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Alteration of Metformin Pharmacokinetic Profile in Rats Exposed to a Low Dose of Chlorpyrifos Insecticide

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Abstract

Chlorpyrifos (CPF) is an organophosphate pesticide widely used by farmers to control pests and has a broad spectrum of action. Research has shown that organophosphate pesticides can affect efflux pumps, specifically P-glycoprotein (P-gp), which can alter drug absorption and metabolism, indicating the potential risk of changes in a drug's pharmacokinetic profile, which could affect the effectiveness of drugs such as Metformin. This study investigated the impact of low-dose CPF exposure on the pharmacokinetic profile of Metformin, a first-line treatment for type 2 diabetes mellitus (T2DM). This study used 16 rats to examine Metformin's pharmacokinetic profile and 12 for the creatinine clearance examination. The rats were divided into two groups: a control group given normal saline (+5% Tween 20) and a group given CPF 5 mg/kg BW/day, each administered for 7 days. Metformin was administered on day 8, and pharmacokinetic parameters were assessed using UV-HPLC by measuring metformin plasma levels at 0.5, 1, 2, 4, 6, 8, 12, and 24 hours. Serum creatinine levels were examined in 12 rats using the Jaffe method on day 8 after treatment. The pharmacokinetic analysis showed that there was a change in the metformin profile following CPF administration: an increase in the area under the curve (AUC) and peak concentration (Cmax), along with a decrease in time to peak concentration (Tmax), half-life (T½), clearance (Cl), and volume of distribution (Vd). Serum creatinine levels in the CPF-administered group increased significantly ($p<0.05$). Further research, including pharmacodynamic assessment and clinical trials, is recommended to guide therapeutic decisions in populations with pesticide exposure.

Keywords: Pesticide; Organophosphates; Antidiabetics; Drug interactions.

INTRODUCTION

Chlorpyrifos (CPF) is an organophosphate pesticide widely used by farmers to control pests and has a broad spectrum of activity (Nurhidayanti & Fadillah Pratama, 2021). However, long-term exposure to low doses of CPF can lead to residue accumulation, which may impact health, including the modulation of drug pharmacokinetics, encompassing drug absorption, distribution, metabolism, and excretion. CPF affects organs involved in drug pharmacokinetics, such as the intestines, liver, and kidneys (Aung et al., 2020; El-Fakharany & Abdel Hamid, 2017; Sakinah et al., 2024)

One drug suspected of undergoing pharmacokinetic changes is Metformin, a first-line medication for type 2 diabetes that is frequently prescribed to patients with type 2 diabetes mellitus (T2DM) (Foretz et al., 2023). The organs involved in Metformin's pharmacokinetics are the intestines (for absorption) and kidneys (for excretion), as Metformin does not bind to albumin and is not metabolized (Lewis et al., 2024). Administration of low-dose CPF for 7, 14, 28, and 56 days has been shown to significantly alter intestinal villi height, increase liver transaminase enzymes (SGOT and SGPT) and blood urea nitrogen (BUN), decrease serum albumin, and change serum creatinine levels in Wistar rats (Sakinah et al., 2024; Wisudanti et al., 2024). In another study, CPF exposure caused edema, glomerular constriction, protein deposits, dilation, and renal tubular atrophy (Albasher et al., 2019). In the jejunum, CPF exposure led to villi changes, loss of epithelial cells, nuclear apoptosis, thickening of the smooth muscle layer, and separation of muscle fibers (Sakinah et al., 2024). An organophosphate insecticide has been shown to modulate efflux pumps such as P-glycoprotein (P-gp), which is physiologically expressed at blood-tissue barriers and in organs responsible for absorption and excretion, including the gut, liver, and kidneys, giving it a critical role in pharmacokinetics (Chedik et al., 2018). These findings suggest a potential interaction that may alter the effectiveness of antidiabetic drugs like Metformin.

