although generally considered safe and well tolerated, paracetamol may, in rare cases, cause severe and life-threatening adverse reactions, including Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). SJS/TEN is a severe drug reaction associated with high morbidity and mortality. We report a case of paracetamol-induced SJS/TEN in a patient with diabetes mellitus. The diagnosis was established based on clinical manifestations and a history of drug exposure. The patient was managed with supportive and pharmacological therapy under close monitoring, including careful glycemic control. This case report highlights the importance of vigilance for severe adverse drug reactions, even when commonly perceived safe medications are used.

Keywords: Steven Johnson Syndrome; Toxic Epidermal Necrolysis; Diabetes Mellitus; Paracetamol.

INTRODUCTION

Paracetamol is the active metabolite of phenacetin that lacks carcinogenic properties and has long been used as an analgesic and antipyretic agent.[1] Paracetamol, also known as acetaminophen, is among the most widely used over-the-counter medications for the management of mild to moderate pain and fever.[2,3] The exact mechanism of action of paracetamol has not been fully elucidated; however, it is thought to act primarily within the central nervous system by reducing prostaglandin levels and other proinflammatory mediators.[1]

Paracetamol exhibits high bioavailability, with peak plasma concentrations achieved within 30–60 minutes following oral administration and an elimination half-life of approximately 120 minutes. It is primarily eliminated via the kidneys in the form of glucuronide and sulfate conjugates excreted in the urine. A small proportion of paracetamol undergoes metabolism by cytochrome P450 enzymes, mainly CYP2E1 and CYP1A2, producing the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI), which is toxic if not promptly detoxified.[1,4]

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In recent years, the sales and consumption of paracetamol have continued to increase and are expected to rise further due to its widespread availability and perceived safety.[2] Although paracetamol is generally considered safe and well tolerated, its use is not without potential adverse effects. Common adverse effects include mild cutaneous reactions and hepatic dysfunction, whereas rare but serious adverse effects include severe cutaneous adverse reactions (SCARs).[5] Severe hypersensitivity reactions such as anaphylaxis, as well as life-threatening cutaneous reactions including Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have also been reported, albeit with a low incidence.[6]

The incidence of SJS–TEN is estimated to range from 2 to 7 cases per million population per year. Analgesics (32.86%), antibiotics (20.14%), and antiepileptic drugs (15.5%) are the most commonly implicated medications associated with SJS–TEN.[7] A study conducted at Dr. Moewardi General Hospital in 2019 reported that paracetamol was the most frequent causative agent of SJS–TEN, accounting for 25.71% of cases.[8] SJS–TEN is an acute mucocutaneous reaction characterized by extensive epidermal necrosis and detachment of the epidermis from the epithelial mucosa, which may be life-threatening. [9]

The pathophysiology of SJS–TEN has not been fully elucidated. However, it is believed to represent an immunologically mediated reaction to more than 100 different drugs, with symptom onset typically occurring within 4–28 days after exposure to the offending agent. Proposed mechanisms include massive keratinocyte apoptosis resulting from cytotoxic reactions mediated by immune cells such as natural killer (NK) cells, $CD8^+$ lymphocytes, monocytes, macrophages, and granulocytes.[9] Another hypothesis suggests impaired drug metabolism, such as slow acetylation, leading to the accumulation of toxic metabolites that subsequently trigger a secondary immune response.[10]

A literature review by Milosavljević et al. in 2021 reported 36 cases of SJS–TEN associated with acetaminophen use, involving patients aged 3–70 years, affecting both males and females, with or without a prior history of drug allergy.[11] Clinically, SJS–TEN typically begins with painful and burning skin lesions, most commonly originating on the face, upper extremities, central body regions, and proximal lower limbs.[9] Management of SJS–TEN includes immediate discontinuation of the suspected causative drug, which has been shown to reduce mortality by up to 21%, along with supportive therapy such as intravenous fluid administration, ocular and mucosal care, wound management, and condition-specific adjunctive therapies.[7,12]

Diabetes mellitus is a chronic metabolic disorder that may impair immune responses, delay wound healing, and increase susceptibility to infections. In patients with severe drug reactions such as Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), the presence of diabetes mellitus as a comorbidity may worsen clinical outcomes and pose additional challenges in management, particularly with regard to systemic corticosteroid use and glycemic control.[9,13,14]

Although the association between paracetamol and SJS–TEN has been previously reported, this case is presented to emphasize that paracetamol, despite being a commonly used and easily accessible medication in Indonesia, still carries the potential to induce severe and life-threatening adverse drug reactions. Therefore, heightened clinical awareness of serious adverse effects remains essential. In this case, SJS–TEN developed after the patient had taken paracetamol at a standard dose for three consecutive days to relieve nonspecific malaise.

