24.06.2022

Concomitant use of oxycodone and itraconazole among long oxycodone users in community pharmacies in the Netherlands, an IADB drug-utilization study

BACHELOR RESEARCH PROJECT

KARINA KOSZARSKA S3937887

Abstract

BACKGROUND The aim of this study was to look at the concomitant use of oxycodone and itraconazole. Oxycodone is a popular widely used opioid which is metabolized mainly by the CYP3A4 enzyme. One of the drugs that interacts with the metabolism of oxycodone by blocking the CYP3A4 enzyme is an antifungal drug itraconazole. Itraconazole increases the plasma levels of oxycodone and leads to stronger experience of the side effects. Therefore oxycodone and itraconazole are not preferred to be used simultaneously.

METHOD For this study the IADB database was used. Oxycodone users with more than one oxycodone prescription with a period of use of at least 14 days were included. This resulted in a study population of 597444 patients. By looking into prescription data of patients from community pharmacies in the north of the Netherlands the incidence of concomitant use of oxycodone and itraconazole was investigated. By using the Chi-square test it was investigated whether there was a significant difference of concomitant use between men and women. The one sample t test was used to see whether there was a significant dose adjustment of oxycodone after the start of concomitant use. Also the distribution of age at the time of concomitant use was visualized by means of a histogram.

RESULTS In a period of 20 years there were 111 cases of concomitant use found. The total incidence of concomitant use decreased over time from 2.75 per 1000 oxycodone users in 2003 to 1.16 per 1000 oxycodone users in 2020. The results also showed that there was no significant difference of concomitant use between men and women. For the dose adjustment of oxycodone the results showed that the mean natural logarithm ratio of the after/before dosage was 1.58E-01 (95% CI -0.005224 to 0.3212498), meaning that there was no significant change in dosage. The age group at which the most cases of concomitant use occurred was age group 51-60.

CONCLUSION Concomitant use of oxycodone and itraconazole does not seem to be an overlooked problem in practise, however further study is needed to gain more information about this topic.

Introduction

Oxycodone is a μ-opioid receptor agonist commonly used for the treatment of moderate and severe pain. Oxycodone was derived from thebaine in 1916 in Germany whereafter it was used in clinical practise in 1917 ("Eukodal, Ein Neues Narkotikum," 1917). Nowadays oxycodone is available in many formulations such as tablets, capsules, oral solution and in some countries even as intravenous and intramuscular injection (Sadiq et al., 2022). The two most commonly used formulations of oxycodone are the immediate-release and controlled-release tablets (Salzman et al., 1999). The immediate release tablets are short-acting and are quickly absorbed, therefore they can be used for the management of acute pain. The controlled-release tablets are long-acting and allow a controlled release of the active compound over a sustained period of time at a constant rate, therefore longer dosing regimens are possible. This formulation is also easier to use for the maintenance therapy. Oxycodone is nowadays mostly used for the treatment of postoperative pain (Curtis et al., 1999; Silvasti et al., 1998), cancer pain (de Conno et al., 1991; Glare, 1993)and chronic non-cancer related pain, such as neuropathic pain (N. Watson & Babul, 1998; Sindrup & Jensen, 1999).

Since oxycodone came on the market in 1917 it has gained popularity due to its ability to improve patients quality of life in pain management and because it has less side effects compared to morphine (Kalso et al., 1991; Kalso & Vainio, 1990; Riley et al., 2008). This increased popularity can be clearly seen in the prescription and consumption rates. In 1990 the worldwide consumption of oxycodone was estimated to be 3 tons (2722 kg), this increased to a consumption of 77 tons (69 853 kg) by the year 2009 (Kenan et al., 2012). In the time period between 2000 – 2010 the average size of oxycodone prescription in United States alone increased by 69.7%, from 923 morphine milligram equivalents to 1566 morphine milligram equivalents (Kenan et al., 2012). In Finland oxycodone is the most commonly used opioid analgesic, administered mainly parentally, since 1960's (Kinnunen et al., 2019; Pöyhiä, 1994). Also in the Netherlands the consumption of oxycodone drastically increased. In the time period between 2008 – 2017 there was a fourfold increase in oxycodone users from 574 to 2568 per 100 000 inhabitants (Kalkman et al., 2019). This increase in oxycodone consumption relates to the recent oxycodone abuse epidemic. From 2011 to 2016 oxycodone overdose contributed to 33154 overdose deaths in America and in 2020 it was the third leading opioid causing the overdose death in America (*Centers for Disease Control and Prevention (CDC). Prescription Opioid Overdose Data*, 2020; Kibaly et al., 2021).

