

**ANAESTHESIA & PSYCHIATRIC DRUGS part 1 -
ANTIDEPRESSANTS
ANAESTHESIA TUTORIAL OF THE WEEK 164
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QUESTIONS

1. Concerning anaesthesia for a patient taking monoamine oxidase inhibitors:
 - a. Hypertensive crisis may occur after administration of ephedrine
 - b. Relapse is likely if the drug is stopped for a few days perioperatively
 - c. Pethidine is the opioid of choice
 - d. Hypotension should be treated with intravenous fluids and cautious use of phenylephrine

2. Selective serotonin reuptake inhibitors:
 - a. May cause gastrointestinal symptoms
 - b. May result in reduced levels of other drugs e.g. warfarin and phenytoin
 - c. Are used to treat depression, panic disorder and obsessive compulsive disorder
 - d. Have fewer side effects than tricyclic antidepressants

3. Tricyclic antidepressants:
 - a. Should be stopped preoperatively to avoid interactions with anaesthetic agents
 - b. May result in serotonin syndrome if given in combination with an SSRI
 - c. Commonly cause dry mouth and postural hypotension
 - d. Are highly protein bound

INTRODUCTION

Depression is common, with a lifetime prevalence of between 10 and 20%. Many surgical patients will therefore be taking antidepressant drugs, and the anaesthetist must be aware of potential interactions with anaesthetic agents. Antidepressants can be divided into 4 groups - tricyclic antidepressants, selective serotonin reuptake inhibitors, atypical agents and monoamine oxidase inhibitors. Lithium is also occasionally used to treat depression but is more commonly used as a mood stabiliser in bipolar affective disorder and will be considered in a later tutorial.

Before discussing each group, it is important to consider the problems which can occur if antidepressant drugs are stopped perioperatively.

DISCONTINUATION SYNDROME

Abrupt cessation of any antidepressant drug is associated with a risk of the patient developing symptoms. This is known as the discontinuation syndrome. The common features include nausea, abdominal pain and diarrhoea, sleep disturbance (insomnia, vivid dreams and nightmares), somatic symptoms (sweating, lethargy and headaches) and finally affective symptoms (low mood, anxiety and irritability). Such reactions may be distinguished from relapse of the depressive illness as they start abruptly within a few days of stopping the antidepressant, are short-lived (a few days to three weeks) and end if the antidepressant is reintroduced. Relapse of the depressive illness itself is unlikely to occur in the first week; the symptoms gradually build up and tend to become chronic. Gradual cessation of the drug (over several weeks) avoids the reaction.

Therefore, with the exception of monoamine oxidase inhibitors (see later), it is important to continue antidepressants throughout the perioperative period.

TRICYCLIC ANTIDEPRESSANTS (TCAs)

These drugs were for many years the standard treatment for depression, but they have now been largely replaced by selective serotonin reuptake inhibitors. They are also used in the treatment of chronic pain and nocturnal enuresis. Examples include amitriptyline, nortriptyline, imipramine and dothiepin.

They work by competitively blocking reuptake of the amines noradrenaline and serotonin (5-HT) from the synaptic cleft, thereby increasing the concentration of these transmitters in the synapse. They need to be given for 2-3 weeks to be effective. They also block muscarinic, histaminergic and alpha adrenoceptors. Consequently, side effects are common, including dry mouth, blurred vision, urinary retention, constipation (all anticholinergic), postural hypotension (alpha blockade) and sedation (blockade of all three types of receptors). They are highly protein bound and therefore their effects may be enhanced by competing drugs (e.g. warfarin, digoxin and aspirin). Metabolism occurs in the liver, and often results in active metabolites.

In overdose TCAs are very toxic. Cardiovascular effects include sinus tachycardia with prolongation of the QT interval, widening of the QRS complex and hypertension at lower doses, progressing to ventricular arrhythmias, and refractory hypotension at higher doses. Central effects are initially due to excitation producing agitation, delirium and seizures, then at higher doses depression, causing coma and respiratory depression. Anticholinergic effects are also marked. Treatment is supportive, often requiring intensive care.

