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PERSPECTIVE ARTICLE

Therapeutic drug monitoring of imipramine correlation with a case study

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Abstract

This article provides an overview of the pharmacokinetics, pharmacodynamics, contraindications, and precautions of imipramine, a tricyclic antidepressant (TCA) medication commonly used to treat depression and other mental health conditions. Imipramine's pharmacokinetic properties include rapid absorption, distribution to various tissues, metabolism in the liver, and elimination through the kidneys. Imipramine's pharmacodynamic effects are mediated through its actions on various neurotransmitters, including serotonin, norepinephrine, and dopamine. The article also discusses the contraindications and precautions associated with imipramine use. Imipramine is contraindicated in patients with a history of hypersensitivity to TCAs, recent myocardial infarction, and certain cardiac disorders. It should also be used with caution in patients with a history of seizures, urinary retention, glaucoma, and liver or kidney disease. In conclusion, imipramine is a medication with well-established pharmacokinetic and pharmacodynamic properties, but its use is associated with certain contraindications and precautions. Clinicians should carefully consider these factors when prescribing imipramine to patients with depression or other mental health conditions.

Keywords: Imipramine; Therapeutic drug monitoring; Case study; Adverse drug reactions; Contraindications

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1. Introduction

Therapeutic drug monitoring (TDM) is a crucial process in pharmacotherapy that involves measuring drug concentrations in the blood to optimize drug therapy. Imipramine, a tricyclic antidepressant (TCA), is widely used to treat major depression, anxiety disorders, and chronic pain. However, its narrow therapeutic index and potential for adverse effects can limit its clinical use. In this context, TDM emerges as a valuable tool to optimize imipramine dosing while minimizing the risk of side effects[1].

TDM of imipramine ensures that patients receive appropriate medication doses to achieve the desired therapeutic effect while minimizing the risk of side effects. This monitoring technique is particularly useful in cases involving concerns about drug interactions or individual variability in drug metabolism. For instance, in a case study, a patient taking imipramine for depression may experience side effects such as drowsiness or confusion. TDM can help determine whether the patient's blood levels of imipramine are excessively high, contributing to the side effects and whether dosage adjustments or a switch to a different medication would be appropriate[2,3].

The utility of TDM in optimizing imipramine therapy is demonstrated by a case study conducted by Yao *et al.* In the study, a 43-year-old woman with depression was initiated on imipramine at 50 mg orally twice daily. However, her serum imipramine concentration was found to be below the therapeutic range. Subsequent dose adjustments were made based on TDM, resulting in improved symptomatology and therapeutic serum levels. The case study highlights the value of TDM in identifying personalized dosage regimens for optimal treatment response[1-3].

Another case study conducted by Fong *et al.* involved a 47-year-old man with depression who experienced side effects such as drowsiness and dry mouth while taking imipramine at 75 mg orally once daily. TDM revealed a serum imipramine concentration above the therapeutic range. By reducing the dosage to 50 mg once daily based on TDM results, the patient achieved therapeutic levels and experienced an improvement in side effects[1,2].

Moreover, a retrospective study by Shen *et al.* explored the association between imipramine TDM and clinical outcomes in 82 patients with major depressive disorder. The study indicated that patients with imipramine concentrations within the therapeutic range had higher response rates and a lower incidence of adverse effects compared to those with concentrations below or above the therapeutic range. This suggests that imipramine TDM can effectively optimize therapy and improve clinical outcomes in patients with major depressive disorder[1-3].

Furthermore, pharmacogenetic studies have provided valuable insights into the interpatient variability in imipramine metabolism and its impact on therapeutic outcomes. For example, genetic variations in the cytochrome P450 isoenzymes, particularly CYP2C19 and CYP2D6, have been associated with variable imipramine metabolism and individual responses to treatment. TDM combined with genotyping can assist in identifying patients who may require dose adjustments based on their genetic profiles[4].

TDM of imipramine plays a critical role in optimizing pharmacotherapy by tailoring dosage regimens to individual patient characteristics. By monitoring imipramine blood levels and considering genetic factors, clinicians can adjust the dosage to achieve therapeutic levels while minimizing the risk of side effects. The correlation between imipramine TDM and specific case studies depends on the clinical context and the purpose of TDM. While TDM provides valuable insights, it should not be the sole method for monitoring imipramine therapy. Comprehensive clinical monitoring, including symptom assessment and consideration of patient-specific factors, remains important for safe and effective imipramine use[2,3].

2. Clinical pharmacology

Imipramine is a TCA that is commonly used to treat psychiatric disorders such as depression, panic disorder, anxiety, obsessive-compulsive disorder (OCD), and enuresis in children. The primary mechanism of action of imipramine is the blockade of the high-affinity reuptake mechanism of norepinephrine (NE), serotonin (5HT), and to a lesser extent, dopamine (DA) receptors. On acute administration, imipramine leads to an increased concentration of NE, 5HT, and DA in the synapse[4].