This is important comprehending this interaction is essential, considering the increasing global prevalence of CPF exposure and its potential to alter the therapeutic effectiveness or toxicity of drugs in affected populations. There has been no research on the interaction between pesticides, particularly CPF insecticides, and oral antidiabetic drugs (OADs) such as Metformin. Therefore, further research is needed to obtain the pharmacokinetic profile data of Metformin following CPF exposure. The urgency of this study lies in its potential to provide a basis for future human research, aimed at evaluating whether dose adjustments of Metformin are necessary for T2DM patients—either increasing the dose to enhance efficacy or reducing it to prevent side effects.

MATERIALS AND METHODS

Research design

This study has received approval from the Ethics Committee of the Faculty of Medicine, University of Jember (Number: 1672/UN25.1.10.2/KE/2024). The pharmacokinetic profile study used 16 Wistar rats, divided into 8 for the control group and 8 for the intervention group. The control group was given normal saline (+5% Tween 20) for 7 days, then administered Metformin on day 8, while the intervention group was given a low dose of CPF for 7 days, followed by Metformin on day 8. CPF (Sigma Aldrich) was administered orally at 5 mg/kg body weight, 1/30 of the LD50 of CPF (Wisudanti et al., 2024), after being diluted with 5% Tween 20 and mixed with 95% 0.9% NaCl. CPF was administered once daily for 7 days. Immediately after metformin administration on day 8, serial blood samples were collected from the orbital plexus for pharmacokinetic analysis of Metformin using UV-HPLC at the following time points: 0.5, 1, 2, 4, 6, 8, 12, and 24 hours. The UV-HPLC analysis of metformin pharmacokinetics used plasma, and plasma deproteinization was performed first.

Pharmacokinetic Examination using UV-HPLC

Standard preparation was carried out by dissolving 1 mg of metformin standard in 10 mL of ddH_2O (100 μg/mL). A stock solution was prepared through serial dilution at concentrations of 1.8, 2.5, 5, 10, 20, 40, and 60 μg/mL. The standard solutions were then stored at 4°C. Sample preparation involved mixing 500 μL of metformin-containing plasma with 1 mL of acetonitrile in a microtube, followed by vortexing for 2 minutes and centrifugation at 10,000 rpm for 10 minutes. The first supernatant was collected, and the extraction process was repeated on the remaining residue by adding 1 mL of acetonitrile and repeating the vortexing and centrifugation steps. The supernatants from the first and second extractions were combined and filtered using a 0.22 μm syringe filter. The samples were stored at −20°C.

Subsequently, plasma metformin concentrations were measured using a Shimadzu High Performance Liquid Chromatography (HPLC) system with a UV LC-20AD detector, manual injection, and UV detection at a wavelength of 233 nm. Separation was performed on a SHIMPACK® VP ODS column using mobile phase A, a mixture of 10 mM potassium dihydrogen phosphate (KH_2PO_4) buffer (70%) and acetonitrile (30%) at pH 5.2, and mobile phase B, consisting of three mM sodium dodecyl sulfate (SDS). The analysis was conducted at a 1.2 mL/min flow rate with an isocratic pump mode of 90% A: 10% B, an injection volume of 20 μL, and the column maintained at 40°C. The chromatogram data were processed using Shimadzu LC Solution software version 1.25.

Creatinine Level Measurement

The serum creatinine level study was conducted using 12 Wistar rat samples, divided into two groups: one group administered a low dose of CPF for 7 days, and a control group. Creatinine levels were measured using rat serum obtained from blood centrifugation, using the Jaffe method. Serum creatinine levels were analyzed using the Creatinine reagent produced by DIALAB. The assay reagent was prepared by mixing reagents 1 and 2 in a 4:1 ratio. A ready-to-use reagent volume of 1000 μL was placed into a microtube. Then, 50 μL of serum was added to the microtube. The mixture was vortexed until homogeneous, and absorbance was measured at a wavelength of 492 nm for absorbance A1. The mixture was then allowed to stand for 2 minutes, and a measurement was taken for A2. ΔA was calculated using the formula: $\Delta A = A1 - A2$.

Data Analysis

The pharmacokinetic profile data were analyzed descriptively, while the serum creatinine level data were analyzed using an unpaired T-test.

