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Antibiotic and Mental Status Change

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Delirium or acute confusional state is an organically caused decline from a previously attained baseline level of cognitive function, which occurs in up to half of hospitalized patients and up to 80% of patients at intensive care units. Increased length of hospital stay and in-hospital complication, such as discharge to long-term care facilities, hospitalization from long-term care facilities, subsequent cognitive impairment, subsequent dependent, and risk of in-hospital and 1-year mortality is associated with delirium (1).

A review of medications as a potential contributing factor should always be prompted by any change in mental status. Neurologic symptoms, including sedation, sleep disturbance, confusion, delirium, seizures, mood changes, psychosis, and hallucinations, are often an overlooked etiology of antimicrobial agents (1).

Increased dose of antibiotics and their different classes can change the type and frequency of mental status, concurrent central nervous system (CNS) disorders, and renal dysfunction. The most common causative agents, with incidence varying from a few isolated case reports to 15% of patients at the intensive care unit, are fluoroquinolones, cephalosporins, and macrolides in cefepime. Over 50% of elderly patients receive high-dose clarithromycin (2, 3).

In view of the fact that antimicrobial agent use has a high frequency, awareness regarding the potential for antimicrobials to induce changes in mental status should be taken into consideration by clinicians. Therefore, recognition and management may reduce morbidity and patients and families should be appropriately educated regarding these adverse effects (2, 3).

The exact mechanisms by antimicrobials agent that lead to an altered mental status are largely unknown. Luoroquinolones, cephalosporins, and penicillins may directly alter CNS function through alteration of neurotransmission such as gamma-aminobutyric acid (GABA) antagonism.

Secondary to another adverse effect of an antimicrobial is altered mental status. For instance, this may be indirectly due to inflammation arising from aseptic meningitis, which has been reported with trimethoprim/sulfamethoxazole in the elderly or immunocompromised patients.

According the US food and drug administration (FDA) safety alert, prescription of fluoroquinolones, which have been used for common infections, should be limited owing to potential adverse effects, including CNS toxicity, while other available alternatives should to be recommended (4).

As side chain differences of beta-lactams differ in causing mental status changes, owing to increased GABA receptor binding, neurotoxicity is more likely with beta-lactams with more basic side chains. This difference may explain why meropenem is less neurotoxic than imipenem, which has a more basic side chain (5).

In one study on 100 patients at the ICU, who had received intravenous cefepime, 15% experienced cefepime-associated neurotoxicity (3). Cephalosporin neurotoxicity is more common with cefepime than other cephalosporins, such as ceftriaxone, as it is less likely to be identified, and delayed diagnosis is common (6).

Psychosis has been linked to combination of metronidazole and disulfiram; this is thought to be due to the co-inhibition of aldehyde dehydrogenase. In a study of 58 males receiving disulfiram for chronic alcoholism, 20%, who were also given metronidazole developed an acute psychosis/confusional state (7). Also, increasing cumulative doses and exposure has been associated with metronidazole neurologic toxicity, thus, limiting its duration of use is recommended due to risk for neurotoxicity with repeat exposure to metronidazole (2).

New antibiotics, such as linezolid can inhibit monoamine oxidase A and B, concomitant use with medications that increase serotonin levels, can lead to serotonin syndrome and subsequent adverse neurologic effects (2, 7).

Voriconazole appears to be particularly associated with neurotoxicity among the azole antifungals. Serum

concentrations > 5.5 μg/mL have been observed in 20% to 33% of patients treated with voriconazole (2). Recent guidelines from the infectious diseases society of America for the treatment of aspergillosis recommend therapeutic drug monitoring to maintain a voriconazole level of < 5 to 6 μg/mL because of the risk for CNS toxicity (8).

Owing to inadequate or /conflicting data and because influenza itself is associated with similar symptoms, the association between oseltamivir and mental status change is controversial. The reported incidence rates are generally low (5% to 12%), yet, can be as high as 67% in patients with specific genotypes (9).

Children and adolescents may be more likely to experience adverse neurologic effects; although, age is not addressed in the US labeling, oseltamivir is contraindicated in this age group in Japan (10). A study from London found that 18% of schoolchildren given prophylactic oseltamivir reported adverse neuropsychiatric effects; however, all of these effects were mild to moderate in severity and resolved with drug discontinuation (11).

Management may involve a decrease in the drug dose, selection of other antimicrobial or discontinuation when possible, if altered mental status related to antimicrobials is suspected. In most cases, discontinuing the offending agent will lead to resolution of symptoms within 48 hours. The temporary use of supportive measures, including pharmacologic agents, may be necessary in some severe cases (2).

In Iran, investigation of prescribed drugs showed that most of them contained antibiotics, and irrational prescription of antibiotics is associated with high degree of side effects, with mental status change being one of the most important side effects of antibiotics, and medical supervision and physician attention to this important issue is the principle for optimal antibiotic use.

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