CASE REPORT

A 60-year-old woman (body weight: 70 kg) presented to the Emergency Department at 21:42 with complaints of nausea, vomiting, pain, lip swelling accompanied by mucocutaneous lesions, and erosive lesions involving the entire facial area. The patient reported the onset of cutaneous lesions following paracetamol ingestion. There was no history of other medication use prior to symptom onset. She had a known history of diabetes mellitus but was not receiving regular treatment. The patient had been taking paracetamol for three consecutive days at a standard dose of 500 mg three times daily. On the first day, the patient initially experienced pruritus. On the second day, the pruritic area expanded, and skin lesions began to appear. By the third day, the skin exhibited a burning sensation, and the lesions had further worsened

On initial evaluation, the patient was in fair general condition and fully conscious (Glasgow Coma Scale score: E4V5M6). Vital signs revealed a blood pressure of 130/60 mmHg, heart rate of 70 beats per minute, respiratory rate of 20 breaths per minute, body temperature of 36.2°C, and a random blood glucose level of 253 mg/dL.

Day 2: vital signs were as follows: blood pressure 130/80 mmHg, heart rate 88 beats per minute, respiratory rate 20 breaths per minute, body temperature 36.5°C, and random blood glucose level 295 mg/dL.

Day 3: vital signs remained stable (blood pressure 130/80 mmHg, heart rate 88 beats per minute, respiratory rate 20 breaths per minute, body temperature 36.5°C, random blood glucose level 295 mg/dL). Later that day, the patient's blood pressure decreased to 110/70 mmHg, with a heart rate of 92 beats per minute, body temperature of 36.2°C, and random blood glucose level of 202 mg/dL.

Day 4: vital signs showed a blood pressure of 110/80 mmHg, heart rate of 88 beats per minute, respiratory rate of 20 breaths per minute, body temperature of 36.3°C, and a random blood glucose level of 209 mg/dL. Cutaneous lesions had markedly improved over most body areas; however, moist erosive lesions persisted on the lips, and the patient reported ocular pruritus. The patient was deemed clinically stable and prepared for discharge.

Laboratory investigations revealed the following: hemoglobin (Hb) 14.3 g/dL, white blood cell count (WBC) 4.96 x 10^3/µL, platelets (PLT): 284 x 10^3/µL, calcium (Ca) 8.6 mg/dL, creatinine 0.61 mg/dL, sodium (Na) 141 mmol/L, potassium (K) 4.0 mmol/L, chloride (Cl): 102 mmol/L, urea: 33.10 mg/dL, and HbA1c 7.7% The patient was subsequently admitted to the inpatient ward for further management.

Treatment consisted of intravenous 0.9% sodium chloride at a rate of 20 drops per minute, intravenous methylprednisolone 250 mg, oral cetirizine 10 mg once daily, tobramycin ophthalmic drops administered four times daily (one drop per application), oral metformin 500 mg three times daily, and subcutaneous insulin aspart 6 IU three times daily. The methylprednisolone dose was gradually tapered to 31.25 mg. Local wound care included cleansing with normal saline twice daily, followed by topical application of mometasone and gentamicin ointments to the affected areas.

By hospital day 4, the patient's clinical condition had significantly improved, and she was discharged with instructions for routine follow-up and continued wound care, including 0.9% sodium chloride compresses applied to the lips and affected skin for 3–15 minutes, topical desoximetasone ointment twice daily, tobramycin ophthalmic drops four times daily (one drop per application), oral metformin 500 mg three times daily, and subcutaneous insulin aspart 6 IU three times daily.

Approximately two weeks later, the patient returned for follow-up at thedermatology outpatient clinic. Vital signs were stable, with a blood pressure of 110/80 mmHg, heart rate of 80 beats per minute, respiratory rate of 18 breaths per minute, and body temperature of 36°C. The patient complained of persistent pain

in the lip lesions. On clinical examination, the cutaneous lesions had dried; however, erosions on the lips persisted and had not fully resolved. The patient was diagnosed with erythematous erosions of the lips and hemorrhagic crusts of the bilateral conjunctiva (oculi dextri et sinistri), and candidal stomatitis. At this visit, treatment included topical mometasone ointment applied twice daily, a single oral dose of fluconazole 150 mg, and oral nystatin drops administered four times daily. Diabetes therapy continued because blood sugar is already controlled (≤180mg/dL)

RESULTS AND DISCUSSION

Paracetamol was introduced in pharmacological market in 1955 as analgesic and antipyretic by McNeil Laboratories.[3] The oral dose of paracetamol is 0,5 g – 1 g every 4 – 6 hours, maximum 4g per day.[5] Dermatological effects of using paracetamol is erythema, peripheral oedema, flushing, pruritus, and purpura fulminans.[15] Hipersensitivyty of paracetamol is rare, manifestation of this hipersensitivity is erythema multiforme-SJS.[16]

The 60-year-old woman reported no previous history of drug allergy. Due to nonspecific malaise, she sought medical care and was prescribed paracetamol tablets by a healthcare professional. After repeated administration, the patient developed generalized pruritus, erythematous skin lesions, severe odynophagia, and abdominal pain. She had consumed paracetamol for three consecutive days at a standard therapeutic dose of 500 mg three times daily. No history of exposure to other medications known to be associated with a high risk of SJS–TEN was identified; therefore, paracetamol was considered the most likely causative agent in this case.