RESULTS AND DISCUSSION

Pharmacokinetics of Metformin

Table 1 presents the calculated pharmacokinetic profile results for the control and intervention groups. The data indicate that exposure to a low dose of CPF for 7 days can lead to an increase in the area under the curve (AUC) and the peak concentration (Cmax) of Metformin. However, it also reduces the time to peak concentration (Tmax), elimination half-life (T½), volume of distribution (Vd), and clearance (Cl) of Metformin.

Table 1. Results of the calculation of pharmacokinetic profiles of control and intervention groups.

Pharmacokinetics profile	Control group	Intervention group
AUC	9.08 µg. h/ml	10.084 µg. h/ml
Bioavaibility	0.901	
Tmax	2.293 h	1.927 h
Cmax	2.283 µg/ml	3.768 µg/ml
T1/2	5.58 h	3.177 h
Vd	0,336 ml	0,199 ml
Cl	0,084 ml/minutes	0,074 ml/minutes

Figure 1 shows the metformin pharmacokinetic profile graph. The intervention group had a higher Cmax and a shorter Tmax than the control group. This result is partly caused by a greater absorption process in the intervention group, as indicated by the AUC value (Table 2). The elimination half-life (T½) of the intervention group was 3.177 hours, faster than that of the control group, resulting from the earlier Tmax. Consequently, the time required for the intervention group to reach a zero drug concentration in the blood was faster.

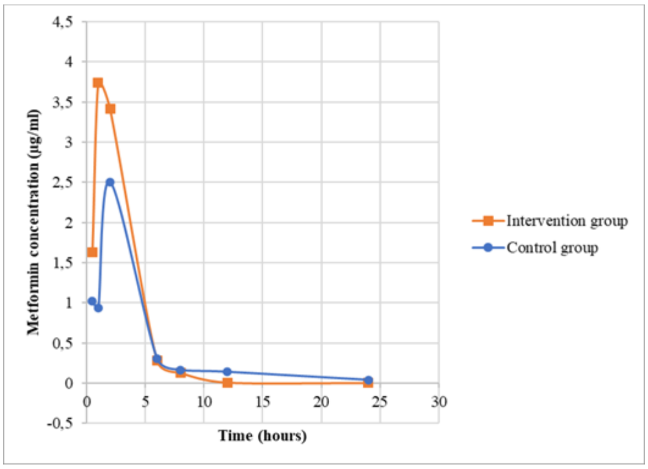

Figure 1. Pharmacokinetic graph of metformin concentration.

Table 2. Results measurement of metformin levels in plasma (µg/ml) based on hours in the control and intervention groups.

Time (Hours)	Metformin plasma levels (µg/ml)	
	Control group	Intervention group
0.5	1.023	1.627
1	0.937	3.738
2	2.507	3.412
6	0.306	0.282
8	0.164	0.131
12	0.139	0.009
24	0.039	0.004

Creatinine Levels

The creatinine results in the intervention group were above normal and higher than those in the control group. The value of the control group was 0,57 ± 0,13, and the value in the intervention group was 1,36 ± 0,06. The results of creatinine serum levels can be seen in Table 3. From the results of the independent t-test, the data show a significance value of 0.031, which means $p<0.05$, so it can be interpreted that there is a significant difference between the control group and the intervention group in the study of creatinine levels. An increase in serum creatinine levels as a kidney biomarker means that there has been a decrease in kidney function or damage.

Table 3. Creatinine levels result.

Sample Groups	Creatinine serum levels (mg/dL)
Control Group	0.57 ± 0.13 *
Intervention Group	1.36 ± 0.06 *

Result represented in Mean ± SD; *Significant results ($p<0.05$)

Discussion

The results of this study indicate that the administration of low-dose CPF caused changes in the pharmacokinetic profile of Metformin, including an increased area under the curve (AUC) and peak concentration (Cmax); decreased peak time (Tmax), half-life (T1/2), clearance (Cl), and volume of distribution (Vd). Metformin's bioavailability reaches 50-60% with a half-life of 1.5-4 hours. In the intestine, Metformin is absorbed via the organic cation transporter 3 (OCT3) into enterocytes and via OCT1 into the blood vessels. Metformin is not bound to plasma proteins in the blood and is polar or hydrophilic (Markowicz-Piasecka et al., 2017). Its plasma half-life is approximately 4-8.7 hours (Rashid et al., 2014). Metformin is not metabolized by the liver; therefore, about 30-50% of an oral dose is excreted unchanged in the urine within 24 hours, and 30% is excreted in the feces. The renal excretion of Metformin occurs via OCT2 (Markowicz-Piasecka et al., 2017).