The drug abuse and dependence that come along with the increased oxycodone consumptions are not the only consequences to look out for. Oxycodone is mainly metabolised by the hepatic P450 (CYP) isoenzymes, only 10% of the free (unconjugated) drug leaves the body via the urinary tract (Kirvela et al., 1996; Poyhia R, 1992). Therefore oxycodone is prone to drug-drug interactions with drugs that interfere with its metabolism by inhibiting or inducing the CYP enzymes. Oxycodone is derived from thebaine by oxidation and hydrogenation whereafter it is metabolised to its active and inactive metabolites (Fig. 1) ("Eukodal, Ein Neues Narkotikum," 1917). The main metabolic pathways of oxycodone are the O-demethylation by CYP2D6 to the active metabolite oxymorphone and N-demethylation by CYP3A4/5 to the inactive metabolite noroxycodone (Fig. 1) (Kalso, 2005; Poyhia R, 1992). Both oxymorphone and noroxcodone are further metabolized by CYP3A4/5 and CYP2D6 respectively to the active metabolite noroxymorphone (Fig. 1) (Kalso, 2005)(Lalovic, 2004). From the two metabolic pathways of oxycodone the N-demethylation to noroxycodone is the major pathway. The intrinsic clearance for N-methylation mediated by CYP3A4 was proven to be 2 to 14 times the intrinsic clearance of O-demethylation to oxymorphone (Lalovic, 2004). Even though noroxycodone is the major metabolite of oxycodone, it does not contribute to the antinociceptive effect of oxycodone as its own antinociceptive activity has a lower potency compared to oxycodone (Kim Pei

Leow & Smith, 1994). Additionally noroxycodone itself has a weak receptor binding to the μ-opioid receptor (Chen et al., 1991). On the other hand oxymorphone which is the minor metabolite of oxycodone has a 3 to 5 times higher μ-opioid receptor affinity than morphine and a 10-fold better opioid activity than morphine (Beaver et al., 1978; Childers et al., 1979). The CYP2D6 enzyme responsible for the conversion of oxycodone to oxymorphone is highly polymorphic and can be divided into four groups: poor metabolizers, intermediate metabolizer, extensive metabolizers and ultra-rapid metabolizers (Zanger & Schwab, 2013). About 5-10% of the Caucasian population are people who are poor metabolizers, 10-17% are intermediate metabolizers, 70-80% are extensive metabolizers and 3-5% are ultra-rapid metabolizers (Sistonen et al., 2009; Zanger & Schwab, 2013; Zhou, 2009). Furthermore the prevalence of poor metabolisers in Asia and India is less than 5% and Northern and Western Afrika show rather high frequencies of ultra-rapid metabolisers (Jakobsson et al., 2021; Sistonen et al., 2009). Since there are no findings indicating clinically important polymorphism of CYP3A4, CYP2D6 seems to be the only factor by which oxycodone metabolism can be distinguished between different population groups. Therefore it can be speculated that Caucasians have the potential to have less efficient clearance of oxycodone, since higher frequencies of CYP2D6 poor metaboliser are found in the Caucasians compared to other population groups. The differences in the metabolism of oxycodone via CYP2D6 will lead to different oxymorphone/oxycodone plasma levels, this can have further consequences for the drug effect or intoxication. Heiskanen et al. studied the role of oxymorphone in the mediation of the opioid effect of oxycodone by blocking the CYP2D6 receptor with quinidine, a potential CYP2D6 blocker (Heiskanen, 1998). The results showed that oxymorphone had no effect on the subjective drug effect ratings or psychomotor performance, meaning that oxymorphone does not contribute to the pharmacodynamic actions of oxycodone (Heiskanen, 1998). Additionally Kaiko et al. studied the pharmacokinetic-pharmacodynamic relationships of controlled-release oxycodone and found that highest oxycodone AUC values and lowest oxymorphone AUC values led to highest drug effect AUC values whether lowest oxycodone AUC values and highest oxymorphone AUC values led to lowest drug effect AUC values (Kaiko, 1996a). These studies show that oxymorphone does not contribute to the drug effect of oxycodone. Nevertheless Jakobsson et al. investigated the frequency of the four different CYP2D6 types in postpartum cases with oxycodone in femoral blood to see whether the activity of this enzyme was associated with certain deaths, concentrations or metabolic rations (Jakobsson et al., 2021). They concluded that the oxycodone concentrations in poor and intermediate metabolizers were higher than in extensive and ultra-rapid metabolizers. However the frequency of the poor and intermediate metabolisers was not overrepresented in the intoxications related to oxycodone. Additionally they concluded that a oxymorphone/oxycodone ratio lower than 0.075 has a high sensitivity for separating oxycodone intoxications from other (non)intoxications depending on the CYP2D6 genotype. This study indicates that too high oxycodone concentrations due to insufficient metabolism to oxymorphone caused by CYP2D6 polymorphism might lead to intoxication followed by death.

