4 Induction of Phase I Systems

4.1 Introduction

The aim of drug therapy is to provide a stable, predictable pharmacological effect that can be adjusted to the needs of the individual patient for as long is deemed clinically necessary. The physician may start drug therapy at a dosage that is decided on the basis of previous clinical experience and standard recommendations. At some point, the dosage might be increased if the desired effects were not forthcoming, or reduced if side effects are intolerable to the patient. This adjustment of dosage can be much easier in drugs that have a directly measurable response, such as a change in clotting time. However, in some drugs, this adjustment process can take longer to achieve than others, as the pharmacological effect, once attained, is gradually lost over a period of days. The dosage must be escalated to regain the original effect, sometimes several times, until the patient is stable on the dosage. In some cases, after several weeks of taking the drug, the initial pharmacological effect seen in the first few days now requires up to eight times the initial dosage to reproduce. It thus takes several weeks to create a stable pharmacological effect on a constant dose. In the same patients, if another drug is added to the regimen, it may not have any effect at all. In other patients, sudden withdrawal of perhaps only one drug in a regimen might lead to a gradual but serious intensification of the other drug's side effects. These effects are shown by some illustrative histories, as detailed below.

History 1

After suffering a head trauma in a motorcycle accident, a 22-year-old male was subject to recurrent grande-mal convulsions that were treated with carbamazepine. After starting on 200mg daily, this dose had to be gradually increased stepwise over four weeks to maintain plasma levels within the therapeutic window to 1200mg daily.
Analysis

Plasma levels were not maintained within the therapeutic window at each dose level for more than a week or so, as carbamazepine clearance appeared to gradually increase, until a dosage was reached where clearance stabilized so that drug levels remained within the therapeutic window.

History 2

A 23-year-old male epileptic was prescribed phenytoin (300mg/day) and carbamazepine (800mg/day). The laboratory assays showed that phenytoin was in the therapeutic range, while carbamazepine was undetectable in the plasma. A 50 per cent reduction of the phenytoin dosage allowed the carbamazepine plasma concentrations to rise to therapeutically effective levels.

Analysis

The lack of carbamazepine in the plasma at a dosage which is known to exert a reasonable therapeutic effect in other patients implied that the drug’s clearance was much higher than normal, to the point where bioavailability was almost zero. Cutting the phenytoin dosage slowed the high rate of clearance of carbamazepine, allowing plasma levels to ascend to the therapeutic window.

History 3

A 49-year-old male epileptic was prescribed phenytoin at 600mg/day and carbamazepine at 2000mg/day. The patient’s condition was controlled with minimal side effects for three months. The phenytoin was then abruptly discontinued; within four days, the patient became gradually more lethargic and confused, until one week later hospitalization was necessary. The carbamazepine dosage was reduced to 1200mg/day and the confusion and sedation disappeared.

Analysis

A stable co-administration of two drugs implies that despite the high dose of carbamazepine, blood levels for both drugs were initially in the therapeutic window. The removal of the phenytoin led to gradual increase in the symptoms of carbamazepine overdose, without any change in the dose. This indicates that carbamazepine blood levels climbed way above the therapeutic window into toxicity. This was caused by a marked, but gradual, fall in carbamazepine clearance when the phenytoin was withdrawn.
*History 4*

A 64-year-old obese male was prescribed simvastatin 10mg daily. Over the next three months, lack of clinical response led to a fivelfold increase in dosage. He was then admitted to hospital with rhabdomyolysis. Unknown to his general practitioner, he self-administered St John’s Wort, which he discontinued when his mood was sufficiently elevated, around 10 days prior to the toxicity manifesting itself.

*Analysis*

The statin was not effective unless considerably higher doses than normal were used, indicating that the drug was being cleared at a higher rate than normal. The general practitioner was unaware that the patient was taking St John’s Wort extract. The patient abruptly stopped taking the herbal extract and the clearance of the statin gradually fell while the dose did not, so the drug accumulated and exerted toxicity.