AUC quantifies the total extent of systemic exposure to the active drug (Rashid et al., 2014). The AUC value of Metformin in the CPF-administered group increased compared to the control group, indicating greater drug exposure over the period in the CPF group. An increase in AUC can result from decreased kidney function, as seen in other studies where renal impairment led to higher AUC values for drugs like vancomycin (Lodise et al., 2022; Oda et al., 2023). The kidneys contain transporters involved in drug excretion, one of which is organic cation transporter 2 (OCT2), which is crucial for the renal clearance of Metformin (Kuehne et al., 2022).

Therefore, impaired kidney function affects OCT2 activity and subsequently reduces metformin clearance. In this study, metformin clearance (Cl) decreased in the group given CPF.

Decreased kidney function is characterized by elevated serum creatinine levels (Williamson & New, 2014). The other result of this study showed a significant increase ($p<0.05$) in serum creatinine levels in Wistar rats induced with a low dose of CPF at 5 mg/kgBW/day for 7 days compared to the control group (Table 3). Several similar studies support this finding (Abduh et al., 2023; Alruhaimi et al., 2024; Rekha et al, 2013). A study on rats administered CPF at 10 mg/kg BW for 28 days demonstrated that CPF increases serum urea and creatinine and causes several histopathological changes. ROS, MDA, NO, NF-κB p65, TNF-α, and IL-1β were increased in the kidneys of CPF-intoxicated rats (Abduh et al., 2023). Another study proved that CPF administration for 28 days significantly increased ($p<0.001$) creatinine and urea, triggered several tissue changes, and elevated renal ROS, malondialdehyde (MDA), NF-κB p65, TNF-α, iNOS, and caspase-3 (Alruhaimi et al., 2024). Furthermore, a study by Rekha et al. (2013) showed changes in kidney structure in albino rats induced with CPF at a dose of 5 mg/kg BW/day for 7 days. The kidneys of CPF-exposed rats exhibited shrunken glomeruli and tubules that were obstructed due to tubular epithelial hypertrophy and loss of lumen.

An increase in creatinine levels occurs due to impaired kidney function, which prevents the excretion of creatinine by the kidneys, leading to its elevated concentration in the blood (Kashani et al., 2020). CPF induces inflammation in kidney tissue, characterized by increased levels of pro-inflammatory cytokines such as TNF-α, IL-1β, and NF-κB. This inflammatory response causes further tissue damage and dysfunction (Mahmoud et al., 2025). CPF promotes apoptosis in kidney cells by upregulating pro-apoptotic genes and proteins such as Bax, caspase-3, and caspase-9, while downregulating anti-apoptotic proteins like Bcl-2 (Abduh et al., 2023; Alruhaimi et al., 2024; Mahmoud et al., 2025; Zhang et al., 2019). Autophagy, a cellular degradation process, is also affected, with CPF exposure causing dysregulation of autophagy-related genes and proteins (Wu et al., 2023; Zhang et al., 2019). CPF disrupts calcium signaling pathways, leading to increased intracellular calcium levels, triggering cell necrosis and worsening kidney damage (Luan et al., 2022). Chronic CPF exposure is associated with increased formation of advanced glycation end-products (AGEs), which contribute to kidney damage by enhancing oxidative stress and inflammation (Aung et al., 2020). CPF affects several molecular pathways, including the AMP-activated protein kinase (AMPK) pathway, the mechanistic target of rapamycin (mTOR) pathway, and the SIRT1/Nrf2/HO-1 signaling pathway, all of which play roles in cellular stress response, inflammation, and apoptosis (Abduh et al., 2023; Mahmoud et al., 2025; Zhang et al., 2019).