Anaesthesia for a patient on TCA

TCAs should be continued throughout the perioperative period to prevent discontinuation syndrome or worsening of depression, but care is required to avoid adverse effects resulting from increased sensitivity to catecholamines. Hypertension and arrhythmias may result from the use of sympathomimetic drugs (e.g. noradrenaline and adrenaline), and indirectly acting sympathomimetics (e.g. ephedrine, metaraminol) should not be used. Anaesthetics known to increase circulating catecholamines such as pancuronium and ketamine should be used with caution. There is a risk of ventricular arrhythmias in patients who develop hypercapnia whilst spontaneously breathing volatile agents (particularly halothane).

TCAs may result in increased response to intra-operatively administered anticholinergics, and those which cross the blood brain barrier, such as atropine, may cause postoperative confusion.

St John's Wort (*Hypericum perforatum*)

This herbal medicine has become popular with patients for the treatment of mood disorders and has been shown to be effective in mild depression. The extract of the plant contains several alkaloids which have a similar structure to TCAs. It may induce some cytochrome p450 enzymes, resulting in increased metabolism of many drugs including warfarin, digoxin, theophylline and oral contraceptive drugs.

SELECTIVE SEROTININ REUPTAKE INHIBITORS (SSRIs)

These drugs are now the most commonly prescribed drugs for depression in the UK, and are also used for panic disorder and obsessive compulsive disorder. Examples include fluoxetine, paroxetine and sertraline. Like the TCAs there is a delay of 2-3 weeks before the patient's mood lifts. They work by selectively inhibiting the neuronal reuptake of 5-HT from the synaptic cleft. Their main advantage is a reduced incidence of side effects compared with the TCAs. They are less sedative, have fewer anticholinergic effects, very rarely cause cardiovascular side effects (occasional bradycardia) and are much safer than TCAs in overdose. They are associated with gastrointestinal side effects (nausea, vomiting and diarrhoea or constipation) and central effects (sleep disturbance, agitation, tremor, headache and sexual dysfunction), but most effects are mild and transient. SSRIs decrease platelet aggregation at high doses, and may increase surgical bleeding if combined with NSAIDs. They inhibit cytochrome p450 enzymes resulting in increased levels of other drugs such as warfarin, theophylline, phenytoin, benzodiazepines and TCAs. Syndrome of inappropriate ADH release has also been described with the use of SSRIs.

Serotonin syndrome

This is a potentially fatal toxic reaction which results from increased synaptic serotonin levels in the brainstem and spinal cord. It typically results from interactions between drugs that increase serotonin activity. In most cases drug intoxication is the cause but it can also appear under normal dose ranges. The commonest combination is an SSRI and a monoamine oxidase inhibitor, but other drugs with serotonergic effects include TCAs, pethidine, tramadol and dextromethorphan. It may also occur after overdose of an SSRI.

The clinical features include changes in behaviour (agitation and confusion), increased motor activity (muscle rigidity, hyper reflexia and clonus) and autonomic instability (hyperthermia, tachycardia, labile blood pressure and diarrhoea). Seizures, rhabdomyolysis, renal failure, arrhythmias, coma and death may also occur. It may mimic the neuroleptic malignant syndrome. The treatment is mainly supportive, usually requiring intensive care.

Anaesthesia for a patient on SSRI

SSRIs should be continued throughout the perioperative period to prevent discontinuation syndrome occurring. Consider the possibility of SIADH especially in the elderly. Avoid the use of other drugs affecting serotonin including pethidine, tramadol, pentazocine and dextromethorphan.

ATYPICAL ANTIDEPRESSANTS

Venlafaxine

At low doses venlafaxine acts much like an SSRI, inhibiting reuptake of serotonin, but at higher doses (above 225mg) it also blocks the reuptake of noradrenaline. Unlike TCAs it does not have effects on alpha-1, cholinergic or histamine receptors. It can cause hypertension, which is dose dependent. It does not have an effect upon the pP450 system and therefore has few drug interactions, although it may potentiate the anticoagulant activity of warfarin.

