

## Anaesthetic genetics and genomics

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### Abstract

Genetic variations have always been implicated in interindividual reactions to various pharmaceutical agents. Some common genetically determined anaesthetic conditions, such as malignant hyperthermia, "scoline apnoea", "halothane hepatitis" and porphyria, are fairly well described, and the genetic differences in enzyme, receptor and ion channel systems are slowly being elucidated. These genomic differences allow some explanation as to why drugs that work well in certain patients produce no or unwanted effects in others.

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### Introduction

Genetic variation contributes to an individual's sensitivity and response to a variety of drugs. Early clinical insights into pharmacogenetics followed the prolonged apnoea after succinylcholine administration. The awareness that thiopentone produces an acute porphyric event and halothane may cause hepatitis, and the relationship between malignant hyperthermia and volatile agents or succinylcholine, awoke an interest in the interaction between pharmacology and genetics. These conditions are well known among anyone practising anaesthetics and will be covered briefly. The expanding science of pharmacogenomics is not well understood, and some detail is provided here on the genetic polymorphisms in pharmacokinetic absorption, distribution, metabolism and excretion, as well as on pharmacodynamic receptor, ion channel and enzyme effects that have resulted in an awareness of interindividual drug responses that have a genetic background.<sup>1</sup>

### Malignant hyperthermia

Volatile agents and suxamethonium trigger a rapid release of calcium from the sarcoplasmic reticulum in susceptible individuals, resulting in a massively accelerated metabolic state, with increased oxygen consumption, hypercarbia and body temperature, leading to circulatory collapse and death. All volatile agents, with the exception of nitrous oxide and xenon, are triggers of malignant hyperthermia. The mechanism of action is still not fully understood,

but the result is stimulation of calcium release from the sarcoplasmic reticulum. This release of calcium from the sarcoplasmic reticulum outweighs reuptake, resulting in an inability to terminate muscle contraction.

Suxamethonium is a far more powerful trigger of malignant hyperthermia (MH) than the volatile agents. The chlorinated agents (halothane, enflurane and isoflurane) have a faster onset and higher incidence of MH than the unchlorinated agents (desflurane and sevoflurane). Data from the North American MH registry show that the median time to onset with suxamethonium is 10 minutes. Onset with the volatile agents, desflurane (260 minutes), isoflurane (140 minutes) and halothane (35 minutes), is much slower. Desflurane also appears to produce less severe forms of MH, with no deaths yet reported. All agents are associated with around 30% incidence of late recrudescence following initial treatment of symptoms.

Specific signs of MH include increased end-tidal carbon dioxide (early sign), marked temperature elevation (late sign), muscle rigidity, myoglobinuria and rhabdomyolysis due to muscle breakdown. Nonspecific signs of MH include tachycardia, acidosis, hyperkalaemia, and tachypnoea.

MH is related to an inherited genetic variation, with around 50 associated mutations having been identified. The RYR1 gene mutation on chromosome 19 is the most common.

Once a presumptive diagnosis of MH is made, treatment should be initiated rapidly. Discontinue the inhalation

agent, hyperventilate with 100% oxygen, cool the patient, treat symptoms and administer intravenous dantrolene. Dantrolene decreases the release of calcium from the sarcoplasmic reticulum. An initial dose of at least 1 mg/kg, up to 10 mg/kg, should be administered.

The administration of dantrolene may be quite a taxing exercise. It suggested that you get help:

- Ensure that dantrolene is available and source sufficient quantities early. Most hospitals only have a few vials as they are infrequently used. A vial contains 20 mg of dantrolene. Around 35 vials may be needed for an adult.
- Dantrolene needs to be dissolved in water, but is poorly soluble in water. Warm the water using 60 ml per vial to aid dissolution. Particles may persist despite the best efforts, so it should be administered via a blood filter.
- Protect the solution from light and use within six hours.

Definitive diagnosis is available for suspected cases of MH, in the form of muscle biopsies with contracture tests and genetic screening of the 17 most common RYR1 mutations. Unfortunately these are not readily available. (Only five centres in the USA do muscle contraction tests and two do genetic screening.)

