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Comprehensive Review of Carbamazepine-Induced Adverse Effects: Clinical Spectrum and Therapeutic Implications

Ms. Rinsana Fathima[1], Dr. Neethu J[2], Dr. Lal Prasanth M.L[3]

[1]5th year pharm D, Pharmacy Practice, Dr. Moopen's College of Pharmacy
[2]Professor, Pharmacy Practice, Dr. Moopen's College of Pharmacy
[3]Principal, Pharmacy Practice, Dr. Moopen's College of Pharmacy

Abstract
Carbamazepine (CBZ) is a widely prescribed antiepileptic and mood-stabilizing drug with proven efficacy in controlling seizures and bipolar disorder. However, CBZ use is often complicated by a diverse range of adverse effects affecting multiple organ systems. This review synthesizes evidence from recent clinical case series, meta-analyses, and mechanistic studies to provide a comprehensive understanding of CBZ-induced hyperammonemia, bone metabolism disruption, Sweet syndrome, thrombocytopenia, and hyponatremia. Recognizing and managing these adverse effects are critical for optimizing therapeutic outcomes and improving patient safety. This paper highlights clinical manifestations, proposed mechanisms, diagnostic considerations, and management strategies for CBZ-induced complications.

Keywords: Carbamazepine; Hyperammonemia; Asterixis; Bone Health; Vitamin D Deficiency; Sweet Syndrome; Thrombocytopenia; Platelet Apoptosis; Hyponatremia; Epilepsy; Adverse Effects.

Introduction

Carbamazepine (CBZ) has long been established as an effective agent for epilepsy, trigeminal neuralgia, and mood disorders. Despite its widespread use, CBZ's side effect profile is extensive and clinically significant, often requiring careful monitoring. The adverse effects can involve metabolic, hematological, dermatological, neurological, and electrolyte abnormalities. Hyperammonemia with neurological signs like asterixis, vitamin D metabolism disturbances leading to bone health deterioration, rare dermatological manifestations such as Sweet syndrome, hematological side effects like thrombocytopenia, and hyponatremia are among the most concerning adverse effects linked to CBZ.
This review aims to provide an integrated and detailed examination of these complications, utilizing data from clinical case series, meta-analyses, and experimental studies. Better understanding of these adverse effects will inform clinical practice in terms of surveillance, early detection, and appropriate interventions, improving the risk-benefit ratio of CBZ therapy.

Body

1. Carbamazepine-Induced Hyperammonemia and Asterixis

Kulkarni et al. presented a case series describing young adults on CBZ who developed elevated serum

ammonia levels (hyperammonemia) accompanied by asterixis, a clinical sign indicating metabolic encephalopathy. Hyperammonemia, often overlooked in CBZ-treated patients, may contribute to cognitive decline, confusion, and other neurological impairments. The pathogenesis likely involves interference with the urea cycle or mitochondrial metabolism, resulting in toxic ammonia accumulation. Clinicians should suspect hyperammonemia in patients with unexplained neurological symptoms on CBZ and measure serum ammonia accordingly. Prompt discontinuation or dose adjustment of CBZ often leads to symptom resolution.

2. Impact of Carbamazepine on Bone Health

Several meta-analyses and systematic reviews have highlighted that CBZ adversely affects bone metabolism. Zhang et al. demonstrated significantly reduced serum 25-hydroxyvitamin D and calcium levels in CBZ-treated patients, along with elevated alkaline phosphatase, a marker of increased bone turnover. Chronic CBZ therapy induces hepatic enzyme cytochrome P450, accelerating vitamin D catabolism and impairing calcium absorption. This can lead to osteomalacia, decreased bone mineral density, and increased fracture risk. Clinicians managing patients on long-term CBZ should monitor vitamin D and calcium levels and consider supplementation or alternative therapies.