*History 5*

A 47-year-old female was stabilised on phenobarbitone and warfarin and her prothrombin time was optimized by substantial increase over the normal dosage of anticoagulant, although blood levels were within normal limits. Within 10 days of the abrupt withdrawal of phenobarbitone the patient suffered a mild haemorrhage.

*Analysis*

As a higher than normal dosage of warfarin was necessary to maintain its plasma levels in the therapeutic window in the presence of the phenobarbitone, it suggests that the latter drug was accelerating the clearance of warfarin. Once the phenobarbitone was stopped, this accelerating effect was lost too, leading to accumulation of the warfarin to the point that blood levels rose above the therapeutic window leading to toxicity, in this case an exaggerated therapeutic effect.

*History 6*

A 55-year-old male being treated for tuberculosis was taking rifampicin (600mg daily), isoniazid (400mg daily), ethambutol (200mg daily) and pyrazinamide (400mg daily), was also epileptic and was taking carbamazepine (2000mg daily). The patient decided to stop all medication over
the Christmas period to enter his annual seasonal alcohol binge, where he drank heavily for several days. After approximately 13 days, he resumed his drug regimen and before the end of the first day, he was drowsy, lethargic, confused and eventually difficult to wake and was hospitalized. Some of the symptoms of the tuberculosis resumed, such as fever, chills and cough.

**Analysis**

The patient was suffering from carbamazepine toxicity and very high plasma levels were found on blood analysis. This indicates that the cessation of all drug intakes over the Christmas period of 13 days had led to a marked reduction in the clearance of carbamazepine, and the resumption of his previous high dosage caused drug accumulation and significant CNS toxicity. The absence of pressure of the anti-tuberculosis drugs had also allowed the disease to partially re-establish itself and may well have led to selection of partly drug-resistant forms of the bacteria.

**Summary**

In all five cases, there are a number of common features:

- Some of the drugs’ clearances were not stable until a relatively high dose was employed.

- One drug (or herbal preparation) was able to grossly accelerate the clearance of another agent(s).

- The changes in plasma levels were sufficiently great to either lead to toxicity or total loss of efficacy.

- The toxic effects occurred gradually over days, rather than hours.

- The increase in drug clearance caused by other drugs was fully reversible.

**4.2 Causes of accelerated clearance**

A number of explanations could be put forward for the effects seen above. There could be changes in absorption of a drug in the presence of another agent, although this is unlikely as most drugs are passively absorbed. Perhaps the renal clearance of the drug could be accelerated in some way; in this context this is also unlikely, as the drug has to be in the plasma before it can be filtered by the kidneys. To enter the circulation from an oral dose, the
drugs must pass through the gut, the portal circulation and then the liver itself. In Histories 1 and 2, the clearance of carbamazepine was initially unstable and in the presence of phenytoin, virtually 100 per cent cleared before it reached the circulation.

Since the liver’s blood flow does not usually change markedly, then the only way such a large effect on drug levels can occur is that the liver is extracting much more of the drug than usual in the presence of the other drug. This acceleration of drug metabolism as a response to the presence of certain drugs is known as ‘enzyme induction’ and drugs which cause it are often referred to as ‘inducers’ of drug metabolism. The process can be defined as: ‘An adaptive increase in the metabolizing capacity of a tissue’; this means that a drug or chemical is capable of inducing an increase in the synthesis of a specific CYP isoform, which is usually (although not always) the most efficient metabolizer of that chemical.

4.3 Enzyme induction

Types of inducer

There are several drugs and chemicals capable of inducing hepatic metabolism: these include:

- **Anticonvulsants**, such as phenytoin, carbamazepine and phenobarbitone; these induce many CYP isoforms, including 1A2, 2C9, 2C19 and 3A4.

- **Steroids**, such as dexamethasone, prednisolone and various glucocorticoids, induce CYP3A4.

