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Review

Drug interactions of cola-containing drinks

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SUMMARY

Cola-containing drinks (CCDs) are among the most common drinks in the world. There are some reports on interactions between CCDs and some drugs. However, there is no review on reported and possible interactions of CCDs. Thus, this paper attempted to provide a comprehensive review on this subject. It is well-accepted that CCDs are acidic and contain caffeine. It has been suggested that these two properties potentiate interactions of CCDs with different drugs in the context of both pharmacodynamics and pharmacokinetic, which includes drug absorption, metabolism, and renal excretion of drugs. It has been shown that serum concentrations of MTX, clozapine, carbamazepine, phenytoin, and ibuprofen increased following CCD consumption; these interactions can be toxic. Additionally, it has been reported that serum levels of lithium and warfarin were decreased and their efficacy reduced when simultaneously administered with CCDs. Serum concentrations of erlotinib and different azoles, including itraconazol, posaconazole, and ketoconazole, have been shown to increase when these drugs were co-administered with a CCD. As proposed and discussed here, CCDs have the potential for interactions with numerous other drugs and thus clinicians should be aware of reported and potential interactions of CCDs with various medications in order to avoid adverse reactions and achieve expected clinical response.

1. Introduction

Cola drinks are among the most widely-consumed beverages worldwide. Different epidemiologic studies, evaluating food and beverage patterns of different populations, have considered the use of cola drinks and their potential for interactions with various drugs as an important parameter for evaluation. For example, a large observational study of Spanish households showed that in 2014, the second most common nonalcoholic beverage was cola [1]. Another study of Polish students of high-school and university age showed that cola-containing drinks (CCDs) were the most common caffeinated beverage consumed by this demographic [2]. Another epidemiologic study on bus drivers in a particular Brazilian city showed that 64.2% of them excessively consumed cola drinks [3]. In Iran, a large study of Tehranian adolescents' snacks showed that they commonly consumed a cola-drink [4].

This wide use of cola-containing drinks is important in light of the fact that is known that such drinks can interact with different drugs, especially when used concomitantly. Thus, this review will first discuss the primary properties of CCDs, which can lead to pharmacodynamic or pharmacokinetic drug interactions. Then, reports and studies evaluating and/or indicating drug interactions with CCDs will be reviewed. These studies have been categorized into potentially toxic or undesirable drug interactions and potentially favorable drug interactions.

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2. Cola and different types of drug interaction

Cola-drinks have two main properties which can lead to drug interactions at different levels.

First, cola drinks are a well-known source of caffeine. However, different amounts of caffeine have been reported for different non-alcoholic cola drinks. The caffeine content in colas may range from 15 mg to 24 mg in an approximate 180 ml serving size [5]. However, in previous studies, as high as 55–56 mg of caffeine per 356 ml cola have been reported [6]. Also, 30 and 70 mg of caffeine for 200 ml of cola was reported by a study conducted in 2003 [7]. The caffeine content of cola drinks, especially in the case of excessive consumption, can be a source of different interactions with drugs, which will be discussed below.

The second property of cola drinks that give rise to CCD/drug interactions results from the acidic pH of most cola drinks, which primarily results from their phosphoric acid content. This low pH and phosphoric acid content can be a source of several drug interactions, which will be discussed below.

There are different types of drug interaction with CCDs. These CCD/drug interactions can be classified as resulting from either a change in the pharmacodynamics of a drug, or a change in the drug's pharmacokinetic parameters.

2.1. Cola-containing drinks and change in a drug's pharmacodynamic properties

Pharmacodynamic interactions are interactions between drugs, which affect similar physiological pathways and directly influence each other's effects [8]. At this level of interaction, the caffeine content of cola, especially in the case of excessive consumption, has the most important role. Caffeine exerts its effects through mechanisms like antagonizing adenosine receptors (A1 and A2A). Through this mechanism, caffeine can increase the release of various neurotransmitters in different regions of the brain. Therefore, it has psychomotor stimulant effects and improves behavioral functions like vigilance, attention, mood and arousal [9]. Hence, it can potentially interfere with different psychiatric drugs like stimulants or sedative drugs. There are reports of potential minor interactions between caffeine supplied from cola drinks with diazepam [10] and barbiturates [11], possibly because of the minor simulant effects of caffeine. However, there is still no clinical evidence to confirm this potential interaction.

