نكات كاربردي در انجام تلفيق داروئي

(جلوگيری از سندرم ترک داروها)

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Beta blocker withdrawal

- Acute withdrawal of a beta blocker can lead to substantial morbidity and even mortality.
- The most important concern with beta blocker withdrawal is the exacerbation of ischemic symptoms, including the precipitation of an acute myocardial infarction, in patients with known coronary artery disease.
- In some cases there may be the precipitation of serious ventricular tachyarrhythmia, including sudden cardiac death.
- This can occur even in patients who have **no** previous history of coronary symptoms

- Upregulation of beta receptors results in an increase in beta receptor responsiveness to circulating catecholamines.
- The degree to which this will occur depends upon the relationship between the rate at which beta blockade wears off and the rate at which the receptors downregulate (the latter has a half-life of 24 to 36 hours)
- Thus, a hyperadrenergic state is most likely with short-acting drugs (such as propranolol), since receptor upregulation will persist after the antihypertensive effect has disappeared. Gradual tapering of the propranolol dose will diminish the risk of withdrawal
- In comparison, withdrawal syndromes are relatively unusual with longer-acting agents (such as atenolol or nadolol)

Approach in patients who must stop taking a beta blocker

- For beta blockers with shorter half-lives which require administration two or more times per day (eg, propranolol, short acting metoprolol, carvedilol),
  - we have patients take their usual dose once daily for one week, then every other day for one week, then stop the medication.
- For beta blockers with longer half-lives that are administered once daily (eg, atenolol, long acting metoprolol, bisoprolol),
  - we have patient take one-half their usual dose once daily for one week, then one-half their usual dose every other day for a week, then stop the medication. However, beta blocker withdrawal can be accomplished in less time if necessary, usually by taking one-half the usual dose every other day for a week.

Withdrawal syndromes with antihypertensive drug therapy

- Abrupt discontinuation of antihypertensive drug therapy can result in one of the following:
  - Relatively rapid, asymptomatic return of the blood pressure (BP) to pretreatment levels
  - Slower, asymptomatic return of BP to pretreatment levels
  - Acute rebound of the BP with symptoms and signs of sympathetic overactivity (a withdrawal syndrome)
  - Overshoot of the BP above pretreatment levels

- Most commonly, discontinuation of antihypertensive therapy leads to a gradual rise in the BP to pretreatment levels over a period of days to as long as six months
- Withdrawal syndromes have been reported most frequently with oral **clonidine** and are thought to reflect a rapid return of catecholamine secretion or receptor sensitivity that had been suppressed during therapy.
- Clonidine should be weaned slowly, if possible, and beta blockers, such as **labetalol** or **atenolol**, can be used to antagonize the rebound hypertension that can occur.
- To prevent withdrawal symptoms, these drugs should be slowly discontinued over a 6-to-10-day interval, ***cutting the dose by one-half every two to three days***

Benzodiazepine withdrawal

- Any abrupt or overly rapid reduction in benzodiazepine (BZD) dose among chronic users can produce withdrawal. Rapid recognition and treatment of BZD withdrawal is crucial because the syndrome can be life-threatening.
- The symptoms and signs of BZD withdrawal can include any of the following :
  - Tremors
  - Anxiety
  - Perceptual disturbances
  - Dysphoria
  - Psychosis
  - Seizures
  - Autonomic instability

- The occurrence and time of BZD withdrawal symptoms are related in part to the pharmacologic properties of the drug, dose, duration of use, and abruptness of discontinuation.
- Heavier use of BZD over a longer period increases the risk for withdrawal.
- The onset of withdrawal can vary according to the **half-life** of the BZD involved. Symptoms may be delayed up to **three weeks** in BZDs with long half-lives, but may appear as early as **24 to 48** hours after cessation of BZDs with short half-lives.

- Chronic ingestion of BZDs leads to ***conformational changes*** in the GABA receptor, which ultimately reduce the receptor's affinity for the agent and result in decreased GABA activity
- This decreased activity manifests as tolerance to the agent. When BZDs are no longer present or present at lower concentrations, this decreased GABA receptor activity has less inhibition of excitatory neurotransmitters, and thus, there is a pro-excitatory state.
- Withdrawal can usually be avoided or minimized through the use of BZDs with a long half-life, such as diazepam or chlordiazepoxide, and a gradual tapering of the patient's BZD dose over several months, depending upon the dosage and degree of dependency.

Treatment

- BZD withdrawal is treated with a BZD that has a prolonged clinical effect, such as diazepam, given intravenously (IV) and titrated to effect. The goal is to eliminate withdrawal symptoms without causing excessive sedation or respiratory depression. Once symptoms are controlled, the BZD dose should then be tapered gradually over a period of months

Thank you for considration