- **Polycyclic aromatic hydrocarbons**; these are found in atmospheric pollution, cigarette smoke, industrial solvents and barbecued meat. These agents include contaminants of foodstuffs and watercourses like dioxins and polycyclic chlorinated biphenyls. These compounds induce the normally non-constitutive CYP1A1 in the liver, as well as CYP1A2, which specializes in polycyclic aromatic amines. Induction of CYP1A1 is also very strong in the lung in smokers and is a standard marker for heavy tobacco use.

- **Antibiotics**, such as rifampicin and griseofulvin, induce most CYPs including 1A2, 2C9, 2C19 and 3A4.

- **Recreational agents**, such as nicotine in tobacco products, is a known inducer of CYP1A2, and heavy alcohol consumption will induce CYP2E1.
• Herbal remedies; although more research must be conducted into the various herbs on the market, St John’s Wort is the most clinically relevant and investigated (CYP3A4).

Common features of inducers

Looking at the structures of the most potent hepatic enzyme inducers there are apparently few common features. These chemicals range in size from very small and water-soluble (ethanol) to very large and lipophilic (rifampicin). However, inducers are usually lipophilic and contain aromatic groups and consequently, if they were not oxidized, they would be very persistent in living systems. CYP enzymes have evolved to oxidize this very type of agent; indeed, an elaborate and very effective system has also evolved to modulate the degree of CYP oxidation of these agents, so it is clear that living systems regard inducers as a particular threat among lipophilic agents in general.

The process of induction is dynamic and closely controlled. The adaptive increase is constantly matched to the level of exposure to the drug, from very minor almost undetectable increases in CYP protein synthesis, all the way to a maximum enzyme synthesis that leads to the clearance of grammes of a chemical per day. Once exposure to the drug or toxin ceases, the adaptive increase in metabolizing capacity gradually subsides to the previous low level.

4.4 Mechanisms of enzyme induction

Introduction

The process by which enzyme induction occurs has three main requirements:

• The hepatocyte must detect the presence of particular potentially persistent lipophilic drugs and/or toxins and correctly sense their concentration.

• The process of detection is translated into an increase in the appropriate metabolic system within the cell, which is capable of clearing the drug and/or toxin as efficiently as possible.

• Complete (detection and action) system is dynamic and reversible, so it is sensitive to further changes in drug concentration.

It is apparent that the main inducible CYPs, 1A1/1A2, 2C9 and 3A4, employ broadly similar systems whereby they regulate their ability to respond to increases in drug concentration. The exception to this rule seems to be 2E1.
Apart from CYP1A1/1A2 induction, these systems are not fully understood, but enough is known to suggest that the method of induction is closely related to a combination of the CYP’s endogenous as well as xenobiotic-responsive functions.

**CYP1A1/1A2 induction**

Although enzyme induction has been known since the 1960s, it was not until the 1970s that the first steps in understanding how CYP enzyme induction was regulated were taken. This work was carried out with one of the most potent toxins known, dioxin, or TCDD. In the cytoplasm of most cells a receptor complex can be found which consists of a ligand-binding subunit and a heat-shock protein (HSP-90: Figure 4.1). This complex is known as the aryl hydrocarbon receptor, or ‘Ah’ receptor. TCDD was found to bind to the Ah receptor and the TCDD/Ah complex migrates to the nucleus, leaving the heat-shock protein behind in the cytoplasm. The TCDD/Ah complex enters the nucleus and heterodimerizes with the nuclear protein ARNT and then the complex binds to specific DNA sequences upstream of the CYP1A1

![Figure 4.1](image-url) **Figure 4.1** Basic mechanism of CYP1A1 and 1A2 induction: the Ah receptor binds the inducer alongside HSP-90, but only the Ah receptor and the inducer cross into the nucleus to meet ARNT and activate the xenobiotic response elements on the DNA to induce expression of the CYP isoforms
or 1A2 genes, which are termed xenobiotic-responsive elements (XRE) or sometimes DREs, or drug-responsive elements.

