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# Main consequences of enzymatic induction and inhibition during the interaction of drugs and the role of CYP3A4, CYP3A45 enzymes

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**ABSTRACT**

The microsomal enzyme system is responsible for the metabolism of pollutants, toxic agents and drugs. With regards to drug metabolism, the activity of the constituent microsomal enzymes results in the reduction of pharmacological and toxicological activity through conversion of hydrophilic (water soluble) compounds to allow urinary excretion. Microsomal enzymes oxidize drugs and steroid hormones in reactions that require adenine nucleotide diphosphate (NADPH). Reversible inhibition reduces enzyme activity through reversible interaction. A covalent bond between the inhibitor and the enzyme can promote the destruction of essential functional groups of the enzyme. Enzyme induction and inhibition are problematic in drug polytherapy. Often the lack of effect of a drug or the side effects that a certain drug exhibits are problems of interaction of drugs with each other in that individually they inhibit or stimulate enzyme activity.

## INTRODUCTION

Many chemical agents interact  stimulate microsomal liver enzymes. These include hypnotics, ankylosing agents, anticonvulsants, antihistamines, anesthetics, etc. Enzymatic induction results in a) hepatocystology (proliferation of the endoplasmic reticulum); b) drug pharmacology; c) *in vitro* metabolism of drugs. In one study, the medical records of patients were categorized chronologically in the registered offices of the province's public hospitals [1]. Accordingly, researchers found a quantitative and unqualified difference in enzyme content. Enzyme induction has several important implications in humans. In multiple-drug therapy, the use of one drug may alter the reception of another [2]. Phenobarbital, for example, can be used to treat neonatal jaundice because its use facilitates the conjugation of bilirubin (Figure 1).

The medical literature, including reviews of domestic journals, is an important source of drug safety information relevant for signal detection, safety profile analysis, and risk-benefit assessment [3]. Drug action can also lead to an increase in liver or kidney toxicity when these are metabolized into toxic metabolites.

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The general characteristics of induction drugs are that the induction process is intended to be relatively slow, usually lasting days or weeks [4]. Changes in drug concentration can cause the drug to become ineffective in the body, but the induction process is usually reversible. In the Central Nervous System (CNS), astrocytes, the structural support cells, play a critical role in contacting neurons and maintaining a stable environment and proper neuronal function [5]. Continuous dopaminergic stimulation (CDS) is a concept that is based on constant drug delivery and continuous stimulation of the striatal DA receptor [6].

### Drug binding – effects

When a drug enters the blood, a percentage of the drug binds to plasma proteins and the rest remains unbound or "free". The degree of protein binding depends on the drug's physical characteristics, such as lipid solubility and degree of ionization. When administered intravenously in adequate doses, these drugs cause a rapid loss of effect [7]. This is often described as "arm-brain time", meaning the time it takes for the drug to travel from the injection site (usually the arm) to the brain. With regard to anesthesia, continuous intravenous infusion or "sedation" maintains the effect much longer [8].

In cases where the patient's organism stabilizes in receiving high doses of induction drugs and if the patient interrupts the therapy for a certain time, then great toxicity may appear in the organism [9]. Drugs stimulate the production of enzymes in microsomes and in this way accelerate metabolic reactions (Table 1). Network pharmacology was first proposed by Andrew Hopkins based on cheminformatics, bioinformatics, network biology and pharmacology During in vitro studies, p-synephrine was discovered to also suppress adipogenesis [10]. Adoption of a diagnostic protocol can often minimize missed diagnoses and narrow the etiology, such as the diagnostic protocol for shock or sudden cardiac arrest [11].