Prognostic evaluation in SJS–TEN can be assessed using the SCORTEN scoring system, which includes age >40 years, heart rate >120 beats/min, presence of malignancy, body surface area involvement >10%, serum urea >28 mg/dL, serum bicarbonate <20 mEq/L, and serum glucose >252 mg/dL, with each criterion assigned one point.[9] In this case, complete SCORTEN calculation was limited by incomplete laboratory data. However, based on the available parameters, the estimated SCORTEN score was 4, corresponding to a predicted mortality rate of 58.3%.[9] Despite this high theoretical risk, the patient demonstrated significant clinical improvement following early diagnosis and prompt supportive management.

The causal relationship between paracetamol exposure and the occurrence of SJS–TEN was further evaluated using the Naranjo Adverse Drug Reaction Probability Scale, which consists of ten structured questions to assess the likelihood of an adverse drug reaction.[17] An adverse drug reaction is defined as a harmful and unintended response to a medication administered at standard doses.[18,19] A total score greater than 9 indicates a definite adverse drug reaction, a score of 5–8 suggests a probable reaction, and a score of 1–4 indicates a possible reaction. [17] A total score of 5–8 indicates a probable relationship. In this case, the Naranjo score was 6, supporting paracetamol as a probable cause of SJS–TEN. This finding reinforces that paracetamol, although widely perceived as safe, can induce rare but potentially life-threatening adverse reactions.

The WHO-UMC (World Health Organization – Uppsala Monitoring Centre) causality assessment system is a combined assessment that takes into account the clinical-pharmacological aspects of the case history and the quality of documentation of the observations.[20] According to the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) causality assessment system, the present case was classified as probable. This classification was supported by the following observations: (1) the patient's symptoms began on the first day after paracetamol administration, establishing a reasonable temporal relationship between drug intake and the onset of Stevens-Johnson syndrome (SJS-TEN); (2) there were no alternative causes identified that could plausibly explain the

development of SJS-TEN, as the patient had only taken paracetamol for fever and was not exposed to other medications or known precipitants; and (3) after discontinuation of paracetamol, the patient's clinical manifestations gradually improved in conjunction with appropriate management according to standard therapeutic protocols.

The pathogenesis of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) is not fully understood. In cases of SJS-TEN, skin biopsy results often show deposits of IgM, IgA, and fibrin, as well as circulating immune complexes. These immune complexes can deposit in the skin and mucosa, leading to tissue damage through complement activation and inflammatory reactions. Drug metabolites may act as toxins, becoming haptens that interact with body tissues and transform into antigens. The presentation of these antigens results in the production of tumor necrosis factor-alpha (TNF-alpha) by dendritic cells in the epidermis, leading to the proliferation of T lymphocytes. Activated cytotoxic T lymphocytes (CD8) then induce apoptosis in epidermal cells. Epidermal cell apoptosis can occur through three main pathways is Fas-FasL Interaction: Interaction of membrane proteins (Fas and Fas Ligand) induces apoptosis through the intracellular caspase activation pathway. Perforin/Granzyme B Pathway: Perforin and Granzyme B contribute to keratinocyte apoptosis. This molecule binds to the cell membrane and disrupts it, leading to cell death. [21] Additionally, research by Ueta et al. has identified a significant association between HLA-A02:06 and HLA-B44:03 and the occurrence of SJS-TEN in patients who previously used paracetamol, compared to healthy controls. [22]

Similar cases have been reported in the literature. Paracetamol-induced SJS–TEN have been reported in India, including a 69-year-old woman who developed erythema, macular lesions, and ocular involvement after taking paracetamol 500 mg for fever.[23] In Korea, a 60-year-old woman with a history of hypertension and diabetes mellitus consumed paracetamol for three days and subsequently developed generalized erythema. She was admitted to the hospital on day seven and experienced clinical deterioration by day fourteen, with extensive exfoliation, multiple bullae, and oral mucositis, necessitating referral to a tertiary care center.[16] In Italy, a 52-year-old woman without comorbidities consumed 1–6 paracetamol tablets daily for two weeks due to headache and subsequently developed maculopapular eruptions on the chest and neck, elevated liver transaminases, and histopathological evidence of keratinocyte necrosis.[24]