These sequences are essentially ‘switches’ which lead to increased transcription and translation of the CYP enzymes. It is thought that the system obeys the law of mass action, so providing there are enough Ah receptors in the cell cytoplasm, then the more TCDD that appears in the cell, will lead to more TCDD/Ah complexes migrating to the nucleus and binding to the DREs, which in turn increase CYP expression. This sensitive system operates constantly and is capable of coordinating a response in terms of increased CYP synthesis, which is capable of eventually clearing (by CYP-mediated oxidation) large amounts of TCDD from the cell.

The Ah and ARNT receptor system is clearly multifunctional, as TCDD induces other enzyme systems as well as CYP1A1/1A2, such as glutathione-S-transferase and aldehyde dehydrogenase; so it is easy to see that exposure to compounds which resemble TCDD will have a significant impact on the concentrations of many other endogenous molecules which are cleared by these enzyme systems.

The Ah/ARNT system is found in virtually all tissues; in mice it appears to be involved with the development of the liver and the immune system, which may be similar to their function in man. As with all induction effects, this process begins within hours of exposure to the toxin or drug, but takes several days to lead to maximal CYP expression, or maximal induction of the enzyme. As well as TCDD, it is thought that polycyclic hydrocarbons and heterocyclic amines induce CYPs 1A1 and 1A2 in this way, as does the anti-ulcer agent omeprazole. Essentially, the ‘default mode’ for CYPs 1A1 and 1A2 is in the ‘off’ or low-level position, so these enzymes are not intended to be constantly expressed as the cell does not normally encounter planar aromatics such as TCDD in any quantity. There is also evidence that the CYP1A1/2 system can be switched off by other agents, such as the ‘orphan’ (currently function unknown) nuclear receptor, the short heterodimer partner (SHP). This receptor can bind to a number of nuclear receptors such as RXR (retinoic acid X receptor) and several other receptors which control thyroid and oestrogen levels. SHP can also block the response of CYP1A1 to TCDD, probably by directly blocking ARNT. There are also likely to be a number of compounds that bind to SHP and regulate CYP1A1 activity.

CYP1A1/2 induction is of high toxicological significance in the lung in non-ciliated ‘Clara’ cells, which are in the forefront of the detoxification of pollutants in inspired air. These cells have more than half their volume given over to smooth endoplasmic reticulum (SER) and induction of 1A1/2 by PAHs in tobacco leads to the formation of reactive epoxides, which attack DNA, forming ‘adducts’ or small PAH-related structures which are covalently bound to DNA and are strongly linked with lung carcinogenicity. It has been suggested that the high state of lung induction of CYP1A1 leads to an increased Clara cell exposure to reactive species of oxygen generated by 1A1
even when it is not metabolizing substrates. This is because 1A1/1A2 are thought to ‘leak’ reactive oxygen species and this ‘drip–drip’ effect might make as great a contribution to DNA damage as the aromatic metabolites. CYP1A1 has also been implicated in the metabolism of nitrosamines such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butane (NNK). In animal studies, DNA was attacked by the metabolites of this compound resulting in an O6-methylguanine adduct. Other lung-specific toxins include CYP2E1-activated vinylidene chloride. The likelihood of the development of lung tumours in response to metabolism depends on the amount of carcinogenic species produced, its detoxification and the efficiency of DNA repair mechanisms.