Mirtazapine

Mirtazapine promotes noradrenergic and serotonergic neurotransmission via alpha-2 antagonism. It also blocks a variety of post-synaptic serotonergic receptors, which cause the side effects of sedation and weight gain. Mirtazapine has little effect upon blood pressure and heart rate and no effect upon the QTc interval.

Both venlafaxine and mirtazapine should be continued throughout the perioperative period.

MONOAMINE OXIDASE INHIBITORS (MAOIs)

These drugs were introduced in the 1950s, and were amongst the first drugs to be used in the treatment of depression. They are now however generally used only in resistant cases of depression due to the incidence of side effects.

They work by inhibition of the enzyme monoamine oxidase, which is present on external mitochondrial membranes and inactivates monoamine neurotransmitters in both the central and peripheral nervous systems. They cause an increase in the level of amine neurotransmitters, which is thought to be the mechanism of their antidepressant effect.

Monoamine oxidase exists as two isoenzymes, A and B, which have different properties. MAO-A acts mainly on serotonin, noradrenaline and adrenaline. It is the main form of MAO found in the human brain. MAO-B preferentially metabolises non-polar aromatic amines such as phenylethylamine and methylhistamine, and is responsible for 75% of MAO activity, predominating in the gastro-intestinal tract, platelets and most other non-neural cells. Tyramine (a precursor of noradrenaline which is found in cheese and other foods) and dopamine are substrates for both A and B.

There are now 2 generations of MAOIs – the original drugs, which inhibit both forms of MAO non-selectively and irreversibly, and the newer generation which reversibly inhibit MAO-A. Selegiline, the anti-Parkinsonism drug is an MAO-B inhibitor.

Non-selective irreversible MAOIs

These drugs are of 2 types – hydrazines such as phenelzine and isocarboxazid, and non-hydrazines such as tranylcypromine. Both types bind covalently to the enzyme causing permanent inactivation. Thus non-neurotransmitter substances which are metabolized by either type of enzyme may precipitate hypertensive crises. Such substances include tyramine, which is present in high concentrations in many foods including cheese, pickled herring, Bovril, chicken liver and chocolate, and is normally inactivated by hepatic MAO. Furthermore administration of indirectly acting sympathomimetic agents e.g. ephedrine, metaraminol, which may displace noradrenaline from neurotransmitter vesicles in very high amounts, may precipitate potentially fatal hypertensive reactions.

Recovery of MAO activity is dependent on formation of new enzyme, which takes 2-3 weeks; therefore the patient remains at risk of metabolic effects for this time. Other side effects of MAOIs include sedation, blurred vision, orthostatic hypotension and liver toxicity. Interactions with opioids also occur (see below).

Reversible inhibitors of MAO-A (RIMAs)

Moclobemide is the only drug of this type currently available in the UK and has very different properties to the older drugs. It selectively inhibits MAO-A, so that the response to tyramine (metabolised mainly by MAO-B) is much less and most patients do not need the same level of dietary restriction. Because it is reversible, and short-acting (elimination half life 2-4 hours) the risk of drug interactions is also less, and MAO activity returns to normal within 24 hours of stopping the drug. Moclobemide is generally much better tolerated than classic MAOIs, with a lack of anticholinergic and hepatotoxic effects.

Interactions between MAOI and anaesthetic drugs

Opioids.

There are 2 distinct type of reaction that can occur between MAOIs and opioids.

Type I (excitatory) reaction only occurs in patients given pethidine and dextromethorphan, both of which inhibit serotonin re-uptake. The features are those of serotonin syndrome – sudden agitation, headache, hyper- or hypotension, muscle rigidity, hyperthermia, seizures and coma. Although it is unlikely to occur with RIMAs, pethidine and dextromethorphan remain contraindicated. The reaction is not seen with other opioids and morphine, fentanyl, alfentanil and remifentanyl can all be used safely.

