Carbamazepine

Side Effects

Gastrointestinal

Very common (10% or more): Nausea (29%), vomiting (18%), constipation (10%) Very rare (less than 0.01%): Colitis, glossitis, stomatitis, pancreatitis Frequency not reported: Dryness of the mouth, with suppositories occasional rectal irritation may occur, diarrhea, oral ulceration Postmarketing reports: Gastric distress, abdominal pain, anorexia A single case of chemical pancreatitis has been reported in association with carbamazepine intoxication.

Endocrine

Carbamazepine increases the rate of T4 and T3 metabolism and may lead to hypothyroidism in patients with hypothyroidism who are being treated with T4. Carbamazepine may also cause a 20% to 40% decrease in serum total and free T4 concentrations and a smaller decrease in serum total and free T3 concentrations in patients who have no thyroid disease.

Chronic administration of carbamazepine may increase total cholesterol and HDL cholesterol levels. Carbamazepine may also transiently increase serum triglyceride and LDL cholesterol levels. One study has suggested that demeclocycline may be useful in prophylaxis of carbamazepine-induced hyponatremia.

Very rare (less than 0.01%): Increase in prolactin (with or without symptoms such as gynecomastia or galactorrhea), impaired male fertility and/or abnormal spermatogenesis, abnormal thyroid function tests (e.g., decreased L-thyroxine [FT4, T4, T3] and increased TSH) Frequency not reported: Hyponatremia, pancreatitis, lower serum testosterone, lower free androgen indexes, increased cerebrospinal fluid thyrotropin-releasing hormone levels

Hematologic

Very common (10% or more): Leucopenia Common (1% to 10%): Eosinophilia, thrombocytopenia, neutropenia Rare (0.01% to 0.1%): Leukocytosis, lymphadenopathy, folic acid deficiency Very rare (less than 0.01%): Agranulocytosis, aplastic anemia, pure red cell aplasia, megaloblastic anemia, acute intermittent porphyria, reticulocytosis, hemolytic anemia Frequency not reported: Aplastic anemia, pancytopenia, bone marrow depression, leukopenia, thrombophlebitis, thromboembolism, adenopathy

Thrombocytopenia is the most common hematologic effect of carbamazepine and may be either mild and transient or severe. Significant decreases in white blood cell counts may

occur although the values may still be within the normal range. Often counts will return to baseline during continued therapy, and therefore, discontinuation of carbamazepine may not be necessary. Dose reductions may also result in normalization of white blood cell counts. Aplastic anemia has been reported (although many of the reported cases had confounding exposures to other medications). The manufacturer reports an incidence of 2 per 1,000,000 patients for aplastic anemia and 6 per 1,000,000 patients for agranulocytosis. Cases of reticulocytosis have been reported rarely in association with carbamazepine therapy as well. In addition, cases of hemolytic anemia and erythroid arrest have been reported.

Both humoral and nonimmune mechanisms have been implicated in the etiology of carbamazepine-induced bone marrow suppression.

Cardiovascular

Rare (0.01% to 0.1%): Disturbances of cardiac conduction Very rare (less than 0.01%): Bradycardia, arrhythmias, AV-block with syncope, collapse, congestive heart failure, hypertension or hypotension, aggravation of coronary artery disease, thrombophlebitis, thromboembolism

Most of the cases of cardiovascular effects reported have occurred in patients receiving carbamazepine for trigeminal neuralgia. The reported effects included congestive heart failure, edema, hypotension, syncope and arrhythmias. In general, the doses were titrated quickly because of severe pain. Many of the doses were higher than those used to treat epilepsy. Many of the reported cardiovascular effects resolved after discontinuation of carbamazepine.

Increased sympathetic activity in the setting of seizure-induced hypoxia could predispose a patient to sudden unexpected death in epilepsy (SUDEP).

Nervous system

Very common (10% or more): Dizziness (44%), somnolence (32%), ataxia (15%) Common (1% to 10%): Headache, tremor, vertigo Uncommon (0.1% to 1%): Abnormal involuntary movements (tremor, asterixis, dystonia, tics) Rare (less than 0.1%): Choreoathetotic disorders, orofacial dyskinesia, oculomotor disturbances, speech disorders (e.g., dysarthria or slurred speech), peripheral neuritis, paresthesia, paretic symptoms, neuroleptic malignant syndrome Frequency not reported: Drowsiness, fatigue, fever and chills[Ref]

Rigidity and oculogyric crises have been reported. Euphoria has also been reported and has led to abuse of carbamazepine in some patients. Impairment of psychomotor function has been noted in association with use of the liquid suspension of carbamazepine. Additionally, impaired cognition, exacerbations of focal seizures and asterixis have been reported in association with carbamazepine treatment. One case of a lingual-facial-buccal extrapyramidal reaction has also been described.

One study has suggested that gradual withdrawal of carbamazepine over ten days results in significantly fewer generalized tonic-clonic seizures compared to rapid withdrawal over four days.

One study has suggested that the epoxide metabolite of carbamazepine may be responsible for the occasional occurrence of seizure exacerbations in patients receiving carbamazepine.