**CYP2B6 2C8/2C9 and 3A4**

Induction of these CYPs appears to be controlled by a markedly different system from the cytosolic receptor-mediated 1A series (Figures 4.2a and b). Typical inducers of these CYPs include phenobarbitone, primidone, phenytoin and rifampicin. These CYPs are controlled by a nuclear receptor called the ‘constitutive androstane receptor’ (CAR). The important word here is ‘constitutive’ which means that CAR constantly mediates CYP expression at

![Figure 4.2(a) Possible mechanism of constitutive androstane receptor (CAR)-mediated control of CYP2 series and CYP3A4. CAR and SCR-1 bind the inducer ligand inside the nucleus, bind retinoic acid X receptor (RXR) and activate the CYP expression](image-url)
a rate that can be slowed or accelerated by factors outside the cell. This is unlike the Ah receptor, which essentially lies dormant if there are no inducers present to bind it, and the 1A series of CYPs are only expressed at a tiny level, if at all. Another aspect of CAR is that it is linked to a co-activator, called SRC-1. Normally, the CAR/SRC-1 complex will then bind to RXR, or the retinoic acid X-receptor, before it can bind DNA (Figure 4.2a). The CAR/RXR complex binds to PBREM (phenobarbitone-responsive enhancer module) in the CYP2B gene and to the ER6 element of the CYP3A4 gene. PBREM triggers induction by barbiturates. So the expression of these CYPs is constantly managed by CAR/SRC-1, in a way analogous to a car engine with the throttle pressed down around halfway. Deactivators of CAR/SRC-1, such as cytokines and some steroids, can slow or even switch off expression of these CYPs as they bind briefly to the CAR/SRC-1 and cause the SRC-1 element to break off and the CAR will not function, so ‘lifting the foot off the accelerator’ (Figure 4.2b). Inducers probably cause CAR to bind SRC-1 even more tightly, thus increasing its effectiveness in binding DNA and leading to the throttle being ‘floored’. Thus the expressions of these CYPs are closely controlled by a variety of different endogenous and exogenous agents. This elaborate and sensitive system illustrates the vital day-to-day role of these CYPs in the metabolism of xenobiotics and endogenous chemicals.

Figure 4.2(b) Possible mechanism for the modulation of CAR-ligand activated CYP induction: a series of endogenous deactivators cause break up of the CAR/RXR/SCR-1/ligand complex and induction is switched off
**CYP2E1 induction**

CYP2E1 is of interest from the standpoint of drug metabolism (it oxidizes isoniazid, paracetamol and chlorzoxazone), hepatotoxin activation (paracetamol, carbon tetrachloride, thioacetamide) and carcinogen activation (N-nitrosodimethylamine, benzene, vinyl chloride and trichloroethylene). The major interest in this isoform lies in its induction by such apparently disparate factors as small hydrophilic molecules, such as ethanol, acetone and pyridine, as well as by systemic stresses, such as diabetes and starvation. It is not yet certain exactly how 2E1 is induced, but it appears that more than one mechanism is involved. When animals are exposed to 2E1 inducers, CYP2E1 protein levels are increased up to eightfold, although the CYP2E1 mRNA levels have not been seen to increase. This suggests that 2E1 is not induced like CYP1A1, rather that somehow the regulatory step is after transcription, i.e. at the stage of the actual synthesis of the enzyme at the rough endoplasmic reticulum. Two possible mechanisms have been suggested to account for this; the first is that the presence of the substrate chemically stabilizes the 2E1 protein and makes it functional, when it would normally be poorly or non-functional. The second mechanism suggests that more 2E1 is made in a set time, indicating greater efficiency of translation (Figure 4.3).

The first mechanism implies that in the absence of substrate, considerable effort is being made within the hepatocyte towards the formation of a poorly functional and perhaps even non-functional protein, on the off chance that

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**Figure 4.3** Proposed mechanism of CYP2E1 induction: this is partly by acceleration of the translation of the protein as well as a direct effect of the inducer on the structure of the isoform so making it functionally competent.
a substrate might appear and then the process would not then be so apparently wasteful. Certainly, when 2E1 is fully induced, the catalytic activity corresponds with the amount of protein present, so it is fully functional at this point.