Moreover, there is a negative association between adenosine and dopaminergic receptors. Thus, caffeine can increase responses from dopaminergic receptors. Theoretically, there is a potential for pharmacodynamic interactions between drugs with dopaminergic or anti-dopaminergic activities and CCDs, especially in the case of excessive use.

2.2. Cola-containing drinks and change in the pharmacokinetic parameters of a drug

Pharmacokinetic interactions include interactions at the level of absorption, distribution, metabolism, and elimination of drug, which all can affect the effective concentration of drug at its site(s) of action [8].

2.2.1. Cola and pharmacokinetic interactions at the level of drug absorption

At the drug absorption level, there are two important steps; the dissolution of drug in gastrointestinal fluids and the diffusion of drug from gastrointestinal (GI) membranes into the blood [12]. Many drugs are weak acids or weak bases and can exist in either the ionized or unionized form depending upon the pH of their environment. The most important factor affecting this proportion is the pK_a of these drugs and the pH of fluids in the GI tract [13]. On the other hand, most CCDs have a low pH, for example, classic cola with a pH of 2.5 has the lowest pH of various cola beverages [14]. However, CCDs have not been shown to change intestinal pH [15] and their effect on gastric pH is controversial. For example, Lange et al. showed that 240 ml of a CCD can lower the gastric pH transiently [16], while, in a study by Walravens et al., 330 ml of a CCD did not change the gastric pH [15]. However, it has been shown that CCDs, when co-administered with drugs that are either weak acids or weak bases can lead to alterations in the rate and/or extent of their absorption due to changes in the rate and/or extent of dissolution or diffusion across a biological membrane. In fact, it has been shown that co-administration of CCDs with weak bases can increase the gastric concentration of drug and subsequently increase its overall absorption [15]. It has been suggested that this phenomenon may be due to the CCD affecting the dissolution or aqueous solubility of weakly basic drug substances due to a lower pH induced by the CCD [15]. Azoles are important examples of weakly basic drugs and are known to undergo an increase in oral absorption when they are co-administered with CCDs [16,17]. Additionally, the absorption of weakly acidic drugs can be affected by their co-administration with CCDs. However, while CCDs may theoretically decrease the dissolution of weak acids, they may increase the proportion of the unionized form of these drugs and increase the extent of diffusion from the GI membranes into the blood. The net effect of a CCD on the absorption of a weakly acidic drug potentially depends on the net amount of the drug affected by each of these steps. For example, in an experimental study, ibuprofen, which is a weak acid, was co-administered with a CCD and the extent of its absorption was shown to increase [18]. The increased absorption of ibuprofen in an acidic environment may be due to an increase in the fraction of the unionized form of ibuprofen [18] and a subsequent increase in its membrane diffusion and overall absorption following oral administration.

Lastly, cola drinks contain phosphoric acid and sugar. There are reports demonstrating prolonged gastric emptying due to these two components of CCDs [19]. Obviously, a prolonged gastric emptying time can affect the rate and extent of drug absorption [19].

It should be noted that the optimal concentration of the acidifying agent used in a CCD may also play a role in modulating drug absorption [17].

It is noteworthy that the results of one study showed that CCDs can affect the dissolution rate of capsule shells, so the authors recommended the avoidance of medications contained in such dosage forms with CCDs [20].