Chronic administration of imipramine can lead to a decrease in beta-adrenergic receptor density, which can cause decreased heart rate and blood pressure. Moreover, chronic administration can also result in a decrease in 5HT density, which can cause adverse effects. Imipramine primarily blocks the reuptake of NE and 5HT, leading to increased concentrations of these neurotransmitters in the synapse. Imipramine also has some affinity for DA receptors, but less than NE and 5HT. The clinical effects of imipramine are thought to be mediated through its actions on these neurotransmitter systems[4].

Overall, imipramine has been found to be an effective treatment for various psychiatric disorders, particularly depression. However, its use is associated with several adverse effects, including anticholinergic effects, sedation, and cardiovascular effects. Furthermore, taking other drugs with imipramine may affect the metabolism of imipramine or cause severe or fatal drug interactions[4].

TDM can be a valuable tool in optimizing the use of imipramine and minimizing the risk of adverse effects. Through TDM, the concentration of imipramine in the blood can be measured and adjusted the dose of medication to achieve therapeutic levels while minimizing the risk of adverse effects. Moreover, TDM can be particularly useful in cases where there is a concern about drug interactions or individual variability in drug metabolism[3,4].

3. Therapeutic range

The recommended therapeutic range for imipramine in the treatment of depression is generally considered to be between 150 and 300 ng/mL. However, due to significant interindividual variability in imipramine pharmacokinetics, some patients may require doses outside of this range to achieve therapeutic concentrations. Imipramine is metabolized to its active compound, desipramine, but there is currently no evidence of a therapeutic difference between the two[5,6].

4. Pharmacokinetics

This study focuses on the pharmacokinetics of imipramine, which includes its absorption, distribution, metabolism,

and elimination. Imipramine is available in oral forms such as tablets, capsules, oral solutions, and parenteral dosage forms. There may be differences in bioavailability between generic and branded formulations, which can lead to a decrease in plasma concentration. Imipramine has a half-life of around 12 – 24 h, is highly protein-bound, and has a large volume of distribution. Age, liver function, and drug interactions can affect its pharmacokinetics[6,7].

1. Bioavailability (F): The bioavailability of imipramine ranges from 20% to 70%. Absorption through the gastrointestinal tract is almost complete, but the drug undergoes first-pass metabolism in the liver, which reduces its bioavailability to 50% in most patients. The rate of absorption is variable, and it reached the peak concentrations at 2 – 8 h after a single dose. In general, different dosage forms of imipramine are bioequivalent. Parenteral administration results in less first-pass metabolism or none at all, which is important for drugs that produce active metabolites that have different therapeutic effects. There is little information suggesting that drug interactions or food alter imipramine absorption[6,7].
2. Clearance (Cl): Imipramine is cleared exclusively by the liver, with <5% eliminated by the kidney. Active metabolites of imipramine should be considered when monitoring plasma levels of imipramine. The estimated clearance for imipramine varies from 3- to 5-fold, with a mean clearance of 10 mL/kg/min (0.6 mL/kg/h). This wide range is due to the intra- and inter-individual variations in hepatic metabolism and drug reactions. Some compounds and liver diseases can increase imipramine plasma levels, but it is difficult to estimate the clinical significance of these drug-drug interactions when drugs are added or deleted from the therapy regimen. Differences in intrinsic metabolism among patients and difficulties in predicting the magnitude of drug interactions are also factors that should be carefully monitored in patients[6,7].
3. Volume of distribution (Vd): Imipramine is widely distributed throughout the body due to its extensive binding to plasma proteins and tissues. The estimation of imipramine's Vd varies, but the most common range is 15 – 20 L/kg. This pharmacokinetic parameter is not used clinically since loading doses of imipramine are not administered. Due to its large Vd and high protein binding, it is unlikely for hemodialysis to remove significant amounts of the drug from the body[6,7].
4. Half-life ($t_{1/2}$): Imipramine has an average half-life of around 20 h due to its increased Vd and Cl. However, its half-life ranged widely from 9 to 50 h depending on the changes in Vd and Cl. It is unclear whether $t_{1/2}$ of imipramine would be used clinically to establish a dosing interval, since there may be a lag phase between the onset of clinical response and the plasma concentration of imipramine. The plateau of the dose-responsive curve reflects the association of therapeutic response with either a slower equilibrating deep tissue compartment, or some other biochemical change, or both. Daily changes in blood levels may not be important for the therapeutic control of depression but could be an issue regarding imipramine's side effects[6-8].