***Table 1***. Stimulating drugs, type of stimulating drug, enzymes on which they act, stimulating effect

| Stimulant drugs | Type of stimulant drug | Enzymes act the stimulating effect | Use of the drug |
|---|---|---|---|
| Anticonvulsants | Phenytoin Carbamazepine Phenobarbital | CYPA2 CYP2C8/C9 CYP2C19 CYP3A4/5 | Sedative during epileptic seizures, nervousness, and headaches |
| Steroids | Dexamethasone Prednisolone Various glucocorticoids | CYP3A4/5 | Rheumatic problems, skin and lung diseases, chemotherapy, etc. |
| Antibiotics | Rifampicin (Rifamor) | CYP1A2, CYPC9, CYP2C19, CYP2B6, CYP3A4 | Destruction of bacteria, treatment of tuberculosis, etc. |
| Herbal medicines | St. John's wort oil | CYP3A4/5 | Antidepressants, anxiety relief |

## Enzymatic inhibition (enzymatic inhibition)

Enzymatic inhibitors are those structures that, in different ways, inhibit and prevent enzymes from developing enzymatic reactions [12]. They do this by impeding the metabolism of many other drugs, but sometimes they do not fully inhibit their metabolism [13]. Competitive inhibition is often reversible inhibition [14]. The enzyme returns to normal because a certain drug competes with the other drug that will be metabolized by this enzyme [15]. To date, for example, researchers have only used conventional methods to study the bioactive alkaloids of Lycopodiaceae and Amaryllidaceae [16], but bioactive approaches have been experimented with. In the applied technique, these desired alkaloids are concentrated exactly in the active center of the extracting enzyme, and are inserted as a template that is connected to its active center [17]. The drug stays for a certain time with the enzyme without providing any effect and is gradually lost. Another example is that of the CYP450 enzyme. Drugs that interact reversibly with the CYP450 enzyme are Azolic antimicrobials, quinidine, cimetidine, etc [18]. When a patient is treated with a drug that will be metabolized by glucuronyl transferase, and at the same time an anti-mycotic is given and this anti-mycotic competes with this drug, with regard to the interaction of the drug with the enzyme, as long as it interacts with the enzyme, metabolism does not occur and the first effect of the drug will be strong (and can be a toxic effect). At the moment when the inhibitor is removed, the metabolism flows normally, and eventually the drug is eliminated (Figure 1). Damage to the skin may occur due to underlying health conditions, such as diabetes [19].

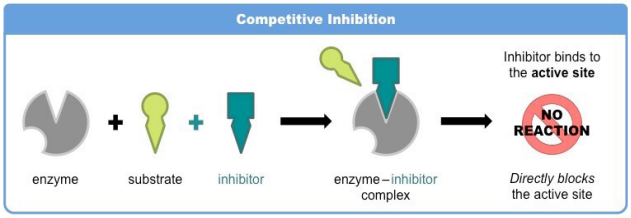


***Figure 1.*** The schematic form of the metabolism and the first effect of the drug when the inhibitor is removed, the metabolism proceeds normally and goes towards the elimination of the drug. In this case the effect is reversible with the CYP450 enzyme

## Non-competitive inhibition

Non-competitive inhibitors are drugs with structures that are different enough as to not compete for the same enzyme, but their overlaps or metabolites during the oxidation process incorrectly bind to, for example, CYP450 enzymes. Inhibition occurs in the oxidation phase and binds by forming a new reversible complex (Figure 2). A complex that is incorrectly placed and not in the center where the enzyme reacts, but in the rest of the enzyme, binds to the enzyme and changes its structure, the enzyme, in this case, will not be able to catch it.

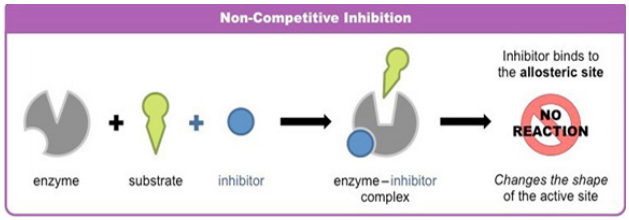


***Figure 2.*** Schematic form of non-competitive inhibition, the oxidation process incorrectly binds to CYP450 enzymes, and will not be able to capture the substrate

Inhibition based on the deactivation of the CYP450 enzyme is another type of inhibition that completely deactivates the enzyme. In this case, the complex that is formed degenerates the enzyme. The enzyme binds to, for example, the iron ion, and the reduced iron forms a complex that completely changes the structure of the enzyme. The enzyme is no longer what it was before and can never be re-transformed into the former enzyme. Hence, this enzyme is out of play, and the drug can only be metabolize after the catalytic cycle has synthesized other (new) enzymes to take over the role of metabolizing this drug. In the catalytic cycle of cytochrome P450, the reaction takes place where the heme group is represented as two forms with iron ($Fe^{2+}$, $Fe^{3+}$), between them. Cysteine thiolate from protein is represented by a hydrocarbon substrate and ROH is the hydroxylated product (Figure 3).