Why 2E1 might function in such an apparently wasteful way could lie in the specific triggers of its induction and the nature of the chemicals 2E1 is designed to oxidize. Insulin levels fall during diet restriction, starvation and in diabetes; the formation of functional 2E1 is suppressed by insulin, so these conditions promote the increase of 2E1 metabolic capability. One of the consequences of these conditions is the major shift from glucose to fatty acid/tryglyceride oxidation, of which some of the by-products are small, hydrophilic and potentially toxic ‘ketone bodies’. These agents could and do cause a CNS intoxicating effect which is seen in diabetics who are hypoglycaemic, they may appear ‘drunk’ and their breath will smell as if they had been drinking. In the non-diabetic individual who is in a state of starvation, any ketone-mediated intoxication would obviously hamper the search for food, so these molecules must be cleared rapidly. The key factor here is the speed at which these compounds could accumulate – the TCDD mechanism of induction, with its time frame of days, might be too slow to cope with the accumulation of ketone bodies in starvation, so the much quicker ‘protein stabilization’ system perhaps might be rapid enough to ensure that adequate levels of 2E1 were present to prevent intoxication of the CNS.

**CYP3A4 induction**

As members of the 3A family are the major P450s in human liver, it is not surprising that they exhibit very broad specificity and are induced by a structurally diverse group of substances. Inducers of 3A4 include steroids, macrolide antibiotics, rifampicin, and imidazole antifungals, barbiturates, and even pesticides, such as organochlorine and organophosphates. The induction process is tailored to species, so animal studies have been less helpful in assessing the possible human enzyme-inducing properties of a novel chemical agent; rifampicin is a potent inhibitor of human and rabbit 3A enzymes, but it is without effect in the rat. The process by which CYP3A enzymes are induced is still the focus of intense study, however some main steps in the process have emerged. 3A differs from the 1A and 2E control systems, and resembles CYP2B6/2C8/9 series induction/repression with one important difference. With CYP3A4 a sensing receptor does bind the xenobiotic for some time and then activates the gene. Like 2B6/2C8/9, the receptor is nuclear. With CYP3A4 induction, it is believed that the xenobiotic reaches the nucleus and then binds to one of a large family of nuclear receptors (classified as NR1I) called PXR, or the pregnane X receptor. This was so named as it responds to the steroid pregnenolone. PXR is found in the
liver and intestine and may be part of an endocrine signalling pathway, as its function is modulated by many other nuclear receptors as well as cytokines and hormones (Figure 4.4).

PXR is capable of binding and becoming activated by such a diverse group of inducers that it must possess a highly flexible recognition site, which only requires a very poor substrate fit for activation to occur. PXR is also termed a steroid and xenobiotic sensing receptor (SXR). The PXR/substrate complex then binds to another nuclear receptor, the RXR (retinoic acid X receptor). The resultant heterodimer binds to the response elements that are ‘upstream’ of the human 3A4 gene, known as the ER6 elements (Figure 4.4). It has also been proposed that there is a second xenobiotic response element module (XREM) which is activated either as well as, or instead of, the ER6 elements. Further research will clarify the balance between the two response elemental systems. The expression of CYP3A4 is then upregulated according to the number of ‘hits’ on the response element system (Figure 4.4).

This process is far from completely understood; it is suggested that RXR as well as other nuclear receptors, such as GR, the glucocorticoid receptor and CAR, are also involved. It is likely that 3A4 can be controlled by CAR as well as PXR, although it appears that PXR is the dominant mechanism of expression control.

The complexity of the regulation of CYPs such as 3A4 will be investigated for many years to come, although the necessity of such systems is understandable as the control of the systemic concentrations of hormones, such as
glucocorticoids and steroids, is achieved through the balance of their synthesis and oxidation, so the regulation of steroid-oxidizing CYPs such as 3A4 must be sensitive to systemic threats such as infection and inflammation. Interleukins negatively regulate PXR and CAR, so it is logical that steroid balances should be regulated in these situations.

Currently humans are exposed to many environmental pollutants, such as nonyl phenols, which can activate PXR and CAR, and the implications of the resultant changes in CYP3A4 expression have not been fully explored, as we still do not understand the full spectrum of the endogenous functions of inducible CYPs such as 3A4.