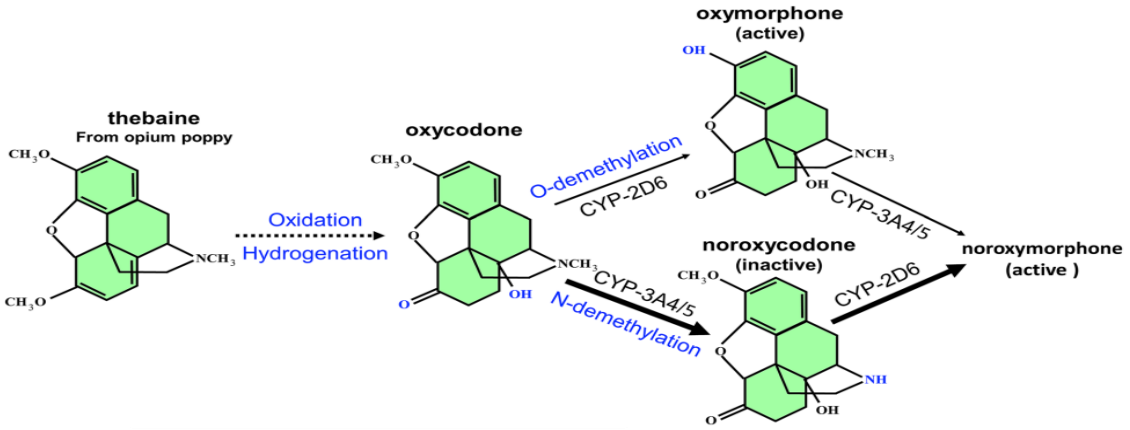


Figure 1. Schematic view of the formation and metabolism of oxycodone. Oxycodone is derived from thebaine whereafter it is metabolised to active oxymorphone and inactive noroxycodone. Both oxymorphone and noroxycodone are metabolized to active noroxymorphone (Kibaly et al., 2021).

When looking at drug-drug interactions CYP3A4, responsible for the formation of noroxycodone, is more susceptible to drug-drug interactions than CYP2D6 (SHANNON, 2007). One of the drugs that blocks the binding of oxycodone to CYP3A4 is itraconazole (Saari et al., 2010). Itraconazole is an anti-fungal drug used for the treatment of fungal and invasive candida infections (Baran et al., 2008; Gafter-Gvili et al., 2008). It is mainly used for the treatment of fungal infections of the skin, nails, mouth, internal organs, vagina and vulva *(*Itraconazole Leaflet*, 2016)*. Itraconazole is a potent CYP3A inhibitor that already showed to interact with other substrates of the CYP3A enzyme (Backman et al., 1998; Varhe, 1994). Saari et al. investigated the effect of itraconazole on the metabolism of intravenous and oral oxycodone (Saari et al., 2010). The results showed that itraconazole had a greater effect on the oral oxycodone as the AUC(0-∞) of the oral oxycodone was increased by 144% compared to 51% of the intravenous oxycodone. Additionally the AUC(0-48) of noroxycodone was decreased by 49% and that of oxymorphone was increased by 359%. Furthermore inhibition by itraconazole after an oral single dose of oxycodone showed to increase the oxycodone-induced drowsiness, drug effect and deterioration of performance. In the study population seven extensive and one ultra-rapid CYP2D6 metabolizers were found. The ultra-rapid CYP2D6 metaboliser seemed to have high oxymorphone concentrations and lower oxycodone concentrations compared to extensive, intermediate and poor metabolizers respectively. This outcome indicates that when CYP3A4 metabolic pathway of oxycodone is blocked the CYP2D6 enzyme can compensate for it and convert oxycodone into oxymorphone. However poor metabolizers will face more clinical consequences as they are not able to switch to the CYP2D6 metabolic pathway leading to increased oxycodone concentrations. This is in correspondence with the study of Grönlund et al. which proved that when both CYP2D6 and CYP3A4 are blocked with paroxetine and itraconazole respectively, the oxycodone concentrations were higher (Grönlund et al., 2010). A previous study also showed that not only itraconazole but also its three metabolites hydroxy-itraconazole, keto-itraconazole and N-desalkyl-itraconazole are potential CYP3A4 substrates that can undergo drug-drug interactions (Isoherranen et al., 2004).

These findings indicate that the drug-drug interaction between itraconazole and oxycodone can lead to increased oxycodone levels, especially in CYP2D6 poor metabolizers. The increased oxycodone levels can further lead to side effects or toxicity. Previous studies showed that there is a relationship between the oxycodone plasma concentration and the drug effect, as well as between oxycodone plasma concentration and experienced adverse events (Benzinger et al., 1997; Kaiko, 1996a; Package Insert Oxycontin, 2007). The study done by Saari et al. already showed that concomitant use of itraconazole and oxycodone led to induction of drowsiness, drug effect and deterioration of performance in study objects after small single dose of oxycodone. Since only a small single dose of

oxycodone was administered the effect of itraconazole on the pharmacokinetics and pharmacodynamics of oxycodone are expected to be greater in clinical practise. This increase in oxycodone plasma levels can lead to a potential risk for the elderly as they already have increased oxycodone plasma concentrations compared to young adults (Liukas et al., 2008). The study by Liukas et al. showed that the mean exposure to oxycodone in patients groups aged 70-80 and 80-90 is 50-80% higher while the plasma oxycodone concentration is doubled compared to young adults. Furthermore age is not the only factor influencing the oxycodone plasma concentration, Kaiko et al. showed that women had higher oxycodone plasma levels due to less metabolism of oxycodone to oxymorphone compared to man (Kaiko, 1996b).