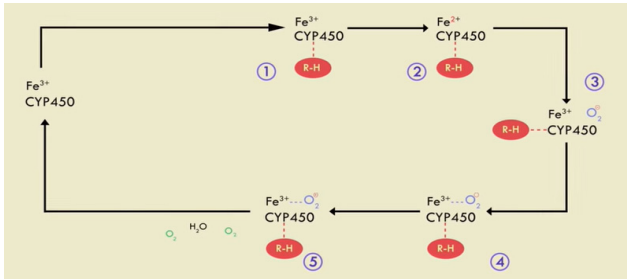


***Figure 3.*** The mechanism of action and the form of the P450 enzyme system in the metabolism of xenobiotics

Azoles as enzyme inhibitors are potent inhibitors of CYP450 enzymes. Ketoconazole is the most used drug in the group of azoles, and is a strong inhibitor of CYP3A4 enzymes. The drug is quite toxic. Ketoconazole belongs to the group of antimycotic drugs. It causes a decrease in the level of testosterone in the blood and, as a result, leads to men's feminization (sterility). It would not be, however, surprising if there are other effectors of this effect since the host network is ruled by a variety of biochemical activities [6]. Age changes are associated with several changes in human organs, which result in variations in pharmacokinetics and pharmacodynamics. Medicines that change the functions of the human body can have toxic and harmful effects (among others, damage to vision, hearing, swallowing, motor activity and cognitive functions) that can affect the intake and adequate administration of drugs. The elderly, and especially patients over 75 years of age, are the main users of many drugs and often are prescribed five or more drugs long-term. As we age, total body water and muscle mass decrease, while body fat percentage increases. These changes can cause drugs to have a longer duration of action and increased effect. In the elderly, the simultaneous use of a cocktail of drugs can cause muscle contraction and dilation of the upper airways, hence playing a crucial role in maintaining the patency of the upper airways, and representing an important counteractive force. It should be noted that certain compounds show promising pharmacological activities, including anti-inflammatory [7].

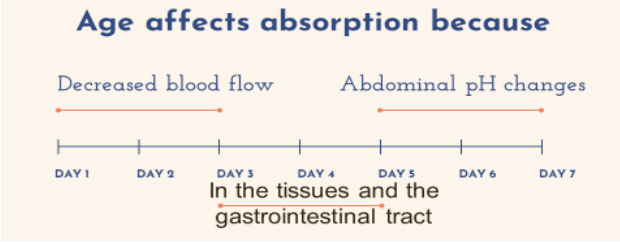


***Figure 4***. The form of drug absorption depends on the age of the human organism.

With age and chronic diseases, the size of the liver and hepatic blood flow decrease, therefore, the dosage of drugs that are significantly metabolized by the liver must be adjusted (Figure 4). The liver is the main organ and target of resistance in in the body, as it plays a role in lipid metabolism, contributing to the development of insulin resistance and obesity [8]. About two-thirds of the population experience a decline in creatinine clearance with aging. This can lead to a prolonged half-life for many drugs and cause toxic levels to rise if dose and frequency are not adjusted.

**Herbal medicines, antibiotics, alcohol or grapefruit co-consumption, antifungals**

There is a long history of herbal medicine use in Kosovo and in the Caucasus region. Herbal drugs are very cheap compared to conventional forms of medication, and are currently the topic of pharmaceutical and public health investigation for use in healthcare.