Preparation of an anaesthetic machine for a patient with a history of MH has recently been raised as an area of concern. The cost of modern anaesthetic machines has precluded keeping a dedicated “halothane-free” machine in each theatre complex. It was proposed that a fresh gas flow of 10 litres for 10 minutes would be adequate to cleanse a machine of volatile agent, but it has been demonstrated recently that newer anaesthesia work stations are more complex and contain more gas-absorbing materials, which require more time for purging anaesthetic gases. Recommendations for machines currently used in South Africa suggest 10 litres of flow for between 30 minutes (Datex AS3/ADU®) and 70 minutes (Drager Primus®) to reduce the volatile agent concentration to less than 10 ppm following the removal of the vapouriser. In addition all circuitry and the carbon dioxide absorbers must be replaced with new. The ventilator should be included in this purge, at a tidal volume of 1 litre and a respiratory rate of 10 litres during this time. The fresh gas flow should be

maintained at 10 litres per minute for the duration of the procedure.<sup>2</sup>

## Abnormalities in butyrylcholinesterase

Scoline apnoea is an uncommon side-effect, well known to all anaesthetists, that is caused by deficiencies in butyrylcholinesterase (previously known as pseudo-cholinesterase), resulting in a prolonged effect of the depolarising muscle relaxant scoline or the nondepolariser mivacurium. This condition is treated either by the administration of butyrylcholinesterase, or sedation and ventilation until the effect of suxamethonium has worn off.

Butyrylcholinesterase deficiency may be either inherited or acquired. The inherited abnormalities in butyrylcholinesterase are all located on chromosome 3 as a point mutation.

Fifty genetic variants of the enzyme have been described (Table I):

- u: The usual variant (96% of the population are u homozygotes).
- a: The atypical or dibucaine-resistant variant.
- k: The Kalow variant has two thirds of the activity of the u variant.
- s: The silent variant has no butyrylcholinesterase activity.

## Porphyria

Porphyria is a group of genetic disorders characterised by partial deficiencies in the haem biosynthetic pathway. The deficiency results in accumulation of haem precursors and porphyrins. Symptomatology is dependent on the specific enzyme that is deficient, and on the types of porphyrin that subsequently accumulate. South Africa is associated with the world's highest incidence of acute variegate porphyria (3:1 000). The genetic defect occurs on chromosome 1, with acute intermittent porphyria (found mainly in Sweden) being an abnormality of chromosome 11.<sup>3</sup>

The anaesthesiologist has two main areas of concern regarding porphyria:

- Avoiding agents that may precipitate an acute porphyric attack.
- Treating an acute attack.

**Table I:** Abnormalities of butyrylcholinesterase

Patient	Genotype	Incidence	Dibucaine number	Block duration with suxamethonium or mivacurium
Homozygous typical	$E_1^u E_1^u$	96%	>70	No change
Heterozygous atypical	$E_1^u E_1^a$	1:500	40–70	20–30 minutes
Homozygous atypical	$E_1^a E_1^a$	1:3 200	<20	4–8 hour
Homozygous fluoride resistant	$E_1^F E_1^F$	1:32 000	70–80	1 hour
Homozygous silent	$E_1^s E_1^s$	1:100 000		> 6 hours

Anaesthesia presents multiple triggers for an acute attack, including dehydration, fasting, stress, infections and drugs. Drug safety in porphyria is difficult to ascertain, as data are usually reliant on clinical case reports. A large proportion of drugs have never been used in porphyria, and therefore commonly used agents may not be recommended for use.

Drugs are usually classified into groups based on reported clinical experience:

- Those that can be safely used in porphyria (safe).
- Those that should be used with care (UWC) or extreme caution (UWEC).
- Those that are definitely unsafe (unsafe).

The list of drugs in each of these groups runs to several pages, and so it is probably better to develop a generic safe anaesthetic formula for all patients with porphyria and check any agent that you may be tempted to use on the porphyria drug database: <http://www.drugs-porphyrin.org>. Table II lists some examples of drugs that are safe to use in porphyric patients.

### Treatment of an acute porphyria attack

Confirm an acute episode with elevated urine porphyrins: aminolevulinic acid (ALA) and porphobilinogen (PBG).

General measures:

- Withdraw any precipitating drug.
- Hydration with 10 % dextrose-saline and oral carbohydrate loading.
- Correct electrolyte abnormalities.

Symptomatic treatment using nontriggering agents:

- Abdominal pain: codeine, morphine or pethidine.
- Nausea and vomiting: prochlorperazine, droperidol or chlorpromazine.
- Hypertension and tachycardia:  $\beta$  blockers which may be anti-porphyrinogenic.

- Psychosis and restlessness: chlorpromazine.
- Convulsions: clonazepam.

Specific treatment requires haem arginate (Normosang®) or hemin (Panhematin®) if symptoms persist or neuropathy develops.

### Variations in drug metabolism and effect (pharmacogenomics)

Pharmacogenomics deals with genetic differences that help explain why people respond differently to a drug. The term comes from the words pharmacology and genomics, and thus combines pharmaceuticals and genetics. The understanding of pharmacogenomics has the potential to improve therapeutic outcomes and individualise drug therapy, while avoiding toxic effects and treatment failure.

The majority of drug metabolism occurs via the cytochrome P450 (CYP) enzyme system, which is made up of 57 genetic subtypes. Variations in genes that code these enzymes may influence their ability to metabolise certain drugs.