In the Netherlands the guidelines for oxycodone state that after introduction of an azole the oxycodone plasma levels should be monitored (*Oxycodon*, 2022). However it is not necessary to directly lower the dose of oxycodone. An interesting finding from a study done by Schepens et al. showed that in the Netherlands the elderly receive more often a prescription for opioids compared to young adults. In 2017 18.8% of the people older than 85 received a prescription for an opioid compared to 4.7% of people between 18 and 55 years (Schepens et al., 2019). Additionally from all the people with one or more opioid prescriptions 60% were women (Schepens et al., 2019). From all the opioids prescribed in the Netherlands oxycodone is the most prescribed opioid (*Gipdatabank*, n.d.). As mentioned before the elderly and women have higher chances of having higher oxycodone plasma levels, so it is interesting to see that those groups are the ones with most opioid prescriptions. Adding on to this fungal infections are a common problem in the elderly as well as vaginal yeast infections in women, both threated with azoles such as itraconazole (Dimopoulos et al., 2013; Gonçalves et al., 2016; Kauffman, 2001).

Even though the concomitant use of oxycodone and itraconazole is not preferred because of the drug-drug interaction, they might be used together in practice as their concomitant use is not contra-indicated. There are only a few studies that look at the simultaneous use of oxycodone and itraconazole, therefore also little is known about the prevalence and incidence of concomitant use of these two drugs. However it is important to know whether simultaneous use of these two drugs is an overlooked problem. Therefore this study will look at the incidence of concomitant use of oxycodone and itraconazole between 1994 and 2020 in the Netherlands. Additionally this study will look at differences in incidences between women and men. In the case of concomitant use it will be investigated whether there was a dose adjustment of oxycodone after the start of concomitant use. Based on the literature it is hypothesised that concomitant use of oxycodone and itraconazole is low, since itraconazole increases the oxycodone plasma levels. Since oxycodone and itraconazole are prescribed mostly for the same patient groups, namely the elderly and women, it is expected to see more cases of concomitant use in those patients. Therefore it is also expected to see a clear dose reduction of oxycodone, since those patient groups are also already more prone to higher oxycodone plasma levels which would be even higher during concomitant use with itraconazole.

Method

Setting

For this study The University of Groningen IADB database was used. IADB is a pharmacy prescription database in the Netherlands that contains prescription data from 1994 to 2020 from approximately 120 community pharmacies with an estimate population of 1,200,000 patients. This database has been widely used for research since it's found to be representative of the Dutch population as a whole. The prescription record provides information on the date of dispensing, the quantity dispensed, the dose regimen, the number of days the prescription is valid, the prescribing physician and the ATC code. The patients record contains the unique anonymous patient number, date of birth and gender. For each patient the medication records are virtually complete, excluding over the counter drugs and medication dispensed from hospital pharmacy.

Study population

The study population were all people who have been prescribed at least one oxycodone (N02AA05) prescription for a period of use of at least 14 days between 1994 and 2020 in the Netherlands. All included patients had to be 18 years or older at the time of oxycodone dispensing. People were excluded if they were also prescribed at least one other drug with known inhibiting activity for the CYP3A4 enzyme during oxycodone use. Those drugs were amiodarone (C01BD01), aprepitant (A04AD12), cimetidine (A02BA01), ciprofloxacin (J01MA02), clarithromycin (J01FA09), diltiazem (C08DB01), erythromycin (J01FA01), fluconazole (J02AC01), ketoconazole (D01AC08), posaconazole (J02AC04), voriconazole (J02AC03), verapamil (C08DA01).

Exposure

A patient was considered exposed from the start of concomitant use of oxycodone and itraconazole until the end of concomitant use. A case of concomitant use was defined as delivery date of itraconazole that fell within the delivery date and end date of oxycodone or as the same delivery date for oxycodone and itraconazole. Patients were exposed until one month after the end of theoretical period of use of the last prescription of itraconazole during concomitant use. The period of use of oxycodone was defined as a period from the start of dispensing of oxycodone until the end of theoretical period of use that was provided in the iadb database. The non-exposed group were all the oxycodone users included in the study who did not receive any itraconazole during the period of use of oxycodone and all the oxycodone users after they ended the concomitant use.

Outcomes

The primary outcome of this study was the incidence of concomitant use of oxycodone and itraconazole. This incidence was calculated with an formula than can be seen in section "Statistical analysis". A patient with concomitant use of oxycodone and itraconazole was counted as one case in an year, even if he/she had multiple itraconazole prescriptions during the oxycodone use. Additionally to the total incidence the incidence for males and females were calculated using the formulas included in the section "Statistical analysis". Furthermore a histogram for the frequency of age at which the concomitant use occurred was made to visualize the distribution of occurrence of concomitant use between different age groups.

The secondary outcome of this study was the dosage change of oxycodone after the start of concomitant use of oxycodone and itraconazole. For this outcome the dose ratio was calculated by diving the DDD's per day of oxycodone after the start of concomitant use by the DDD's per day of oxycodone before the start of concomitant use. To determine the DDD's per day of oxycodone

before the start concomitant use the last oxycodone prescription before the start date of concomitant use or oxycodone prescription with the same delivery date as itraconazole were used. To determine the DDD's per day of oxycodone after the start of concomitant use the first oxycodone prescription after the start date of concomitant use was used. This oxycodone prescription after the start of concomitant use had to be not older than 2 months compared to the start date of concomitant use.