Today, 1/3 of all patients with epilepsy are treated with a combination of anti-epileptic/ anticonvulsant drugs. If these inducing drugs are administered together with drugs that are metabolized precisely by CYP enzymes, (enzymes that are induced), then the drug that was administered with the inducing drug will decrease the plasma concentration level. This effect is readily apparent in cases in which patients are treated with valproic acid (Table 2).

***Table 2.*** Anti-epileptic drugs, plasma concentration level (valproic acid)

| Type of grass | The concentration of ac. valproic |
|---|---|
| Carbamazepine + Valproic Acid | The concentration level of ac. valproic decreases by about 70% |
| Phenobarbitone + Valproic | The concentration level of ac. valproic decreases by about 80% |
| Phenytoin + Valproic Acid | The concentration level of ac. valproic decreases by about 50% |

The wrong use of the drug, and wrong drug combinations can lead to serious health problems. Therefore, there is a need to include less aggressive therapies in the treatment of patients. In this way, the possibility of using medicinal plants is created. For example, St John's wort (*Hypericum perforatum*) has biologically active compounds that act as selective serotonin reuptake inhibitors (SSRI), and St. John's wort (*Hypericum perforatum*) has found application for treating major depression. Moreover, pharmaceutical investigation has demonstrated that Cantonese oil has bioactive compounds such as hyperforin, hypericin, flavonoids and tannins.

The clinical consequences that appear during the use of certain herbal medicines are as follows:

1. Depending on the drug, doubles the elimination of alprazolam (a drug used in cases of panic attacks, which acts directly on the CNS);
2. Accelerates the metabolism of ciclosporin (a drug given during kidney transplantation), does not allow the transplanted tissues to attach, but constantly causes their rejection, and as a result of this comes extreme nephrotoxicity, followed by the death of the organism.
3. The extracted chemicals stay in the body for 16-47 hours and it takes 3 weeks until the body is completely cleansed.
4. Great care should be taken in the quality, purity and content of active chemicals during the preparation of herbal medicines.

With regard to the use of different antibiotics such as: (ritonavir, nevirapine and indinavir), are metabolized by the CYP3A4 enzyme. It can be concluded that antibiotics are metabolized and induce the same enzyme, which means that it is self-stimulating. The study cases were carried out in the clinical centers of Kosovo and North Macedonia (Table 3,4,5,6,7 8).

The liver is sensitive to a variety of drug interactions. For example, in the cytotoxic assays at low concentrations of two tested compounds (Chromium III, and Cobalt II), stimulation of cell proliferation was observed [9]. Alcohol in combination with several pharmaceutical compounds has a range of effect. The liver is the main organ of alcohol metabolism in humans (Table 6). Ethanol is metabolized in the hepatocytes which represent about 70% of the total liver mass. In the absence of excessive alcohol consumption, viral hepatitis and other causes of hepatic steatosis include a spectrum of conditions, among others, simple hepatic steatosis, non-alcoholic steatohepatitis (NASH), hepatic fibrosis,

and cirrhosis. Adequate antimicrobial therapy, hence, is essential to maximize the survival of critically ill patients [10].

***Table 3.*** Treatment of patients who suffered from accidents (treated with carbamazepine)

| No. of patients/ samples | Treatment / Medication | Analysis/Result |
|---|---|---|
| 5 | Carbamazepine once a day 200mg/1200mg | |
| Age (25-45) | As a result of motor accidents, patients have experienced great trauma with headaches.<br>The patients were initially treated with 200 mg of carbamazepine per day, but the dose was gradually increased for 4 weeks to 1200 mg.<br>It failed to keep the drug concentration within the therapeutic window.<br>Why should the dose of carbamazepine be increased? | Since the plasma levels are not maintained within the therapeutic window, we conclude that carbamazepine is rapidly eliminated.<br>It has not given the effective effect it was expected to give and there was definite need to increase concentration.<br>Once it was achieved, the drug level remained within the therapeutic window |