2.2.2. Cola and pharmacokinetic interactions at the level of drug metabolism

As mentioned previously, CCDs can be considered as a source of caffeine. The biotransformation of caffeine is mainly restricted to the liver and involves the isoenzyme CYP1A2 [9]. This isoenzyme is the most important metabolic pathway of some drugs, for example, clozapine. Therefore, the caffeine contained in cola-drinks can potentially competes for binding to CYP1A2 and may competitively inhibit CYP1A2-dependent metabolism of other CYP1A2 substrates. This interaction is more important for medications with a narrow therapeutic index. This competitive inhibition by caffeine of medications that are metabolized by CYP1A2 may result in increased serum levels of this medication, which could give rise to toxic effects. Thus, all drugs which are substrates of CYP1A2 could potentially be affected when they are ingested with excessive volumes of cola-containing drinks

containing caffeine. Clozapine [21], olanzapine [22], theophylline [23], and zolmitriptan [24] are all examples of drugs that are substrates for CYP1A2. There is a case-report of the interaction between clozapine and a CCD [25] and another study evaluated the possible interaction between theophylline and a CCD [26]. The area of research that evaluates drug/drug interactions deserves more attention as it pertains to CCD/drug interactions and their potential adverse side effects.

2.2.3. Cola and pharmacokinetic interactions at the level of drug excretion

It has been shown that CCDs can lower the pH of urine [27]. This is attributed to the phosphoric acid content of most CCDs. Phosphoric acid is an inorganic acid and is excreted intact in the urine and, consequently, lowers the pH of urine [28]. This fact is important considering that most drugs exist as either weak acids or weak bases and the fraction of the unionized and ionized forms is pH dependent. Renal excretion involves three processes: glomerular filtration, tubular secretion, and/or tubular reabsorption [29]. The sum of these processes determines the extent of the drug's renal excretion. Tubular reabsorption for several drugs is accomplished by passive diffusion and, consequently, the degree of ionization is an important factor influencing the rate and extent of reabsorption of weakly acidic or weakly basic drug substances [29]. CCDs, by lowering the pH of urine, can affect the proportion of a drug that exists in the ionized form, which cannot be reabsorbed. For weak bases in acidified urine resulting from the consumption of CCDs, the proportion of drug in the ionized form increases and, therefore, its reabsorption is reduced and, in turn, its overall renal excretion increases. Conversely, for drugs which are weak acids, the overall renal excretion decreases in acidic urine [29]. The pH-dependent nature of renal excretion for drugs that are either weak acids or weak bases also includes some metabolites as well. Despite the significance of CCD-induced changes in the renal excretion of some drugs, there are few studies designed to evaluate the interaction between these drugs and CCDs. Additional studies that evaluate the interaction between various weakly acidic and weakly basic drugs and CCDs is extremely important, especially if these drugs possess a narrow therapeutic index or are primarily eliminated from the body by renal excretion. Phenobarbital is an example of a drug, which its renal elimination, is reduced when the urine is acidified [30]. Another important example of a drug that has reduced renal elimination in acidified urine is methotrexate, which is a weak acid. In fact, there are two case-reports of toxic effects from methotrexate when simultaneously administered with excessive amounts of CCDs [28,31].

In addition, the effect of CCDs on the pH of urine can be important, especially for drugs that have the potential to precipitate in the kidneys and exert a nephrotoxic effect. Again, methotrexate (a weak acid), when in acidic urine, precipitates in the kidneys in the form of crystals and may lead to nephrotoxicity [28].

Overall, CCDs, by lowering the pH of urine, can affect the renal excretion or precipitation of drugs which are weak acids or weak bases.

Lastly, as mentioned above, CCDs are a well-known source of caffeine. Caffeine exerts a natriuretic effect and, therefore, a diuretic effect [7]. Caffeine, by antagonization of A1 receptors in kidney, can inhibit the tubular reabsorption [32] of sodium and then induce natriuresis and, subsequently, diuresis [33]. While the glomerular filtration rate (GFR) did not change in this study [33], nevertheless, this inhibition in the reabsorption of sodium can lead to clinically significant adverse effects, especially in the context of excessive consumption of CCDs. An important example, but not the only one, is lithium, which will be discussed in detail below.