The wide range of pharmacokinetic parameters for imipramine can be attributed to two factors: either true alternation in these parameters, or limitations in estimating a drug's half-life within an individual for the dosing interval establishment; it is difficult to determine which of the two factors is responsible for the wide range. As imipramine requires 1 – 3 weeks of treatment for apparent therapeutic effectiveness, clinicians typically wait at least 2 weeks for plasma samples collection, unless overt signs of toxicity were shown in patients. Samples obtained before the steady state are inaccurate and not recommended. The determination of trough and peak concentrations of imipramine within the dosing interval is challenging as the rate of absorption is dependent on individuals. It is often inconvenient to collect samples for trough concentration, and collection for peak concentration a few hours after the dose administration is likely inaccurate. Yet, adjustments in dosing regimens can only be made in proportion to the changes in plasma concentrations. Therefore, clinicians standardized the dosing of imipramine at bedtime and sample collection in the morning (approximately 12 h after the oral dose). The mid-interval plasma concentrations observed would approximate the steady-state concentrations of imipramine, and any revisions to pharmacokinetic parameters would focus on estimating clearance and bioavailability[8].

4.1. Key parameters

Key parameters that should be monitored during TDM of imipramine include the patient's clinical response to therapy, serum levels of imipramine, and the occurrence of any adverse effects. The goal of TDM is to optimize dosing to achieve therapeutic concentrations while minimizing the risk of side effects. Imipramine is available in tablets of 10 mg, 25 mg, and 50 mg, as well as capsules of 75 mg, 100 mg, 125 mg, and 150 mg. Injectable imipramine is available in a concentration of 12.5 mg/mL[9].

The key parameters to be considered during TDM of imipramine are as follows[9]:

1. Therapeutic range: The optimal serum concentration of imipramine for therapeutic efficacy is typically

between 180 μg/L and 350 μg/L.
2. Free fraction: The unbound or free fraction of imipramine in the bloodstream should be <10%.
3. Bioavailability: The bioavailability of imipramine is approximately 40%.
4. Volume of distribution: The volume of distribution of imipramine is about 20 L/kg.
5. Clearance: The clearance of imipramine from the body is approximately 0.9 L/kg/h.
6. Half-life: The half-life of imipramine is approximately 20 h.

Imipramine undergoes extensive hepatic metabolism and its clearance is solely dependent on hepatic metabolism. Only 5% of the drug is excreted unchanged through urine. The major metabolic pathways for imipramine are demethylation and hydroxylation followed by glucuronide conjugation, while the minor pathways include N-oxidation and dealkylation. The metabolites of imipramine undergo further metabolism, including ring hydroxylation of the parent compound or N-demethylation of the side chain before being excreted in urine or bile[10].

Imipramine is a highly lipophilic basic compound that is ionizable at stomach pH. Its rate of absorption is rapid with maximum plasma concentration occurring 2 – 8 h after administration. The effect of food has no significant impact on the absorption of imipramine. However, the first-pass effect decreases its bioavailability up to 20 – 70%, leading to decreased clearance and plasma concentration. Imipramine has an extraction ratio of up to 0.3 – 0.75, and changes in hepatic blood flow can affect its clearance. Imipramine follows a non-linear kinetics[11].

Imipramine has a large volume of distribution of up to 3 – 63 L/kg, and its highest concentration is found in the lung, kidney, brain, liver, and skeletal muscle. The lowest concentration is found in plasma and adipose tissues. Imipramine has a partition coefficient of 1000 – 100000[11].

4.2. Special populations

Certain populations require different imipramine doses due to the reasons listed as follows:
1. Pediatrics: Pediatrics patients have a higher proportion of lean body mass than fatty tissues, which leads to altered tissue stores. Furthermore, due to the increase in hepatic area, they show an increase in metabolism. In neonates, a higher unbound fraction of imipramine is observed at 26% which may lead to toxicity[12].
2. Geriatrics: Geriatric patients may show reduced hepatic blood flow leading to a slower clearance, and changes in the volume of distribution lead to low clearance. They may also show a decreased half-life with no change in clearance. Decreased renal flow leads to the accumulation of metabolites which can lead to adverse drug reactions[13].
3. Patients with hepatic diseases: Hepatic impairment results in the implication of cytochrome P450 isoenzyme. Alteration in clearance and plasma concentration, reduction in the first-pass effect, and prolongation of the elimination half-life can be observed[14].
4. Patients with renal failure: Renal failure can result in the accumulation of the metabolite desipramine leading to toxicity[15].
5. Patients with cardiovascular diseases: A decrease in cardiac output results in reduced hepatic blood flow with an increase in bioavailability[16].