Creatinine is freely filtered by the glomerulus and is not reabsorbed in the renal tubules. Injury or damage to the glomerulus reduces the kidney's filtration of creatinine, making creatinine a valuable biomarker for detecting kidney disorders (Sakinah et al., 2024). These structural changes impair the kidney's functions in blood filtration, urine production, and the excretion of metabolites from the body. Decreased kidney function will reduce the clearance of drugs excreted through the kidneys (Stefani et al., 2019).

Bioavailability is a critical determinant of a drug's pharmacological efficacy, indicating the rate and degree to which its active form is absorbed into the bloodstream after administration. It is practically defined as the proportion of the administered dose that reaches systemic circulation in an active form and is thus able to produce a pharmacodynamic response (Stielow et al., 2023). The bioavailability of Metformin reaches 50-60%. Based on the results of this study, the bioavailability of Metformin was 0.90 in both the control and CPF-administered groups. This result indicates that CPF did not alter the bioavailability of Metformin. These results differ from the hypothesis of this study, which suggested that CPF could affect the absorption and subsequent bioavailability of Metformin. The absorption of Metformin involves several transporters in the apical membrane of intestinal cells, including organic cation transporter 1 (OCT1), OCT3, plasma membrane monoamine transporter (PMAT), serotonin reuptake transporter, and high-affinity choline transporter (Han et al., 2015).

Although there is no direct evidence that CPF affects metformin absorption, its impact on oxidative stress and inflammation could theoretically influence Metformin's pharmacokinetics. For example, CPF-induced oxidative stress could alter the expression or function of transporters involved in Metformin's absorption (Daniali et al., 2022; Farhadi et al., 2024). Furthermore, CPF's potential to cause systemic inflammation could affect the integrity of the intestinal barrier, which may influence the absorption of orally administered drugs like Metformin (Di Tommaso et al., 2021).

Another change in the pharmacokinetic profile of Metformin was that the Cmax in the CPF-administered group was higher than the Cmax in the control group. The maximum plasma drug concentration (Cmax) indicates the peak plasma concentration achieved after oral drug administration. Cmax is an indicator of the drug's absorption rate; a higher peak concentration suggests a faster absorption rate. In addition to being influenced by the absorption rate, Cmax is also affected by drug clearance. Rapid absorption increases Cmax, while high clearance lowers the drug concentration after Cmax is reached. Cmax can serve as a warning for potential drug toxicity (Rashid et al., 2014). Cmax levels are typically higher in subjects with kidney impairment due to reduced drug clearance compared to normal subjects (Urva et al., 2021). This condition can increase the likelihood of side effects from Metformin, ranging from the most common side effects such as gastrointestinal disturbances (diarrhea, nausea, vomiting, abdominal pain) (Kelly et al., 2023) to serious side effects, especially in vulnerable groups, such as the risk of lactic acidosis in subjects with impaired liver and kidney function (Aydar et al., 2022).

Metformin is primarily excreted unchanged by the kidneys, and its pharmacokinetics can be influenced by renal function. Impairment of kidney function due to chlorpyrifos has the potential to alter the volume of distribution and clearance of Metformin. The volume of distribution (Vd) describes the extent to which a drug is distributed from the blood into the body's tissues (Rashid et al., 2014). Metformin has a relatively low Vd due to its hydrophilic nature; the drug does not easily penetrate cell membranes and its distribution is highly dependent on organic cation transporters (OCTs), particularly OCT1 on the sinusoidal membrane of liver cells and also on the basolateral membrane of enterocytes, and OCT2, which is expressed basolaterally in renal tubular cells (Foretz et al., 2023). Metformin requires the OCT1 transporter to enter its target cells, such as hepatocytes (liver cells), one of its primary sites of action. Effective distribution to these tissues contributes to its Vd. A low Vd to target tissues can reduce Metformin's effectiveness as an antidiabetic agent (Higgins et al., 2012).