2.3. Reported interactions between cola-containing drinks and different drugs

Available studies and reports on the interactions between CCDs and different drugs have been listed in Table 1 and will be discussed below.

2.3.1. Potentially toxic or undesirable drug interactions

2.3.1.1. Methotrexate (MTX). Bauter et al. conducted a study on a small pediatric population with acute lymphoblastic leukemia (ALL). The patients received high doses of MTX. The authors reported a decrease in the rate of MTX renal elimination, since the major route of elimination of MTX from the body is *via* the kidneys [28]. It has been reported that a 56-year old man with non-Hodgkins lymphoma, who received high doses of MTX, developed acute renal failure [31]. These observations were attributed to the simultaneous consumption of CCDs and the administration of MTX [28,31]. The explanation for these observations is that the primary route of elimination for MTX is renal excretion. Since MTX is a weak acid, alkaline urine would increase excretion. Therefore, the alkalization of urine is an important part of MTX therapy, especially in the case of high-dose MTX therapy. Interestingly, CCDs, with their acidifying properties due to phosphoric acid, can transiently neutralize the effect of standard alkalization regimens. In fact, this phenomenon occurred in patients who received MTX in both of the above-mentioned studies [28,31]. As Santucci et al. reported that urine pH unexpectedly decreased from 8.5 to 6.5 when urine sample has been taken after consuming 330 ml of a CCD [31]. Moreover, in the case of treatment with high-dose MTX, a urine pH lower than 7 can result in crystal formation in the urine, which can be nephrotoxic [28], which can contribute to the development of acute renal failure [31].

Therefore, it is recommended that patients who receive high doses of MTX avoid any CCD at least 24 h before, and during the period over which MTX administration occurs until complete elimination of the MTX has taken place [31].

2.3.1.2. Lithium. There is one case report of decreased serum concentrations of lithium in a patient with bipolar disorder who was a 58-year-old man. He was admitted to a psychiatric hospital due to unexplainable low lithium levels. The authors attributed this observation to excessive consumption of CCDs [7].

It is well-established that lithium is freely filtered and excreted into the urine, but 80% of filtered lithium is reabsorbed [34]. However, the reabsorption and excretion of lithium is mainly dependent on the sodium concentration of urine [7]. Excessive consumption of a CCD causes significant accumulation of caffeine. Caffeine, by inhibiting the tubular reabsorption of lithium [32] and increasing the urinary concentration of sodium, can lead to an increase in lithium clearance [7].

Due to fact that lithium has a narrow therapeutic index, clinicians should inform the lithium patient about the potential interaction between lithium and CCDs and other caffeinated drinks. It is recommended that the amount of these drinks be limited.

2.3.1.3. Clozapine. In one case report, elevation of clozapine serum concentrations, as well as its main active metabolite, norclozapin, has been reported. The elevation in clozapine serum concentrations was attributed to excessive consumption of CCDs by the patient [25].

This observation can be explained by the fact that clozapine is primarily metabolized by CYP P 450, especially CYP1A2 [35]. Additionally, excessive consumption of CCDs containing results in excessive consumption of caffeine, which is almost exclusively metabolized by CYP1A2 [9,35]. The caffeine competes with

Table 1
Reports and studies indicating interactions between cola-contain drinks and drugs.