Hypersensitivity

Rare (0.01% to 0.1%): A delayed multi-organ hypersensitivity disorder (of serum sickness type) with fever, skin rashes, vasculitis, lymphadenopathy, disorders mimicking lymphoma, arthralgia, leucopenia, eosinophilia, hepato-splenomegaly and abnormal liver function tests, occurring in various combinations, other organs may also be affected (e.g., lungs, kidneys, pancreas, myocardium, colon) Very rare (less than 0.01%): Aseptic meningitis (with myoclonus and peripheral eosinophilia), anaphylactic reaction, angioedema Frequency not reported: Multiorgan hypersensitivity reactions occurring days, weeks, or months after initiating treatment

Rash and pruritus often resolve after discontinuation of carbamazepine therapy. Both cases of lupus-like syndrome resolved after discontinuation of carbamazepine. Stevens-Johnson syndrome, erythema multiforme, and a mononucleosis-like syndrome have also been reported.

Hepatic

Very common (10% or more): Elevated gamma-GT (due to hepatic enzyme induction) usually not clinically relevant Common (1% to 10%): Elevated alkaline phosphatase Uncommon (0.1% to 1%): Elevated transaminases Rare (0.01% to 0.1%): Cholestatic and hepatocellular jaundice, hepatitis of cholestatic, parenchymal (hepatocellular), or mixed type Very rare (less than 0.01%): Granulomatous hepatitis, hepatic failure Frequency not reported: Liver function test abnormalities, variegate porphyria, porphyria cutanea tarda

Alterations in liver function tests may progress to hepatotoxicity including cholangitis, granuloma formation, fever and hepatocellular necrosis. Discontinuation of carbamazepine often results in improvement in laboratory abnormalities and liver injury.

Renal

Very rare (less than 0.01%): Interstitial nephritis, renal failure, renal dysfunction (including albuminuria, hematuria, oliguria, and elevated BUN/azotemia)

Respiratory

Very rare (less than 0.01%): Pulmonary hypersensitivity (characterized by fever, dyspnea, pneumonitis or pneumonia), pulmonary embolism

Dermatologic

Very common (10% or more): Allergic skin reactions, urticaria Common (1% to 10%): Pruritus, rash, paresthesia Uncommon (0.1% to 1%): Exfoliative dermatitis, erythroderma Rare (0.01% to 0.1%): Systemic lupus erythematosus-like syndrome Very rare (less than 0.01%): Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), photosensitivity, erythema multiforme, erythema nodosum, alterations in skin pigmentation, purpura, acne, sweating, alopecia, hirsutism, unusual bruising, pruritic and erythematous rashes, diaphoresis, onychomycosis, dermatitis Frequency not reported: Psoriasiform eruption

Dangerous, sometimes fatal skin reactions (Stevens Johnson syndrome and toxic epidermal necrolysis), that can be caused by carbamazepine therapy are significantly more common in patients with the human leukocyte antigen (HLA) allele, HLA-B 1502. This allele occurs almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians. Patients with ancestry from areas in which HLA-B 1502 is present should be screened for the HLA-B 1502 allele before starting treatment with carbamazepine. If these individuals test positive, carbamazepine should not be started unless the expected benefit clearly outweighs the increased risk of serious skin reactions. Patients who have been taking carbamazepine for more than a few months without developing skin reactions are at low risk of these events ever developing from carbamazepine. This is true for patients of any ethnicity or genotype, including patients who test positive for HLA-B 1502.

Ocular

Common (1% to 10%): Diplopia, accommodation disorders (blurred vision) Very rare (less than 0.01%): Lens opacities, conjunctivitis Postmarketing reports: Diplopia, oculomotor disturbances, nystagmus, photosensitivity, visual hallucinations, scattered punctate cortical lens opacities, overall impairment of the chromatic and achromatic systems, increased intraocular pressure

Oncologic

Frequency not reported: Disorders mimicking lymphoma

Immunologic

Frequency not reported: Antibody deficiency Postmarketing reports: Aseptic meningitis (with myoclonus and peripheral eosinophilia

Psychiatric

Common (1% to 10%): Abnormal thinking Rare (0.01% to 0.1%): Hallucinations (visual or acoustic), depression, loss of appetite, restlessness, aggressive behavior, agitation, confusion, talkativeness Very rare (less than 0.01%): Activation of psychosis, rebound mania following discontinuation of therapy

Genitourinary

Very rare (less than 0.01%): Sexual disturbances/impotence, abnormal spermatogenesis (with decreased sperm count and/or motility) Frequency not reported: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, albuminuria, glycosuria, elevated BUN, microscopic deposits in the urine

Metabolic

Common (1% to 10%): Hyponatremia, fluid retention, edema, weight gain, reduced plasma osmolarity due to an antidiuretic hormone (ADH)-like effect (leading in rare cases to water intoxication accompanied by lethargy) Very rare (less than 0.01%): Disturbances of bone metabolism (decrease in plasma calcium and 25-OH-cholecalciferol) leading to osteomalacia, elevated cholesterol (including HDL cholesterol), elevated triglycerides

Musculoskeletal

Rare (0.01% to 0.1%): Muscle weakness Very rare (less than 0.01%): Arthralgia Postmarketing reports: Leg cramps[Ref]

Other

Very rare (less than 0.01%): Taste disturbances, tinnitus, hyperacusis, hypoacusis, changes in pitch perception[Ref]

Pregnancy Warnings

- US FDA pregnancy category D
  - Associated with congenital malformations
    - Spina bifida, Craniofacial defects, cardiovascular malformations, hypospadias
  - Developmental Delay

Breastfeeding Warnings

- Excreted in human milk 25% to 60% of plasma levels
- Infants can have therapeutic drug concentrations

References

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