Statistical analysis

The total incidence was calculated per year with the formula:

$$Incidence = \frac{cases\ of\ concomintant\ use}{total\ oxycodone\ users}$$

The incidence was then expressed as incidence per 1000 oxycodone users by multiplying the outcome with 1000. Also the incidence for males and females was calculated per year with the formulas:

$$Incidence\ male = \frac{male\ cases\ of\ concomitant\ use}{total\ male\ oxycodone\ users}$$

$$Incidence\ female = \frac{female\ cases\ of\ concomitant\ use}{total\ female\ oxycodone\ users}$$

These incidences were also expressed as incidence per 1000 (male/female) oxycodone users by multiplying the outcomes with 1000.

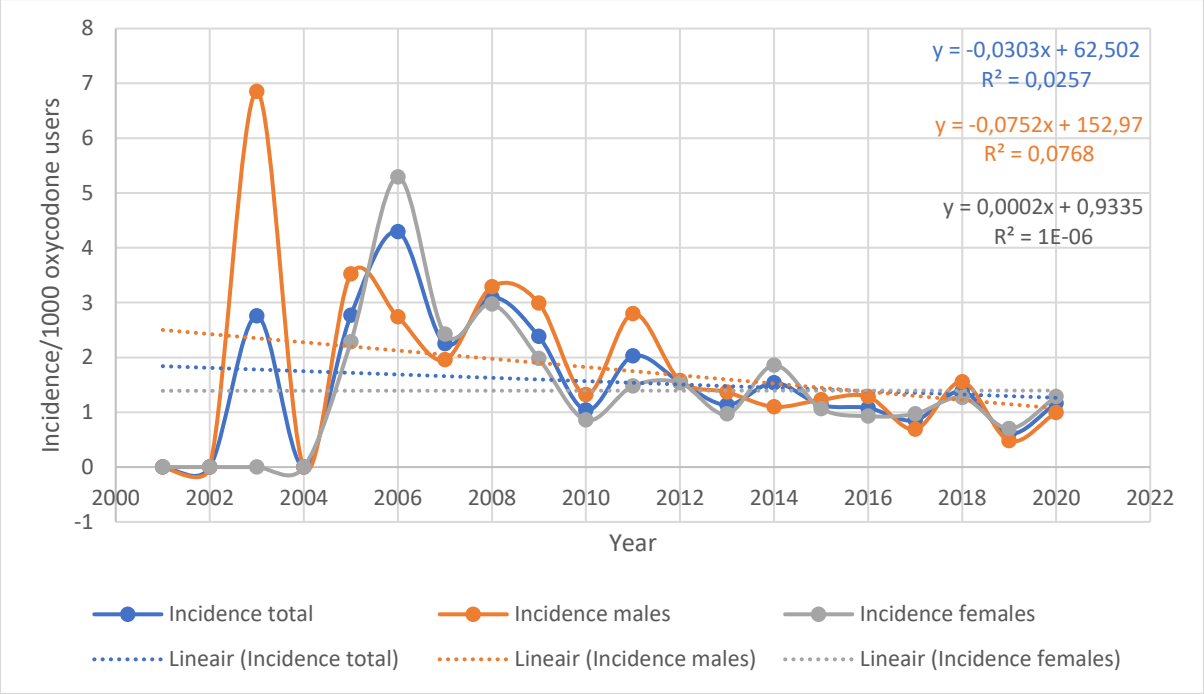
To test whether there is a significant difference between incidence of males and females the Chi-square test was used. This test looked at the association between the gender and concomitant use whereby the null hypothesis stated that there was no difference in the incidence of concomitant use between women and men and the alternative hypothesis stated that there was a difference in incidence of concomitant use between women and men. To perform this test SPSS was used.

For the dosage change of oxycodone the dose ratio was calculated by dividing the DDD's per day after the start of concomitant use by the DDD's per day before the start of concomitant use. Then the natural logarithm of the dose ratio was calculated in order to create a more normal distribution. This natural logarithm of the dose ratio was used to perform a one sample t test. The t test was performed to see whether the mean of the natural logarithm of the dose ratio was different than 0. Therefore the null hypothesis stated that the mean was not different than 0 and the alternative hypothesis stated that the mean was different than 0. To perform the one sample t test SPSS was used.

Results

Incidence

The results show that the total incidence and male incidence decrease over time, meanwhile the female incidence has a slight increase (*Graph 1*). This can be seen by looking at the slope of the trendline. For both total incidence and male incidence the slope of the trendline has a negative value, meaning that there is a decrease over time. The slope of the trendline for female incidence has a positive value, meaning that there is an increase over time. It can be also seen that each set of data has a wide range and when looking at the distribution of data points around the trendline each set of data has a large spread. The highest total incidence was measured in 2006 and had a value of 4.29 cases/1000 oxycodone users (*Appendix 1*). In the same year the highest female incidence was measured, which had a value of 5.29 cases/1000 female oxycodone users (*Appendix 1*). It can be also seen that there were no cases of concomitant use among women before 2005. The highest male incidence was measured in 2003 and had a value of 6.85 cases/1000 male oxycodone users (Appendix 1). In Graph 1 it can be seen that the data for the incidences start from 2001. This is due to the fact that there were no oxycodone users before 2001.