drug	Cola amount	PK or PD outcome	Study design/reference
MTX (high dose)	NA	Delayed elimination of MTX	Case-report [28]
MTX (high dose)	Repeated consumption of 330 ml Coca-Cola per day	Decreased pH of urine after cola consumption and accumulation of MTX in serum, which resolved after discontinuing of cola consumption	Case-report [31]
Lithium	Upto 3 L/day of Coca-Cola zero	Decreased serum concentration lower than therapeutic range which resolved after discontinuing of cola consumption	Case-report [7]
Clozapine	6 glasses of cola/day containing 150 −180 mg of caffeine	Increased serum concentration, unexpectedly, which resolved after discontinuing of cola consumption	Case-report [25]
Carbamazepine	NA	Increased AUC and C_{max} and decreased t_{MAX}	two-way cross-over study [36]
Warfarin	1.5 L/day	Decreased INR, indicating decreased serum concentration. INR increased after cola restriction to 350 ml	Case-report [39]
Halofantrine	Co-ingestion of halofantrine and kolanut	Decreased AUC and C_{MAX}	Randomized, crossover [42]
Itraconazole	Coadministeration with approx. 240 ml of cola	Increased AUC and C_{MAX} and decreased T_{MAX}, in the group of H_2 blocker + CCD, compared to the group used H_2 blocker, alone AUC and C_{MAX} of H_2 blocker + CCD users were similar to control group	Open-label, randomized, three-way crossover study [16]
Itraconazole	Coadministeration with approx. 240 ml of cola	Conducted on fasted patients with AIDS; Increased AUC and C_{MAX} occurred	Open-label, randomized, two-way crossover [47]
Itraconazole	Coadministeration with 325 ml of cola	Increased AUC, C_{MAX} and T_{MAX} have been reported	Randomized, two-way crossover [49]
Posaconazole	Coadministeration of 330 ml	Increased gastric and plasma AUC compared to esomeprazole group	Crossover clinical trial [15]
Ketoconazole	Coadministeration with 240 ml of Coca-Cola Classic	Increased serum AUC compared to omeprazole group	Prospective, Randomized, three-way crossover study [17]
Erlotinib	Coadministeration with 250 ml Coca-Cola Classic	Increased mean AUC compared to esomeprazole group	Randomized, cross-over [52]
Ibuprofen	Coadministeration with 5 ml/kg of cola	Increase in C_{max} and AUC	Animal study on rabbits [18]
Phenytoin	Coadministeration with 5 ml/kg of cola	Increase in C_{max} and AUC	Animal study on rabbits [44]

PK: pharmacokinetic, PD: pharmacodynamics, MTX: methotrexate, NA: not available, AUC: area under the curve, C_{max}: peak plasma concentration.

clozapine for binding to CYP1A2 and then may competitively inhibit the CYP1A2-dependent metabolism of clozapine [35], leading to increased serum concentrations.

2.3.1.4. Carbamazepine. In a two-way cross-over study, Malhotra et al. evaluated the effect of concomitant consumption of a cola containing acidic drink compared to water on the pharmacokinetics of a 200 mg dose of carbamazepine. They showed that a CCD increased the rate and extent of absorption of carbamazepine [36]. This increased absorption may be due to enhanced aqueous solubility of this basic compound in the more acidic environment of the stomach, because of the concomitant use of acidic CCDs.

Importantly, an increase in the oral absorption of carbamazepine when ingested with CCDs means an increased bioavailability of carbamazepine, which is accompanied by an increase in hepatotoxicity and the anticonvulsant effects of the drug as reported in experimental animals [37].

On the other hand, and as mentioned above, CCDs are well-known caffeine-containing drinks. This is noteworthy, because there are preclinical and clinical studies indicating that caffeine can significantly reduce the anticonvulsant effects of carbamazepine without affecting the plasma concentrations of the drug. Therefore, caffeine may have a pharmacodynamic interaction with carbamazepine [38]. However, to the best of our knowledge, there is no study that has evaluated the effect of CCDs on the anticonvulsant activity of carbamazepine.

Overall, there is no study evaluating the net effect of acidic, caffeine-containing CCDs on the anticonvulsant effects of carbamazepine and, thus, furtherer studies are warranted.

In summary, it is recommended that clinicians be aware of the time of day and the daily intake/consumption of CCDs by patients using carbamazepine so that physicians may inform their patients about potential CCD/carbamazepine interactions.

2.3.1.5. Warfarin. In one case report, a man who drank about 1.5 L of regular cola per day and used warfarin at a dose of 20 mg/day had a consistent INR below 1.5. When his daily intake of cola was limited to 350 ml, the value of the INR stabilized between 2.5 and 3 with warfarin dose 7.5 mg/day. After being within, or above, the target range for several years, during a regular checkup, his INR was found to be 1.1. He reported a regular coffee intake of more than five espressos per day. However, when his coffee was limited to one cup of espresso per day, his INR stabilized within the therapeutic range [39].