***Table 4.*** Treatment of patients who had epilepsy (treated with carbamazepine)

| No. of patients/ samples | Treatment/Medication | Analysis/Result |
|---|---|---|
| 7 | Carbamazepine once a day 300-800 mg | |
| Age (35-65) | Patients who had epilepsy were treated with 300 mg per day of phenytoin and 800 mg per day of carbamazepine.<br>Laboratory analyses have shown that phenytoin was within the reference values, while carbamazepine was not detected at all in the blood plasma.<br>Why does this happen and what measures should be taken next? | The lack of carbamazepine at the plasma level is due to the rapid elimination of carbamazepine.<br>For carbamazepine to show its active effects, the concentration of phenytoin in the body will need to decrease, as it stimulates the CYP3A4 enzyme that metabolizes carbamazepine. |

***Table 5***. Treatment of patients with tuberculosis disease (alcohol consumers)

| No. of patients/ samples | Treatment/Medication | Analysis/result |
|---|---|---|
| 21 | Rifampicin/Isoniazid/ Ethambutol 300-800 mg | |
| Age (45-65) | Patients (sample) with tuberculosis disease were treated with drugs such as rifampicin 600 mg per day, isoniazid 400 mg per day, and ethambutol 200 mg per day.<br>Three patients out of 21 (sample) diagnosed with epilepsy were treated with 2000 mg of carbamazepine per day.<br>However, three patients decided to not to be treated by this drug therapy and, for a few days, returned to consuming alcohol.<br>After 13 days, their condition worsened and they returned to accepting the same therapy.<br>After the end of any treatment with antibiotics, it takes 2-3 days to remove the antibiotics from the body, and only after this time can alcohol be consumed<br>Why does this happen and what measures should be taken next? | Shock is presented as a result of toxicity from carbamazepine which is present at very high levels in the blood plasma.<br>This indicates that discontinuation of all other drugs during the 13 days had stopped the elimination of carbamazepine.<br>Resuming the previous dose demonstrated drug accumulation and great toxicity occurred. The the lack of anti-tuberculosis drugs has allowed the disease to progress |

***Table 6.*** Tabular presentation of some drugs and interactions of alcohol with some drugs

| Drug class | Generic name | Type of interaction |
|---|---|---|
| Analgesics | Aspirin | Aspirin increases gastric emptying, which leads to rapid absorption of alcohol in the small intestine |
| | Acetaminophen | Alcohol increases the metabolism of acetaminophen into a toxic product, causing liver damage |
| Antibiotics | Erythromycin | Erythromycin increases gastric emptying, which leads to rapid absorption of alcohol in the small intestine |
| | Isoniazid | Alcohol increases the risk of liver disease with isoniazid |
| Anticonvulsants | Phenytoin | Chronic alcohol consumption causes the breakdown of phenytoin |
| Antihistamines | Diphenhydramine<br>Cyproheptadine<br>Hydroxyzine | Alcohol increases their effects on the central nervous system, such as sleepiness, sedation, etc. |
| Anticoagulants | Warfarin | Acute alcohol consumption inhibits the metabolism of warfarin and consequently increases anticoagulation.<br>Chronic alcohol consumption promotes the metabolism of warfarin, and as a result, anticoagulation decreases |

Grapefruit juice generates a variety of side effects if it is taken together with drugs that are metabolized by the CYP3A4 enzyme, such as Diazepam, Erythromycin and Cyclosporine (Table 7).

***Table 7.*** Presentation of the analysis of the use of grapefruit pulp and juice

| No. of patients/ samples | Treatment/Medication | Analysis/Result |
|---|---|---|
| 4 | Terfenadine (anti-allergic drug) | |
| Age (29-33) | One of the four sample patients, 29 years old, used terfenadine (an anti-allergic drug), but he also consumed grapefruit juice 2-3 times a week.<br>One day he took the drug together with 2 glasses of grapefruit juice, unfortunately after an hour the first symptoms of the patient's deterioration appeared.<br>The patient collapsed and then died.<br>Why does this happen and what measures should be taken? | The presence of grapefruit juice caused the appearance of a high level of the drug in the blood plasma.<br>The components found in the liquid enable inhibition of drug elimination by inhibiting CYP3A4 enzymes, which were the drug's metabolizers.<br>In this way, the drug accumulated in the body, which caused cardiovascular problems in the patient, and a fatal arrhythmia occurred, which the patient was unable to cope with |

Drug therapy combination involving antifungals can have perilous effects on the body (Table 8).