There is no direct explanation regarding the interaction of chlorpyrifos with Metformin or its volume of distribution via OCT1 and OCT2. However, there is relevant information on the role of OCT1 and OCT2 in Metformin's pharmacokinetics and the potential for drug interactions. OCT1 mediates the uptake of Metformin in the liver, while OCT2 is responsible for its clearance in the kidneys (Ailabouni et al., 2025; Higgins et al., 2012). These transporters are crucial for the drug's distribution and elimination. In Oct1/Oct2 knockout mice, the clearance of Metformin was significantly reduced, and the volume of distribution decreased by 3.5-fold, demonstrating the importance of these transporters in Metformin's pharmacokinetics. Exposure to chlorpyrifos is known to cause oxidative stress and inflammation. These conditions can disrupt the expression and function of various membrane proteins, including transporters like OCT1. If OCT1 function is impaired, Metformin's ability to leave the bloodstream and enter liver tissue may be reduced. This would trap more Metformin in the blood circulation, which is pharmacokinetically manifested as a decrease in the Volume of Distribution (Vd) (Higgins et al., 2012).

Although OCT2 in the kidneys is more directly related to excretion (clearance), proper kidney function indirectly supports fluid homeostasis and an optimal environment for drug distribution. Chlorpyrifos has been proven to cause nephrotoxicity, characterized by increased serum creatinine. Kidney damage can impair OCT2 function (Ailabouni, 2012). Disruption of the kidneys and their transporters can contribute to the accumulation of Metformin in the blood (increasing AUC and Cmax), which is consistent with the finding of more limited distribution (a lower Vd). To confirm an interaction between chlorpyrifos and Metformin via OCT1 and OCT2, specific research is needed to evaluate the effects of chlorpyrifos on these transporters. Specific studies are required to determine whether chlorpyrifos interacts with OCT1 and OCT2 and affects the pharmacokinetics of Metformin.

Based on the results in Table 1, it was found that the clearance of Metformin in the CPF-administered group was lower than in the control group. Several factors underlie this result, particularly in the CPF-induced intervention group, where an imbalance between ROS and antioxidants occurs, resulting in disrupted cellular function and potential tissue damage. Furthermore, impaired kidney function due to the toxic effects of CPF can be caused by the neurotoxic impact of CPF's active metabolite, chlorpyrifos oxon, on the proximal tubules (Aung et al., 2020). Therefore, a decrease in metformin clearance occurred in the intervention group, caused by kidney damage or impairment due to CPF administration in the rats of the intervention group.

In other studies, the Tmax results for Metformin show a value of 2.056 ± 0.151 hours. Based on a previous simultaneous study, the Tmax of Metformin was 2.6 hours (Rashid et al., 2014). Compared to these results, the Tmax of Metformin in this study is still within the same range, specifically 2.293 hours in the control group and 1.927 hours in the CPF-administered group. The Tmax result is inconsistent with the hypothesis, as Tmax should have been prolonged due to slower elimination resulting from kidney impairment. These Tmax results influence the half-life (T½), which was also shorter in the CPF-administered group (Table 1). This outcome is likely caused by the fact that CPF can disrupt the autonomic nervous system (by inhibiting acetylcholinesterase), leading to cholinergic overstimulation. In the gut, this can initially cause hypermotility (accelerated transit) due to excessive muscle contraction (Karami-Mohajeri & Abdollahi, 2011). Accelerated transit can speed up absorption (shorter Tmax). This is a well-established pharmacokinetic principle that connects changed motility to a change in Tmax and Cmax, without affecting the drug's bioavailability (Koziolek et al., 2019).

A limitation of this study is that the research on the pharmacokinetic profile was still conducted using different groups of test animals at each time. Therefore, for subsequent research, it is recommended to consider using the same group of test animals each time. Additionally, it is necessary to increase the number of research samples to obtain more data, enabling statistical analysis. To utilize a larger sample size, the study must have adequate facilities, infrastructure, and supporting human resources. For example, an alternative method, such as serial blood sampling using a cannula in the same test animal, can be employed, which falls under the competency of a veterinarian.

CONCLUSIONS

This study demonstrates alterations in the pharmacokinetic profile of Metformin in the group administered low-dose CPF. Further research can be conducted to analyze the pharmacodynamic effects and perform clinical trials as a basis for drug dosage adjustments in individuals exposed to organophosphate insecticides, particularly CPF. Evaluation of pharmacokinetic profile changes in other drugs under CPF exposure is also necessary, especially for drugs with a narrow therapeutic index.

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