3. Carbamazepine-Induced Sweet Syndrome

Sweet syndrome, or acute febrile neutrophilic dermatosis, is a rare but serious dermatological adverse reaction to CBZ. Gomes et al. reported cases of Sweet syndrome triggered by CBZ, characterized by painful erythematous plaques accompanied by fever and neutrophilia. The exact immunopathology remains unclear but likely involves a hypersensitivity reaction. Recognition of drug-induced Sweet syndrome is essential to avoid misdiagnosis and inappropriate treatment. Discontinuing CBZ and initiating corticosteroids typically leads to clinical improvement.

4. Thrombocytopenia through Platelet Apoptosis

Xiao et al. explored the mechanisms underlying CBZ-induced thrombocytopenia. Their study revealed that CBZ activates protein kinase A pathways, inducing platelet apoptosis and leading to decreased platelet counts. Thrombocytopenia poses risks of bleeding and complicates management. Regular hematological monitoring is advised for patients on CBZ, particularly in the early months of treatment or when symptoms such as easy bruising or bleeding appear.

5. Hyponatremia and Electrolyte Imbalances

Hyponatremia is a well-documented side effect of CBZ and its analog oxcarbazepine, especially in epilepsy patients. Berghuis et al. provided a systematic review indicating that CBZ-induced hyponatremia results from inappropriate antidiuretic hormone secretion or renal tubular effects, leading to water retention and sodium dilution. Symptoms range from mild fatigue and nausea to seizures in severe cases. Clinicians should routinely check serum sodium levels during CBZ therapy, especially in elderly patients or those on concomitant diuretics.

6. Stevens–Johnson syndrome

Stevens–Johnson syndrome (SJS) is a rare but potentially life-threatening mucocutaneous adverse drug reaction characterized by extensive epidermal necrosis, skin detachment, and involvement of mucosal surfaces. Lerch et al. described SJS and toxic epidermal necrolysis (TEN) as severe cutaneous adverse reactions occurring on a spectrum, with the extent of epidermal detachment being an important factor in classification and prognosis. Drugs are considered the most common triggers of SJS, with anticonvulsants such as carbamazepine, phenytoin, phenobarbital and lamotrigine, along with allopurinol, sulfonamide antibiotics and certain non-steroidal anti-inflammatory drugs, being frequently

implicated. Harr and French reported that the condition is associated with an immune-mediated process involving cytotoxic T lymphocytes and extensive keratinocyte apoptosis, ultimately resulting in epidermal necrosis and detachment.Clinical manifestations generally begin with nonspecific symptoms such as fever, malaise and flu-like symptoms, followed by painful erythematous or dusky macules, blister formation and epidermal detachment. Mucosal involvement is particularly characteristic and may affect the oral, ocular and genital mucosa. Mockenhaupt emphasized the importance of early recognition and identification of the responsible medication because prompt withdrawal of the offending drug is a critical component of management. Management primarily involves immediate discontinuation of the suspected causative drug and intensive supportive care, including fluid and electrolyte management, nutritional support, wound care, pain control and prevention of complications. Ophthalmological evaluation is particularly important in patients with ocular involvement because SJS can result in severe and permanent ocular complications.Overall, the literature indicates that early diagnosis, prompt withdrawal of the causative drug, appropriate supportive treatment and prevention of re-exposure are essential for reducing morbidity and mortality associated with Stevens–Johnson syndrome.

Significance

This review underscores the multifaceted nature of CBZ adverse effects. Given the drug's extensive use, awareness of these complications is paramount to minimize morbidity. The adverse effects can significantly impact patient quality of life and complicate disease management, necessitating interdisciplinary collaboration among neurologists, dermatologists, hematologists, and primary care providers. Early recognition, monitoring protocols, and timely interventions are critical to improving patient outcomes.

Conclusion

Carbamazepine remains a valuable therapeutic agent for epilepsy and other neurological disorders. However, its potential to induce hyperammonemia, bone metabolism disturbances, Sweet syndrome, thrombocytopenia, and hyponatremia demands vigilance. Regular clinical and laboratory monitoring, patient education, and individualized risk assessment are essential components of care. Future research should focus on elucidating mechanisms of toxicity and developing preventive strategies to enhance the safety profile of CBZ therapy.

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