**Non-inducible CYPs: CYP2D6**

CYP2D6 (sometimes known as debrisoquine hydroxylase) accounts for only a single figure percentage of human P450s, although it is important as the main source of clearance for a number of drugs, such as tricyclic antidepressants, some antipsychotics (haloperidol, risperidone), some beta-blockers and SSRIs. It is not thought to be inducible, and in cases where the clearance of a 2D6 substrate is accelerated in the presence of a known inducer, it is usually because 3A4 has been induced and this isoform is responsible for the increased clearance. CYP2D6 substrates dextromethorphan and mirtazapine clearances are markedly increased by rifampicin and carbamazepine respectively in this way. Interestingly, some studies such as those with the benzodiazepines and citalopram have shown that CYP2D6 activity increases in pregnancy. Whether this is a true induction process remains to be determined.

4.5 **Induction – general clinical aspects**

From a clinical standpoint, important features of enzyme induction can be summarized:

- The process is relatively slow, i.e. usually days or even weeks;
- The potential changes in drug concentrations can be great enough to cause treatment failure;
- The induction process is usually, but not always, reversible over a similar time frame to its appearance, although reversal can be slower;
- Where a patient is stabilized on a high ‘induced’ drug dosage, if there is a treatment break of up to several days, drug accumulation and toxicity will occur.
The timescale of the induction process does largely depend on the potency of the inducer. Pentobarbitone causes a marked decrease in nortriptyline blood concentrations within only two days, doubling its clearance. The gradual fall-off in drug levels will lead to a commensurate loss of drug efficacy. Some of the most clinically relevant drug interactions caused by enzyme induction are described below.

### Anti-epileptic agents

#### Drug combinations

In approximately one-third of cases of epilepsy control of the condition can only be achieved with a combination of anticonvulsants, and this leads to potential problems with the induction effects of carbamazepine (2C9, 2C19, 3A4; History 2), phenytoin (1A2, 3A4) and phenobarbitone (1A2, 2C8, 3A4). In a combination of anticonvulsants, co-administered compounds metabolized by these CYP enzymes will have their plasma concentrations significantly reduced. A good example of this is valproic acid, where plasma levels can be reduced by 80 per cent in the presence of phenobarbitone, and by half with phenytoin and nearly 70 per cent with carbamazepine co-administration. Among the second generation of anticonvulsants, drugs such as topiramate and tiagabine are also cleared more rapidly in the presence of inducers.

#### Drug withdrawal

Problems may arise when the combination of anticonvulsants is changed, or when one drug is completely withdrawn (History 3). The remaining drug plasma levels might rise over the following few days as the inductive effect recedes and clinical signs of an intensification of the pharmacological effect will gradually become apparent. It is most desirable to anticipate this effect by tapering the dosage of the other drugs over days or weeks as appropriate. However, this is not such an easy process, as there is relatively little literature on how long it takes for the effects of standard inducers to fully wear off. There is some evidence that in some drugs it can take longer to disappear than the original onset time. It is better to taper the dose, or the patient might be subject to increased side effects, which they may or may not complain about. Overall, it is important that the drug levels remain within the therapeutic window.

#### Other drug combinations

Anticonvulsants are co-administered with other CNS modulating drugs, such as antipsychotics, tricyclic antidepressants (TCAs), benzodiazepines and
newer agents such as SSRIs. With respect to enzyme induction, anticonvulsants can greatly accelerate the clearance of antipsychotics like haloperidol and benzodiazepines such as midazolam, although temazepam clearance is not dependent on 3A4 and is not affected by inducers of this isoform. CYP3A4 inducers can also accelerate the clearance of some TCAs.