Unpredictable effects may be seen as a result of:

- Increased metabolism:
  - Drug effect may be diminished or shortened.
  - Prodrugs need to be metabolised to produce an effect (e.g. codeine). Increased metabolism may result in an increase in production of the active compound, resulting in an inadvertent overdose.
- Decreased metabolism:
  - Prolonged effect of highly metabolised drugs.
  - Prodrugs may not work as insufficient active drug is formed.

The most common CYP subtypes affecting anaesthetic drug metabolism and the agents they metabolise are:

- CYP2D6: codeine, tramadol, methadone and ondansetron.

**Table II:** Drugs that are safe to use in porphyric patients

<b>Regionals</b>	Bupivacaine or lignocaine
<b>Premedication</b>	Triazolam (Halcion®) is the only safe agent available Minimise the fasting period
<b>Induction</b>	Propofol
<b>Muscle relaxants</b>	Suxamethonium is safe, but all the nondepolarising agents have a use with caution advisory Atracurium has been used safely
<b>Maintenance</b>	Total intravenous anaesthesia using propofol and remifentanyl The safest volatile agents appear to be isoflurane and desflurane Halothane is not advocated as safe by all sources and sevoflurane should not be used
<b>Analgesia</b>	Morphine, pethidine, fentanyl, alfentanil, sufentanil and naloxone
<b>Reversal</b>	Neostigmine and glycopyrrolate
<b>Postoperative</b>	Morphine, pethidine, codeine, paracetamol and ibuprofen
<b>Antiemetics</b>	Prochlorperazine (Stemetil®) and droperidol (Inapsin®)
<b>Antibiotics</b>	Penicillin, ampicillin and cephalosporins

- CYP3A4: midazolam, diazepam, fentanyl, alfentanil, sufentanil, dexamethasone, methylprednisolone and granisetron.
- CYP2C9: celecoxib and naproxen.<sup>4</sup>

### Codeine

The liver converts codeine into morphine using the enzyme CYP2D6. The clinical effects of codeine are mainly attributed to its metabolism to morphine, which has 200 times higher affinity and 50 times higher intrinsic activity at opioid receptors than codeine itself.

Following a single 30 mg oral dose of codeine, 86.1% was recovered in urine:

- 59.8% as codeine-6-glucuronide
- 11.8% as unchanged codeine
- 7.1% as morphine
- 6.9% as norcodeine.<sup>5</sup>

Increased activity of CYP2D6 converts more codeine into morphine, a situation that can cause excessive sedation, severe constipation and respiratory depression. Incidence is low in Caucasians (4%), but higher in Mediterranean races (10%), Arabs (20%) and Africans (30%). Drugs like rifampicin, phenobarbital and St John's wort all induce CYP activity.

Decreased CYP2D6 activity results in less morphine production and little or no pain relief from codeine. The incidence is 6–10% in Caucasians, 2–5% in Africans and 1% in Asians. Medication like antihistamines, calcium-channel blockers, erythromycin and grapefruit juice will also decrease CYP2D6 activity.

### Tramadol

The analgesic effect of tramadol is slightly decreased with diminished CYP2D6 metabolism. Tramadol is regarded as a prodrug and undergoes metabolism by CYP2D6 to the active metabolite, O-desmethyltramadol, which is considerably more potent at the  $\mu$  opioid receptor than tramadol. Tramadol has some effect on the  $\mu$  receptor, so a reduction in CYP2D6 is less of a concern than with codeine.<sup>4</sup>

### Intrathecal fentanyl

Genetic variations in the  $\mu$  opioid receptors may explain differences in analgesic effects when adding fentanyl in spinal anaesthesia in labour. Females with the G variant of the OPRM1 304 receptor require half the amount of fentanyl when compared to females exhibiting the A variant.<sup>6</sup>

### Postoperative nausea and vomiting

Some patients treated with ondansetron for postoperative nausea and vomiting do not respond to therapy. One

possible mechanism for this failure is ultra-rapid drug metabolism via CYP2D6. Ultra-rapid metabolism is seen in patients with more than three copies of the CYP2D6 allele. Patients exhibiting ultra-rapid metabolism of ondansetron have a five times higher incidence of vomiting, but no difference in their incidence of nausea.<sup>7</sup>

Similarly, genetic variation in the serotonin receptors 5-HT<sub>3A</sub> and HT<sub>3B</sub> seem to be associated with an increased risk of postoperative vomiting.<sup>8</sup>

### Muscle relaxants

Gender differences have been demonstrated in the dosing, onset and recovery from vecuronium and rocuronium with females requiring up to 30% less rocuronium and having prolonged muscle weakness when compared to males. The differences only appear to be present with the aminosteroidal drugs.<sup>9,10</sup>

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