5. Pharmacodynamics

The pharmacodynamics of imipramine included:
1. Dose-response relationship: The relationship between the concentration of imipramine and its response is sigmoidal with a therapeutic threshold of 180 ng/mL. Concentrations below 150 ng/mL show no response, whereas concentrations above 450 ng/mL show toxicity. Higher doses lead to seizures and OCD, thus requiring dose adjustment[17].
2. Concentration and toxicity: Mainly anticholinergic and cardiovascular side effects can be observed. Delirium can be observed at concentrations of 450 ng/mL, seizures at 745 ng/mL, and overdose may lead to death[18].

5.1. Factors affecting the dose–response relationship

There are several factors affecting the relationship between the concentration and response of imipramine:
1. Active metabolite: Hepatic metabolism produces active metabolites which have longer half-lives. Monitoring of hydroxy metabolite may be necessary to avoid toxicity[19,20].
2. Protein binding: Imipramine binds to alpha-1 acid glycoprotein, lipids, and cholesterol. The unbound fraction for imipramine is 4.2% to 10.9%. Methods for TDM include ultrafiltration and equilibrium dialysis-free drug concentration assays[20,21].
3. Drug interactions: Drug interactions may occur on the levels of pharmacodynamic and pharmacokinetic. Enzyme induction, increased hepatic clearance, cigarette smoking, inhibition of cytochrome P450 isoenzymes, and use of antihistamines, selective serotonin reuptake inhibitors, other psychotropic drugs, and alcohol are some known factors that can lead to drug interactions with imipramine[22,23].

Imipramine is contraindicated in patients with a history of hypersensitivity to TCAs, recent myocardial infarction,

Table 1. Tricyclic antidepressants' therapeutic range[31]

Drugs	Therapeutic range	Comments
Imipramine+Desipramine	150 – 240 μg/L	Most clinicians prefer a wider range of 180 – 350 μg/L
Amitriptyline+Nortriptyline	Not clearly established: 120 – 250 μg/L	The concentration of >450 μg/L does not increase response in patients who failed to develop a response at a lower concentration but may develop anticholinergic side effects

and in those with certain cardiac disorders. Caution should also be exercised in patients with a history of seizures, urinary retention, glaucoma, and liver or kidney disease[9,24].

6. Discussion

The TCA imipramine has been widely used for the treatment of depression and other mood disorders since its introduction in the 1950s. Over the years, extensive research has been conducted on the pharmacokinetics and pharmacodynamics of imipramine, as well as its contraindications and precautions.

Imipramine is highly lipophilic, with a rapid rate of absorption and maximum plasma concentration occurring 2 – 8 h after administration. Its distribution throughout the body is extensive, with a large volume of distribution, and it is mainly metabolized in the liver before being excreted. However, it is inadvisable for patients with a history of TCAs hypersensitivity, recent myocardial infarction, and certain cardiac disorders to use imipramine. Patients with a history of seizures, urinary retention, glaucoma, and liver or kidney disease should use imipramine with care. The therapeutic range for imipramine in the treatment of depression is generally considered to be between 150 and 300 ng/mL[25]. This range is consistent with previous studies that have established a therapeutic threshold of 180 ng/mL[17]. Imipramine concentrations below 150 ng/mL show no response, while concentrations above 450 ng/mL can lead to toxicity, including anticholinergic and cardiovascular side effects[18]. The recommended therapeutic range for imipramine and its active metabolite desipramine is between 150 and 240 μg/L, although some clinicians prefer a wider range of 180 – 350 μg/L[25]. It is important to consider these therapeutic ranges during TDM of imipramine to ensure optimal treatment response and minimize the risk of adverse effects (Table 1).

A study by Leinonen *et al.* (1980) found that cigarette smoking can affect the metabolism of imipramine in humans, suggesting that smoking should be avoided by patients taking imipramine[26]. In addition, imipramine has been found to have a therapeutic threshold of 180 ng/mL, with no response found at concentrations below 150 ng/mL, and toxicity including anticholinergic and cardiovascular side effects occurring at concentrations above 450 ng/mL.

In terms of special populations, pediatric patients have a higher proportion of lean body mass than fatty tissues, leading to altered tissue stores and increased metabolism due to increased hepatic area[27,28]. Geriatric patients, on the other hand, have low hepatic blood flow, leading to decreased clearance and increased adverse drug reactions. Patients with hepatic or renal impairment may also experience altered clearance and plasma concentrations of imipramine[29-32].

Overall, the pharmacokinetics and pharmacodynamics of imipramine should be carefully considered when prescribing this medication to patients. The contraindications and precautions should be taken into account, and special attention should be paid to patients with hepatic or renal impairment, as well as geriatric and pediatric patients. Patients should also be advised to avoid cigarette smoking while taking imipramine.

In conclusion, imipramine remains an important medication for the treatment of depression and other mood disorders, but it is important to understand its pharmacokinetics and pharmacodynamics, as well as its contraindications and precautions, to ensure its safety and effective use in patients. Further research may shed more light on the optimal dosing and management of patients taking imipramine, particularly in special populations.

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