As suggested in the case report [40], warfarin resistance may be due to decreased absorption or increased clearance. Warfarin is a weak acid. Theoretically, co-administration with an acidic drink could lead to decreased absorption. A similar decrease in INR and apparent resistance to warfarin has been reported in the case of patients using ascorbic acid, which can decrease gastric pH. After discontinuing ascorbic acid, the value of the INR increased [41]. It is notable that in the absorption stage, interactions occur only if the drug is taken together with CCDs. However, it should be emphasized that the intake status of warfarin remains unclear in these case-reports. Another explanation was suggested by Clapauch et al.; the authors of the case-report. They attributed this interaction to the caffeine content of CCDs. They suggested that warfarin occurs as a pair of enantiomers: R-warfarin is metabolized primarily by cytochromes P450 (CYP) 1A2, 3A4, and by carbonyl reductases, and S-warfarin is metabolized primarily by CYP2C9. Because S-warfarin has a higher potency than R-warfarin, the efficacy of warfarin is affected primarily when metabolism of S-warfarin is altered. Exposure to caffeine induces the expression of the enzyme CYP1A2, but at a higher caffeine concentration, the contribution of CYP1A2 to caffeine metabolism decreases in favor of CYP2C9, a situation that could affect the metabolism of S-warfarin. Additionally, CYP450 polymorphisms could explain the variability of responses to caffeine in warfarin users [39].

These authors recommended that the intake of coffee and other caffeine-containing beverages be assessed for warfarin users and that in the case of warfarin resistance, caffeine restriction can be evaluated as a way to overcome this issue [39].

2.3.1.6. Halofantrine. Halofantrine is an anti-malarial drug. In a randomized crossover study on 15 healthy individuals, concomitant ingestion of halofantrine and kola nut, which is used in producing cola-containing drinks, resulted in a significant decrease in the values of the C_{max} and AUC of halofantrine and its metabolite. However, neither the rate of absorption (T_{max}), nor its rate of elimination ($t_{1/2}$), was significantly changed. The authors suggested that this observation may be attributed to the adsorption of the drug and the formation of an insoluble complex [42].

2.3.1.7. Ibuprofen. In an animal study with cross-over design, the concomitant administration of ibuprofen with a CCD resulted in a significant increase in the values of the C_{max} and the AUC of the drug. These changes suggest an increase in the extent of drug absorption of ibuprofen [18], which is potentially harmful.

These results may be due to the increased absorption of ibuprofen [18]. In humans, there is evidence for an association between the simultaneous use of antacids and the bioavailability of ibuprofen following oral administration [43]; namely, a reduction in the overall bioavailability of ibuprofen. These observations may be explained by the fact that ibuprofen is a weak acid. Therefore, it is possible that the co-administration of ibuprofen with an acidic CCD increases the proportion of the unionized form of the drug, which, in turn, increases the extent of membrane diffusion and ultimately increases the extent of absorption [18]. However, this example should emphasize the fact that further studies are needed, especially well-designed human studies.

2.3.1.8. Phenytoin. An experimental cross-over study showed that the concomitant administration of phenytoin with a CCD resulted in a significant increase in various pharmacokinetic parameters indicating an increase in the oral absorption of phenytoin [44]. An increase in the extent of absorption of phenytoin (a narrow therapeutic index drug) could potentially be toxic [45]. However, since this was an experimental preclinical study in animals, there is a need for similar studies in humans.

Phenytoin is also a weak acid [44], so the explanation provided above for ibuprofen may be true for phenytoin as well. Just as with ibuprofen, additional studies need to be conducted with phenytoin.