Graph 1. The incidence of concomitant use of oxycodone and itraconazole represented per 1000 oxycodone users for the total incidence, incidence of males and incidence of females.

The results of the Chi-square test showed that the p value was 0.0853 (*Table 1*). This p value is higher than 0.05 which means that the null hypothesis cannot be rejected. Therefore the outcome of the Chi-square test shows that there is no evidence of association between the gender and the concomitant use, meaning that there was no significant difference between the male incidence and female incidence in the population.

Chi-square test		
Value	**df**	**Asymptotic significance (2-sided)**
0.034	1	0.853

Table 1. The results of the Chi-square test for the association between gender and concomitant use.

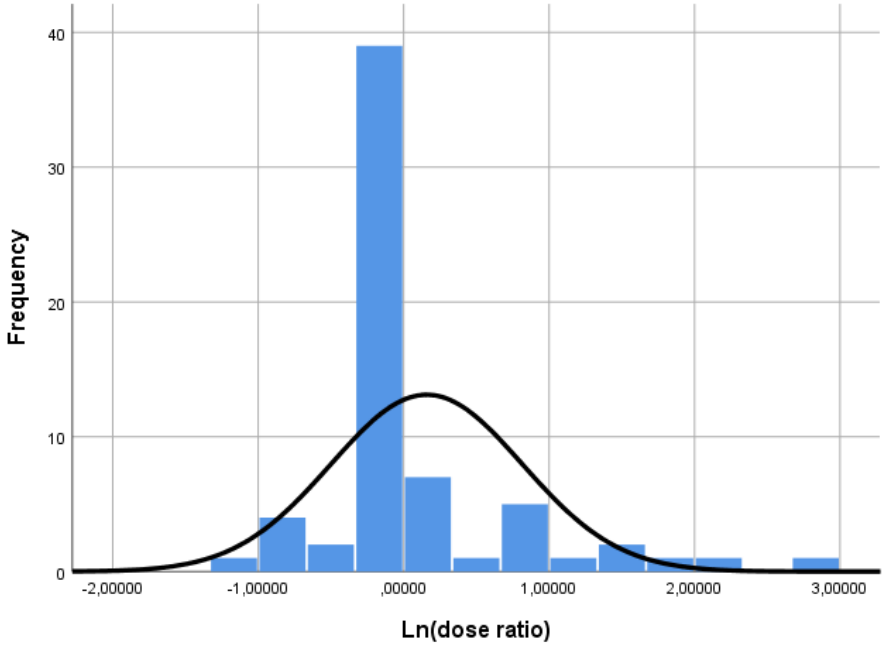
Dosage change of oxycodone

The results of the one sample t test showed that the mean of the natural logarithm of dose ratio was 1.58E-01. However the t test showed that the p value was 0.058. This p value is higher than 0.05 which means that the null hypothesis cannot be rejected. The dose adjustment is thus not significant and therefore there was no dose adjustment of oxycodone in the population.

One sample t test						
Test value	t	df	Sig. (2-tailed)	Mean Difference	Lower 95% CI of the Difference	Upper 95% CI of the Difference
0	1.934	64	0.058	0.15801283	-0.0052241	0.3212498

Table 2. The results table of the one sample t test performed for the logarithm of the dose ratio of oxycodone.

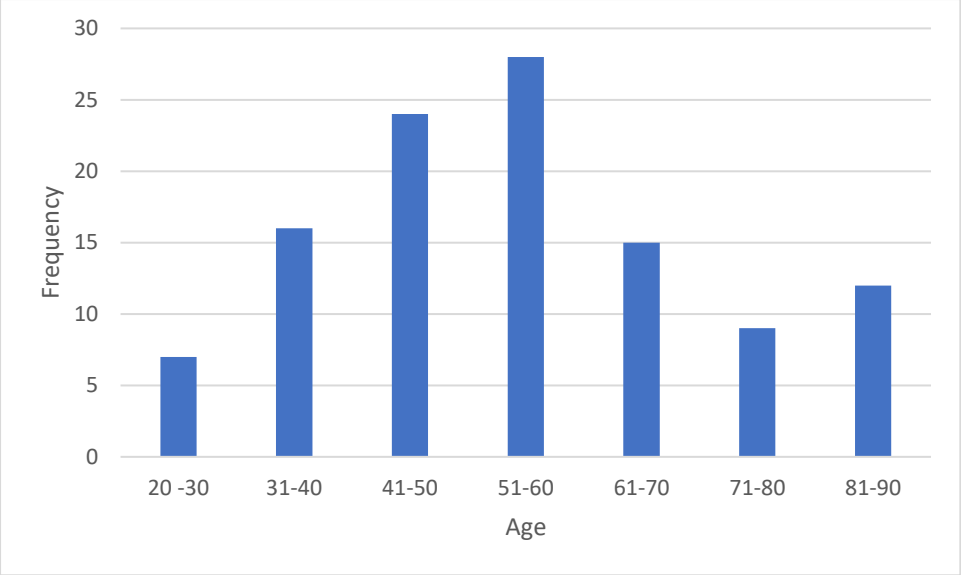
The histogram in Graph 2 shows the frequency distribution of the natural logarithm of the dose ratio of oxycodone. In this histogram it can be seen that the frequency of the natural logarithm of the dose ratio is slightly more distributed towards the right side. This is in line with the results of the t test showing that the mean of the natural logarithm of the dose ratio is 1.58E-01.



