Question 63

Which one of the following medications is most appropriate for the treatment of nausea and vomiting in Parkinson's disease?

A. prochlorperazine
B. promethazine
C. droperidol
D. metoclopramide
E. domperidone

Answer E: domperidone

The pathognomonic histological feature of Parkinson's disease is a loss of neuromelanin-containing dopaminergic cells in the substantia nigra pars compacta. Microscopically, this cell loss is accompanied by the presence of intracytoplasmic inclusions known as Lewy bodies in the substantia nigra. Neurologically, this loss of cells in the substantia nigra results in a loss of dopaminergic input to the basal ganglia via the nigrostriatal pathway, and therefore an imbalance in the output pathways of the striatum, which form the extrapyramidal motor system. The imbalance in this motor system produces the motor symptoms that characteristic of this disorder.

Diagnosis of PD — Correct diagnosis is fundamental to the appropriate therapy of Parkinson's disease (PD), although the same menu of antiparkinson drugs is used to treat all of the various parkinsonian syndromes. The four cardinal signs of parkinsonism are rest tremor, rigidity, akinesia, and gait disturbance. Usual criteria for a clinical diagnosis of PD require the presence of at least two of these four features; diagnostic certainty increases in proportion to the predominance of rest tremor as a finding, especially if it is unilateral.

Treatment

Levodopa — Levodopa (L-dopa) is well established as the most effective drug for the symptomatic treatment of idiopathic or Lewy body PD. It is particularly effective for the management of akinetic symptoms and should be introduced when these become disabling and are uncontrolled by other antiparkinsonian drugs. Tremor and rigidity can also respond to levodopa therapy, but postural instability is less likely to do so.

Levodopa is combined with a peripheral decarboxylase inhibitor to block its conversion to dopamine in the systemic circulation and liver (before it crosses the blood-brain barrier) in order to prevent nausea, vomiting, and orthostatic hypotension. In the United States, the decarboxylase inhibitor is carbidopa. The combination drug carbidopa/levodopa (immediate-release Sinemet) is available in tablets of 10/100, 25/100, and 25/250 mg, with the numerator referring to carbidopa and the denominator referring to the levodopa dose. An immediate-release formulation of carbidopa/levodopa (Parcopa) is available that dissolves on the tongue and can be taken without water, but there are no published studies of this formulation, and its onset of action is no different from Sinemet.

In Europe and Canada, benserazide is the peripheral decarboxylase inhibitor. The combination drug benserazide/levodopa (Madopar or Prolopa) is available in 25/100 and 50/200 mg tablets.

Controlled-release formulations of carbidopa/levodopa and benserazide/levodopa are available as Sinemet CR and Madopar HBS, respectively.

Ref


Prochlorperazine - stemetil

Prochlorperazine is a phenothiazine with a piperazine moiety in the side chain. It possesses strong antiemetic and antipsychotic activity with less sedative action than chlorpromazine.

Pharmacology. As with other phenothiazines, prochlorperazine has actions on several neurotransmitter systems as follows.

Antidopamine action, which probably contributes to both the therapeutic effect and unwanted effects including extrapyramidal disorders and endocrine disturbances.
alpha-Adrenoreceptor antagonism, which contributes to cardiovascular side effects, e.g. orthostatic hypotension and reflex tachycardia.
Potentiation of noradrenaline by blocking its reuptake into nerve terminals.
Weak anticholinergic action. Weak antihistamine action. Weak serotonin antagonism.
Promethazine also has an effect on temperature control and blocks conditioned avoidance responses.

Promethazine
Promethazine, a phenothiazine derivative, is a long acting antihistamine with mild atropine-like anticholinergic effects and some antiserotonin effects, and because of its marked effect on the central nervous system (CNS), acts as an antiemetic, hypnotic, tranquilizer, and a potentiator of anaesthetics, hypnotics, sedatives and analgesics.

Droperidol
Neuroleptic drug of the butyrophenone group, which also includes haloperidol.
**Pharmacology.** Droperidol produces general quiescence and a reduced responsiveness to environmental stimuli in several animal species.
There is little or no effect on respiration or myocardial contractile force, heart rate and cardiac output in dogs.
The blood pressure is lowered, in part as a direct vasodilator effect and in part because of adrenergic blockade.
Droperidol markedly reduces the ability of apomorphine to produce emesis in dogs. It is effective in protecting rats against experimentally induced traumatic shock and in protecting dogs against adrenaline induced ventricular arrhythmias.
**Human pharmacology.** Droperidol produces marked tranquilization and sedation. It also produces an antiemetic effect as evidenced by the antagonism of the emetic effect of apomorphine in dogs. It potentiates other CNS depressants, e.g. pentobarbitone and narcotic analgesics such as fentanyl. It also produces mild alpha-adrenergic blockade, peripheral vascular dilatation, and reduction of the pressor effect of adrenaline.
Droperidol can produce hypotension and decrease peripheral vascular resistance. It may decrease pulmonary arterial pressure, particularly if it is abnormally high. It may reduce the incidence of adrenaline induced arrhythmias but it does not prevent other cardiac arrhythmias. The onset of action is from three to ten minutes following intravenous or intramuscular administration. The full effect, however, may not be apparent for 30 minutes. The duration of the sedative and tranquilizing effects of droperidol generally is two to four hours. Alteration of consciousness may persist as long as 12 hours.

Metoclopramide
Maxolon stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary or pancreatic secretions. Its mode of action is unclear. It seems to sensitise tissues to the action of acetylcholine. The effect of Maxolon on motility is not dependent on intact vagal innervation, but it can be abolished by anticholinergic drugs. Maxolon increases the tone and amplitude of gastric (especially antral) contractions, relaxes the pyloric sphincter and the duodenal bulb, and increases peristalsis of the duodenum and jejunum resulting in accelerated gastric emptying and intestinal transit. It increases the resting tone of the lower oesophageal sphincter. It has little, if any, effect on the motility of the colon or gall bladder.
Maxolon has dopamine antagonist activity. Like the phenothiazines and related drugs, which are also dopamine antagonists, Maxolon produces sedation and may produce extrapyramidal reactions (see Precautions). Maxolon inhibits the central and peripheral effects of apomorphine, induces release of prolactin and causes a transient increase in circulating aldosterone levels.

Domperidone
Motilium is a dopamine antagonist with antiemetic properties similar to those of metoclopramide and certain neuroleptic drugs. Unlike these drugs, however, Motilium does not readily cross the blood-brain barrier. It seldom causes extrapyramidal side effects, but does cause a rise in prolactin levels. Its antiemetic effect may be due to a combination of peripheral (gastrokinetic) effects and antagonism of central dopamine receptors in the chemoreceptor trigger zone which lies in the area postrema and is regarded as being outside the blood-brain barrier.