2.3.2. Potentially favorable interactions

2.3.2.1. Azole antifungal drugs. Azole drugs are weak bases and their absorption is pH-dependent. They are primarily absorbed at a low pH. However, the ingestion of antacids increases the pH and may affect the absorption of azole drugs [16]. Therefore, there exist many studies evaluating the consumption of cola-containing acidic beverages and their effects on the absorption and serum concentrations of different azole drugs, which are described below.

2.3.2.1.1. Itraconazole. The absorption of itraconazole is usually very limited. Poor aqueous solubility is the rate-limiting step in the oral absorption of this antifungal drug and its absorption is pH-dependent [16,46]. Several studies have evaluated the effects of acidic, cola-containing beverages on the bioavailability of itraconazole.

Lange et al. conducted an open-label, randomized, three-way crossover study on healthy individuals who were pretreated with ranitidine. Before receiving itraconazole, they had a gastric pH of at least 6.0. This study showed that the co-administration of itraconazole capsules with acidic, cola-containing beverages can improve the usual low bioavailability observed following itraconazole administration [16]. Lange et al., in another similar study, showed that in fasted AIDS patients, who exhibit an increase in gastric pH, the rate and extent of itraconazole absorption was enhanced by the co-administration of a cola beverage when compared to the co-administration of itraconazole and water [47].

The increased bioavailability of itraconazole with concomitant consumption of CCDs has been reported to result from a transient reduction of gastric pH [16], which has been suggested to improve the rate and extent of dissolution of itraconazole [48] and its aqueous solubility [16]. Thus, in patients with hypochlorhydria or concomitant use of agents that suppress gastric acid, the rate and extent of itraconazole absorption can be improved by the co-administration of itraconazole with acidic beverages like CCDs.

However, the increased bioavailability of itraconazole with concomitant consumption of CCDs may not be limited to patients with reduced gastric pH. This is because a small study similar to a study by Lange et al., which was conducted with healthy fasted volunteers, showed that the oral absorption of itraconazole was improved by concomitant consumption of CCDs as compared to itraconazole dosed with plain tap water [49].

Clinicians need to be aware of the increased bioavailability of itraconazole when dosed with CCDs, since itraconazole itself can interfere with the metabolism of many drugs. For example, in a study on lung transplant recipients using cyclosporine (CSA), the co-administration of cola with itraconazole improved its bioavailability and enhanced the interaction between itraconazole and cyclosporine. The CSA dosing interval over time was significantly prolonged in patients using itraconazole with cola drinks compared to those patients that ingested water with itraconazole. Interestingly, the mean cost of CSA therapy was significantly lower for the itraconazole-CCD group of patients [50]. However, it is important to point out that this altered drug response could be toxic if the clinician was unaware of the CCD/itraconazole interaction.

2.3.2.1.2. Posaconazole. A crossover clinical trial on five healthy individuals showed that co-administration of posaconazole with a CCD in fasted patients could increase the bioavailability of posaconazole. Using a potent acid suppressant, esomeprazole, it was demonstrated that the bioavailability of posaconazole was significantly reduced. The co-administration of posaconazole with a CCD improved the bioavailability of posaconozole, however, it did not completely compensate for the overall net reduction in posaconozole bioavailability due to the esomeprazole-induced increase in gastric pH [15].

This study also showed that CCDs significantly increased the gastric concentration of posaconazole without any change in gastric pH. Therefore, this observation was attributed to improved aqueous solubility of posaconazole when ingested with CCDs, which resulted in an increase in bioavailability [15].

2.3.2.1.3. Ketoconazole. A similar randomized, three-way crossover study was conducted with ketoconazole on 9 healthy individuals. Co-administration of ketoconazole with a cola drink improved its bioavailability compared to ketoconazole administered with water. Achlohydria induced by another potent acid suppressant, omeprazole, and similar to the study using posaconazole described above, consumption of CCDs were shown to partially compensate for the reduction in the bioavailability of ketoconazole when simultaneously administered with omeprazole [17].