Graph 2. Histogram showing the frequency distribution of the logarithm of the dose ratio of oxycodone.

Age

The histogram in Graph 3 shows the frequency distribution of age at the time of concomitant use. The most cases of concomitant use of oxycodone and itraconazole were found in the age group 51-60. The least cases of concomitant use were found in the age group 20-30. The age group 71-80 has the second least amount of cases of concomitant use and the age group 81-90 has the third least amount of cases of concomitant use.



Graph 3. Histogram of the frequency of the age at which the concomitant use of oxycodone and itraconazole occurred.

Discussion

The aim of this study was to investigate to what extend oxycodone and itraconazole are used simultaneously in the Netherlands. The results of this study showed that in total there were 111 cases of concomitant use over a period of 20 years. The incidence of concomitant use of oxycodone and itraconazole was low and decreased over time. Additionally there was no significant difference found between concomitant use of women and men. Furthermore there was no significant difference between the defined daily dose per day of oxycodone before and after the start of concomitant use.

The results showed that the total incidence of concomitant use of oxycodone and itraconazole is decreasing over time (*Graph 1*). The same is true for the male incidence of concomitant use. Opposite to those two incidences the results showed that the female incidence is slightly increasing over time. This might have been influenced due to the fact that before the year 2005 there were no cases of concomitant use among women. However after the year 2005 the female incidence is rather decreasing. The decrease of the incidence over time can be caused by gained knowledge about the drug-drug interactions through new literature, just like the study done by Saari et al., 2010. The purpose of such studies is to prevent or limit prescriptions of drugs that interact with each other. Another reason for the decrease of incidence could be the improvement of drug monitoring due to which the concomitant use of oxycodone and itraconazole could be better monitored (Vervolgonderzoek Dienstapotheken: Medicatiebewaking Nog Verre van Sluitend , 2009).

The highest measured incidences were 4.29, 6.85 and 5.29 cases per 1000 oxycodone users for total, male and female incidence respectively. From this results it can be concluded that the incidence of concomitant use of oxycodone and itraconazole in the Netherlands is low as per 1000 oxycodone users there is less than 1% of concomitant use. A reason for this low incidence of concomitant use of oxycodone and itraconazole could be that itraconazole is not the first choice drug for the most indications that it's used for (*Dermatomycosen Behandelplan*, n.d.; *Orofaryngeale Candidiasis Behandelplan*, n.d.; *Vulvovaginale Candidiasis Behandelplan*, n.d.). This decreases the chance of concomitant use with oxycodone. Another reason for the low incidence of concomitant use of oxycodone and itraconazole might be that in practise general practitioners and specialist indeed try to limit the co-prescription of those two drugs.

An interesting finding regarding the oxycodone users in the Netherlands was that there were none before the year 2001. There is not much information that could explain this observation, except for one article publishes by "Geneesmiddelen Bulletin Medische Hulpmiddelen" in 2001 that indicates that oxycodone came onto the Dutch market around the year 2001 (*Oxycodon (OxyContin®), Opioïde Analgeticum*, 2001).

In the period from 2017 to 2020 the amount of itraconazole users decreased by almost 16% (*GIP Databank*, 2022). This could also have influenced the decrease of concomitant use, however this only refers to a small period of time. Additionally when looking at the total incidence between 2017 to 2020 there is an increase of about 36% due to the fluctuation of the data, so it does not correspond with the decrease of itraconazole users. Because oxycodone came onto the Dutch market around the year 2001 there were not so many oxycodone users in the beginning. The oxycodone users started to increase throughout the years, this was observed in the IADB database. A good explanation of the decrease of the incidence could be that the increase of oxycodone users through the years is so high that it determines the incidence more than the cases of concomitant use as the oxycodone users are in the denominator of the incidence. This could have also explained why there was no incidence of concomitant use among women before 2005. Since there were not that

many oxycodone users at the beginning, the chance of concomitant use was also lower. The high incidence for men in the year 2003 was actually caused by only one case of concomitant use, but because the oxycodone users were also low in that year the incidence is higher than in the years that follow.

The Chi-square test results showed that the male incidence and female incidence were not significantly different (*Table 1*). This means that the occurrence of concomitant use of oxycodone and itraconazole in this study did not differ between men and women. The results of the one sample t test showed that the mean of the natural logarithm of the dose ratio has a positive value of 1.58E-01 (*Table 2 & Graph 2*). However the p value was 0.058 which is higher than 0.005. This means that the null hypothesis stating that the mean is not different than 0 could not be rejected. Therefore there was no significant difference between the oxycodone prescriptions before and after the start of concomitant use.