**OTC preparations**

St John’s wort (*hypericum perforatum*) is a freely available over-the-counter antidepressant agent, which has found considerable popularity (History 4). This appears justified, as it has been shown to be clinically effective. Of course, patients are usually unaware that the active component, hyperforin, is one of the most potent activators yet found of the human PXR receptor, leading to induction of CYPs 3A4 and 2C9. Hyperforin itself undergoes extensive metabolism by 3A4 to hydroxylated products. A recent study with this herbal remedy demonstrated that a 14-day course of St John’s wort and dosage of a total of 900mg daily was capable of doubling alprazolam clearance. Many other herbal remedies are available (gingko, ginseng, etc.), although the enzyme-inducing properties of most have not been substantiated. However, commercial and other pressures suggest that these agents are recommended to be taken for long periods of time, so the opportunity for even mild CYP induction is clear. This is potentially a serious problem when a patient terminates their consumption of St John’s wort when they have been stabilized on a prescribed dosage regimen of other drugs (History 4). Many patients do not consider herbal remedies as ‘drugs’ in that they believe that the remedy will not have any side effects, yet somehow exert a strong therapeutic action. In addition, these herbal extracts vary enormously in quality, purity and percentage of the active component, which will all depend on the source and preparation of the extract. It is important that patients are asked if they have taken, or would consider taking, herbal remedies during a drug treatment regimen. This is particularly a problem where a course of conventional antidepressants is embarked upon and the patient’s symptoms do not improve quickly. Consequently they may understandably resort to assistance from an herb extract such as hypericum.

**Anticoagulant drugs**

Anticoagulants such as warfarin are mainly dependent on CYP2C9 for their clearance, with some contribution from 3A4 and 1A2. Inducers of these enzymes will make a substantial reduction in the plasma levels of these drugs and therefore their anticoagulant effects (History 5). There is no substitute for checking the patient’s coagulation function to ensure that they remain within the therapeutic window. If an enzyme-inducing drug is withdrawn,
there is the danger of accumulation of the anticoagulants, which will lead to haemorrhaging. This situation would be exacerbated if a substitute drug were to be a CYP inhibitor. In that case, anticoagulant drug concentrations would climb so rapidly that the patient’s life could be in danger.

**Oral contraceptives/steroids**

The CYP3A4 inducers can accelerate the clearance of ethinyloestradiol; this is a particular concern with low-dose oral contraceptive preparations. Increasing the contraceptive dose, or a recommendation to use other methods of contraception, may negate this effect. Other prescribed steroids such as corticosteroids will also be cleared more rapidly in the presence of inducers of CYP3A4.

**Antiviral/antibiotic drugs**

Of the newer anti-HIV antiviral compounds, ritonavir, nevirapine, indinavir and saquinavir are all metabolized by CYP3A4, so it is possible that inducers may affect their clearances *in vivo*. However, this situation is complicated by the fact that for example ritonavir is a potent inhibitor of 3A4 and induces its own metabolism. This induction effect means that at least 14 days’ therapy is required before plasma levels stabilize. Potent inducers such as rifampicin do exert some effect on ritonavir plasma levels, but only to a relatively modest (~35 per cent) degree. Any changes in the plasma levels of an antibiotic or antiviral agent can lead to subcurative drug concentrations and a possible selection of resistant variants of the infectious agent, so plasma levels should be closely monitored to ensure minimum inhibitory concentrations (MICs) are exceeded while toxicity is minimized. Certainly abruptly stopping and restarting inducing antibiotics such as rifampicin (History 6) will lead to severe disruption of the clearances of co-prescribed agents and lead to drug levels climbing above the therapeutic window until the inducing effect is re-established. Patient drug tolerance may be severely impaired during this period.

**Anti-cancer drugs**

Any changes to the plasma levels of antineoplastic agents can have serious repercussions in terms of toxicity and therapeutic effects. A number of these agents are ‘pro-drugs’ and CYP3A4 activates them to their therapeutic metabolites. Cyclophosphamide is known to cause more toxicity in the presence of 3A4 inducers, and similar effects can be seen with taxol and etoposide. Up to a threefold increase in the clearance of these antineoplastic drugs can be seen in the presence of 3A4 inducers.