***Table 8.*** Use of drugs and consumption of antifungal drugs such as econazole

| No. of patients/ samples | Treatment/Medication | Analysis/Result |
|---|---|---|
| 5 | Antifungal like Reconazole | |
| Age (30-59) | Patients who suffered from lung infections (such as bronchitis) were treated with erythromycin and simultaneously consumed antifungal drugs such as econazole.<br>After a few hours, two patients collapsed and were hospitalized.<br>Why did the patient collapse and what measures should be taken further? | The patient's collapse was presented as a result of treatment with econazole, a drug that inhibits the enzymes that metabolize erythromycin and thus enabled the increase in the level of erythromycin in the blood plasma.<br>Where the drug accumulates in the body, toxic effects are presented.<br>In this case, the dose of the inhibitor should have been either reduced or replaced with an antifungal drug that is not an enzyme inhibitor |

Research conducted at the cancer center (Cedares), Dublin in Canada on the use of medicinal cannabis in cancer patients has shown a much more efficient effect than the use of drugs such as EGFR erlotinib, Gefitinib, etc. The research has lasted three years, and the number of patients who have been studied is over 350. Even against the CYP3A4 enzyme, in comparison with conventional drug treatments, on ant-cancer drug therapy, the metabolism of the drug is increased and plasma concentrations are reduced. In this study, the use of medicinal cannabis for cancer treatment has resulted in pain relief and a reduction in the use of other drugs in cancer patients (Table 9).

***Table 9.*** Use of anti-cancer drugs (EGFR erlotinib, Gefitinib), and complementary results, use of medicinal cannabis

| No. of patients/ samples | Treatment/Medication | Analysis/Result |
|---|---|---|
| 350 | EGFR erlotinib, Gefitinib 250 mg | |
| Age (45-60) | Inducers of the CYP3A4 enzyme increase the metabolism of the drug gefitinib, thereby reducing plasma concentrations of the drug gefitinib | Administration of CYP3A4 enzyme inducers (eg phenytoin, carbamazepine, rifampicin, barbiturates, or herbal preparations containing *Hypericum perforatum*), may reduce the efficacy of treatment |
| | Treatment/Medication | Analysis/Result |
| | *Medicinal cannabis* | |
| | Safe complementary treatment for pain relief in cancer patients.<br>¼ of the participants were prescribed a THC-dominant product.<br>17% of all participants were prescribed CBD-dominant products.<br>38% balance of both | The treatment has achieved the balance of tetrahydrocannabinol (THC) and Cannabidiol (CBD), very effective for the relief of advanced cancer pain.<br>38% of patients feel moderate pain.<br>66% of patients with advanced metastatic disease felt pain.<br>Patients have experienced a reduction in pain.<br>Patients have decreased the use of other painkillers.<br>Medicinal cannabis has given results and is a safe, complementary option for use in patients with tumor diagnosis |

## CONCLUSIONS

From the summary of information, , examples, laboratory analyses, and clinical aspects, we conclude that the consumption of inducing drugs is an undesirable feature during interactions with other drugs. They enable the ineffectiveness of the drug at the site of action, as a result of the rapid elimination of the drug. Meanwhile, the consumption of inducing drugs is even more dangerous, since the drug constantly accumulates in the body. It is not eliminated and exhibits high toxicity in the body that can lead to fatal consequences.

## RECOMMENDATIONS

Identifying and resolving medication administration errors will improve patient care. However, it should be noted that it is important to consider the pharmaceutical form of the drugs and the chemical and physical properties of each drug, as well as the characteristics of the person in the administration of drugs. Therefore, administration of drugs through different routes may represent a change in the bioavailability of the drug and consequently alter its therapeutic response. It is recommended to read the instructions for the indications and contraindications of the drug before consuming it.

## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest in this work.

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