A reason why the dose did not show a significant difference could be that it is too soon to look at the first oxycodone prescription after start of concomitant use. The Dutch guidelines state that after introduction of an azole, such as itraconazole, during period of use of oxycodone the patient should be first monitored rather than directly lower the dose of oxycodone (*Itraconazol*, 2022). If the concomitant use of oxycodone and itraconazole has a long duration then the lowering of the dose of oxycodone might occur later during the concomitant use. Additionally oxycodone should be tapered off gradually instead of reducing the dose at once (A. Lambooij et al., 2021), therefore a significant dose reduction might not be directly detectable in the first oxycodone prescription after the start of concomitant use. Furthermore this study was done by looking at the prescription data, which do not represent the real drug use of patients. If the patients were not adherent to one of the drugs during the period of concomitant use it might be that they experienced less side effects. Therefore the dose reduction might not be needed.

The results showed that the age group with the highest count of concomitant use was the age group 51-60. After the age of 70 the cases of concomitant use are lower than for the age groups before, expect for the age group 20-30. This is an positive result since the exposure to oxycodone and plasma levels of oxycodone are higher in patient groups aged 70-80 and 80-90 (Liukas et al., 2008). Therefore the concomitant use does not occur in the most vulnerable age groups. The reason for why the age group 81-90 has more cases of concomitant use than age group 71-80 might be that patients over the age of 85 receive more oxycodone (Schepens et al., 2019). This is however still less than the age groups between 31-70, so it does not seem to be problematic.

All with all the study showed that there was no dosage change of oxycodone due to concomitant use with itraconazole. The distribution of age frequency at the time of concomitant use showed that the most cases of concomitant use do not occur in the most vulnerable age group. After the age of 70 the concomitant use is less frequent, this does not correspond with the hypothesis stating that the expectation was to see more cases of concomitant use in the elderly. The hypothesis stated that there would be low incidence of concomitant use and the results showed this to be true. The expectations to see more concomitant use in women than in men was also not detected, so as the expectation to see dose reduction of oxycodone.

Evaluation of data and methods

Looking at the r^2 of the trendline of female incidence the value of 1E-6 is much smaller than 1.0, therefore the data does not fit the trendline. Because the r^2 value of the trendline of the female incidence is so small the trendline cannot be seen as a reliable representation of the data. When

looking at the distribution of the data points of the female incidence it can be seen that there is a wide range of the data points. It can be also seen that before 2005 there was no female incidence found. However when looking at the period after 2005 the general distribution of the data seems to decrease over time rather than increase. The slope of the trendline might thus have been influenced by the increase in incidence between 2004 and 2005. When looking at the r^2 of the trendline of the total and male incidence both values are higher than the r^2 of the female incidence. Nevertheless both values for the r^2 of total and male incidence are also not close to 1.0. This means that also for these two incidences the data does not perfectly fit the trendline. The datasets for the total and male incidences do also have a wide range. When looking at the distribution of the data for total and male incidence the incidences do indeed seem to decrease. In conclusion linear regression is not the best method to be used for time trend analysis a better method such as time series analysis could be used in further research.

For the statistical analysis both the results of the Chi-square test and the one sample t test could have been influenced due to a small sample size. In total there were only 111 cases of concomitant use over 20 years of time and for the dose reduction only 65 cases met the requirement to be included for this testing. For statistical tests small sample sizes lead to decreased power of the study and in some cases it can lead to type ll error, which leads to a failed rejection of a false null hypothesis.

This study showed that incidence might not be the best method to represent the concomitant use of oxycodone and itraconazole. Since itraconazole is a drug with a period of use varying from 3 day to 8 months (*Itraconazole Leaflet*, 2016) a further study could look at the duration of concomitant use to see how long oxycodone and itraconazole are used together. This could be also more advantageous for the significance of the dose adjustment to see whether long term effects of concomitant use influence the dose of oxycodone.

Conclusion

From this study it can be concluded that concomitant use of oxycodone and itraconazole is not an overlooked problem in practise. However further study is needed to increase the knowledge about this topic.

Appendices

jaar	total incidence	male incidence	female incidence
2001	0	0	0
2002	0	0	0
2003	2,754820937	6,849315068	0
2004	0	0	0
2005	2,770083102	3,521126761	2,283105023
2006	4,291845494	2,739726027	5,291005291
2007	2,247191011	1,956947162	2,427184466
2008	3,092145949	3,289473684	2,973240833
2009	2,380952381	2,989536622	1,978239367
2010	1,03950104	1,319261214	0,857632933
2011	2,024877061	2,797202797	1,480019734
2012	1,553829079	1,578947368	1,535508637
2013	1,134215501	1,367365542	0,968992248
2014	1,538698261	1,099706745	1,856271546
2015	1,131790744	1,226617602	1,065870816
2016	1,077818495	1,283697047	0,928850084
2017	0,854295206	0,689338235	0,970402717
2018	1,385553298	1,553484243	1,265822785
2019	0,609013398	0,480884828	0,702617249
2020	1,161072409	0,994035785	1,28440367

Appendix 1. This is the data that was used to make the graphs for the incidences shown in Graph 1. The incidences in this appendix are shown as values per 1000 oxycodone users.

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