Type II (depressive) reaction, which is very rare, is thought to be due to MAOI inhibition of hepatic enzymes, resulting in enhanced effects of all opioids. It is reversed by naloxone.

Sympathomimetics

As described above indirect sympathomimetics may precipitate potentially fatal hypertensive crises, and are absolutely contraindicated with any MAOI. The interaction is most common with the non-hydrazine derivatives, but may still occur weakly with moclobemide. Direct acting sympathomimetics (adrenaline, noradrenaline and phenylephrine) should be titrated to effect in patients on MAOIs as they may have an enhanced effect due to receptor hypersensitivity.

Neuromuscular blocking agents

Phenelzine decreases plasma cholinesterase concentration and prolongs the action of suxamethonium. This does not occur with other MAOIs. Pancuronium should be avoided as it releases stored noradrenaline. Other muscle relaxants can be used safely.

Intravenous induction agents

MAOIs may cause a reduction in the hepatic metabolism of barbiturates resulting in reduction of dose requirements of thiopentone. Propofol, ketamine and etomidate can be used safely.

Local anaesthetics

Apart from cocaine these can be used safely but care should be taken with preparations containing adrenaline. Felypressin is a suitable alternative if a vasoconstrictor is required.

Benzodiazepines, inhalational anaesthetic agents, anticholinergic drugs and non-steroidal anti-inflammatory drugs can all be used safely in patients taking MAOIs.

Perioperative withdrawal of MAOIs

Many anaesthetic guidelines advise stopping MAOIs at least two weeks before surgery in order to allow regeneration of the enzyme. However this leaves the patient at risk of two serious consequences. Symptoms of discontinuation syndrome may be seen within a few days of abruptly stopping an MAOI, Relapse or recurrence is unlikely to occur within the first week of stopping medication, but subsequently becomes a major risk, with up to 20% of patients relapsing within two weeks after stopping phenelzine.

Moclobemide can be safely stopped for 24 hours before surgery.

Selegiline does not need to be stopped if taken at doses < 10mg/day. At this dose there is no reaction with sympathomimetics, but pethidine should still be avoided.

Anaesthesia for a patient on MAOI

For elective surgery, the decision as to whether to stop MAOI therapy preoperatively should be made in advance, on an individual basis, after discussion between the anaesthetist, psychiatric team and patient. Although continuation of MAOI carries risks, by careful anaesthetic technique these risks can be minimised, and must be balanced against the risks of relapse and discontinuation syndrome.

If the MAOI is to be stopped, this should be for the minimum period, with gradual reduction of dose and regular psychiatric review. Late cancellations of surgery should be avoided, and treatment restarted as soon as possible post operatively.

If the decision is made to continue the MAOI, or in the emergency situation, the following steps should be taken to minimise risks:

- (1) Avoid sympathetic stimulation – consider benzodiazepine pre-med.
- (2) Ensure patient is adequately hydrated.
- (3) Treat hypotension initially with intravenous fluids, then with cautious doses of phenylephrine (e.g. 10-20 mcg).
- (4) Pethidine and indirectly acting sympathomimetics are absolutely contraindicated.

Regional anaesthesia avoids the risks of general anaesthesia, but care must be taken in treating hypotension as described above.

Anaesthesia for a patient on moclobemide

If possible, including in emergency situations, the drug should be stopped for 24 hours preoperatively. If this is not possible, the same precautions described above are required. The risk of interactions is less however.

ANSWERS TO QUESTIONS

1. TFFT
2. TFTT
3. FTTT

SUMMARY

- Selective serotonin reuptake inhibitors and tricyclic antidepressants should be continued throughout the perioperative period to avoid discontinuation syndrome
- Serotonin syndrome, which is potentially fatal, may occur in patients on SSRIs who are given pethidine or tramadol.
- Careful planning is required for patients on MAOIs.
- Pethidine and indirectly acting sympathomimetics are absolutely contraindicated in patients on MAOIs.
- Moclobemide is a reversible inhibitor of MAO-A which has a better safety profile than traditional MAOIs.

WEBLINKS

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