Therefore, in patients with inadequate food intake and who exhibit abnormal gastric pH levels due to co-administration of an acid-suppressive agent, the co-administration of posaconazole [15], ketoconazole [17], or itraconazole with CCDs could be a partially effectivet strategy to increase drug absorption, although it is important to point out that the long-term ingestion of CCDs has its own health risks due to the sugar content of such beverages.

2.3.2.2. Erlotinib. There is a known drug interaction between erlotinib and proton pomp inhibitors (PPIs) [51]. A randomized, cross-over study on patients with non-small-cell lung cancer showed that concomitant ingestion of a CCD could improve this unfavorable drug interaction. In this study, concomitant ingestion of an acidic CCD during combination erlotinib and esomeprozole therapy increased the mean value of AUC_{0-12h} by 39% (range was between 136% and 212%; P = .004) [52]. This observation was attributed to improved aqueous solubility of erlotinib, since it is a weakly basic drug [53,54] that is subjected to a transient acidic environment produced by the simultaneous ingestion of a CCD. Therefore, concomitant use of CCDs with erlotinib might represent an efficient strategy to compensate for the reduction in the bioavailability of erlotinib when erlotinib (an anticancer drug that is an epidermal growth factor receptor inhibitor – protein-tyrosine kinase inhibitor) is used together with a PPI such as esomeprozole. However, before widespread clinical application, further studies are required needed, since this clinical trial demonstrated a significantly wide range in the mean values of the AUC and the maximum serum concentrations achieved. Thus, the inter-individual variability in drug absorption should be considered and close monitoring of serum concentrations of erlotinib is recommended [53].

It is notable that in the case of concomitant use of erlotinib with CCDs and no PPI, the mean values of the AUC_{0-12h} were also slightly higher (9%; range, 210% to +30%; P = .03) [52]. This may represent an unfavorable interaction and clinicians should be aware of this variability in the overall bioavailability of erlotinib when dosed with CCDs.

2.3.2.3. Iron. There is some evidence indicating that sugar may be a good vehicle for iron fortification. When iron-fortified sugar was administered with two CCDs, iron absorption increased compared to the amount of iron absorbed when iron-fortified sugar was administered with a meal containing one or more vegetables. However, the mean absorption of iron from iron-fortified sugar administered with CCDs was still lower than iron absorption from iron ascorbate [55]. In addition, a randomized, crossover study on sixteen healthy women showed that CCDs did not increase non-heme iron absorption resulting from the ingestion of a vegetarian meal [56].

3. Conclusion

CCDs are common beverages worldwide. CCDs are acidic and caffeine-containing drinks. We discussed how these two properties potentiate the interactions between CCDs and various drugs in relation to pharmacodynamics and pharmacokinetic, which included the processes of drug absorption, drug metabolism, and renal excretion. As it relates to altering the metabolism of various drugs that are taken with CCDs, it should be emphasized that caffeine-related interactions are usually important only in the case of excessive consumption of CCDs, although it should be pointed out that pH- and phosphoric acid-related drug interactions may occur with more typical amounts of CCD ingestion. It has also been discussed in this review and reported elsewhere that serum concentrations of MTX, clozapine, carbamazepine, phenytoin, and ibuprofen are increased following simultaneous consumption of CCDs, which suggests the potential for drug-related adverse effects. Additionally, it has been reported that serum levels of lithium and warfarin were observed to decrease when administered with CCDs, which ultimately causes a reduction in their efficacy. Moreover, serum concentrations of erlotinib and different azoles, including itraconazole, posaconazole, and ketoconazole, increased when these drugs were co-administered with a CCD. Importantly, these interactions could be favorable with regard to the therapeutic efficacy of erlotinib. With regard to the physicochemical properties of CCDs, the many and varied interactions of CCDs with various drug classes cannot be limited to those reported here. As discussed in this review, CCDs have the potential for interactions with many other classes of drugs. It is absolutely imperative that clinicians be made aware of the reported and potential interactions of medications with consumption ofCCDs, especially if those medications have a narrow therapeutic index.

Conflicts of interest

None.

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