Management of SJS–TEN should be conducted under the direct supervision of a dermatologist, preferably in a private care setting, with a recommended nurse-to-patient ratio of 1:1. Patients with SJS–TEN require careful fluid and electrolyte management, including potassium, sodium, and chloride supplementation, as approximately 20% of patients develop electrolyte imbalances due to extensive skin loss and reduced oral intake.[25] In the present case, crystalloid fluid therapy with 0.9% sodium chloride at a rate of 20 drops per minute was administered

Systemic corticosteroids are commonly used in the management of SJS–TEN due to their anti-inflammatory effects in hypersensitivity reactions; however, their use remains controversial. Corticosteroid therapy may increase the risk of infection, although other studies have reported clinical improvement with corticosteroid administration.[26] In this patient, intravenous methylprednisolone 250 mg was administered in the Emergency Department, resulting in clinical improvement, with reduced erythema and burning sensation.

The patient's history of diabetes mellitus represented an additional risk factor, as diabetes has been associated with increased mortality in patients with SJS–TEN. Blood glucose levels in SJS–TEN patients should be closely monitored and maintained between 110 and 180 mg/dL.[25] In this case, the patient's HbA1c level was elevated at 7.7%, and the initial random blood glucose level on admission was 253 mg/dL. Consequently, combination therapy for diabetes

mellitus was initiated using oral metformin 500 mg three times daily and subcutaneous insulin aspart 6 IU three times daily, with a target blood glucose level of ≤180 mg/dL.

Diabetes mellitus is a frequent comorbidity in patients with SJS[27]. It is a metabolic disorder associated with immune dysregulation and chronic low-grade inflammation, potentially contributing to the development and severity of Stevens–Johnson syndrome.[28] Cytotoxic T lymphocytes and proinflammatory cytokines play crucial roles in the pathogenesis of both conditions. Early diagnosis and prompt, appropriate management are essential to achieving favorable clinical outcomes and prognosis.[27,29] Elevated glucose concentrations have been shown to upregulate the expression of pro-inflammatory and pro-allergic cytokines, increase the secretion of tumor necrosis factor-alpha (TNF-α), and enhance both intracellular and extracellular β-hexosaminidase activity in human mast cells.[30]

SJS patients with diabetes have a higher mortality rate (4.3%) compared to SJS patients without comorbidities.[31] Compared to other comorbidities in SJS/TEN patients, diabetes has the highest mortality rate (14.3%), followed by pneumonia (7.6%) and sepsis (4.7%). Compared to the obesity group, diabetes has a higher mortality rate (11.6%). Compared to tobacco use, diabetes has a higher mortality rate (12.4%).[32] Therefore, blood sugar in SJS/TEN patients must be controlled as well as possible to prevent the prognosis from worsening.

Although analgesics such as paracetamol or opioid analgesics may be used for pain management in SJS–TEN, the primary management strategy in cases of drug-induced hypersensitivity is strict avoidance of the suspected causative agent[26,33] Given the patient's history of analgesic-induced reaction, no additional analgesic therapy was administered in this case.

One month after being hospitalized, the patient followed up with a dermatologist in the dermatology clinic. The condition: Blood pressure 110/80, pulse 80bpm, temperature 36°C, respiration rate 18 bpm. The patient's skin condition has improved, but the lips have not yet healed.

This case highlights that although paracetamol is a widely used and easily accessible analgesic, it may still precipitate severe adverse drug reactions such as SJS–TEN. Elevated glucose concentrations have been shown to upregulate the expression of pro-inflammatory and pro-allergic cytokines, increase the secretion of tumor necrosis factor-alpha (TNF-α), and enhance both intracellular and extracellular β-hexosaminidase activity in human mast cells.[30] Therefore, heightened clinical vigilance for early signs of severe cutaneous adverse reactions following paracetamol use is essential, particularly in elderly patients and those with comorbid conditions, to enable early diagnosis and optimal management.

CONCLUSION

Paracetamol, although widely regarded as safe, can rarely cause life-threatening reactions such as SJS–TEN. In this case, temporal association, causality assessment (Naranjo and WHO-UMC), and clinical improvement after drug withdrawal supported paracetamol as the probable trigger. Despite a high predicted mortality based on SCORTEN, early diagnosis, prompt discontinuation of the drug, intensive supportive care, and glycemic control resulted in a favorable outcome. Clinicians should remain vigilant for severe cutaneous adverse reactions, particularly in elderly patients and those with comorbidities such as diabetes mellitus.

AUTHORS' CONTRIBUTIONS

Nidya Tri Fitria Febriola took research data and wrote this journal. Sekar Puspita Lilasari as a dermatologist. Binti Muzayyanah, Jainuri Erik Pratama, Fauna Herawati, Adji Prayitno Setiadi and Marisca Evalina Gondokesumo reviewed and supervised the journal. All authors have read and approved the final journal.

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