The optimisation of methadone dosing whilst treating with rifampicin: a pharmacokinetic modelling study

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ABSTRACT

Background: The use of oral methadone in opioid substitution treatment (OST) for the management of opioid use disorder is established clinical practice. Confounding treatment is the increased risks of contracting *Mycobacterium tuberculosis*, the mainstay treatment of which incorporates the potent CYP 2B6 inducer rifampicin.

Methods: This study applied pharmacokinetic modelling using virtual clinical trials, to pharmacokinetically quantify the extent and impact of rifampicin-mediated drug-drug interactions (DDI) on methadone plasma concentrations. An R-methadone model was developed and validated against 11 retrospective clinical studies prior to use in all subsequent studies. The aims were to investigate: (i) the impact of the DDI on daily methadone doses of 60 mg, 90 mg and 120 mg; (ii) dose escalation during rifampicin and (iii) dose reduction following rifampicin cessation.

Results: A dose increase to 160 mg daily during rifampicin treatment phases was required to maintain peak methadone plasma concentrations within a derived therapeutic window of 80-700 ng/mL. Dose escalation prior to rifampicin initiation was not required and resulted in an increase in subjects with supra-therapeutic concentrations. However, during rifampicin cessation, a dose reduction of 10 mg every 2 days commencing prior to rifampicin cessation, ensured that most patients possessed a peak methadone plasma concentration within an optimal therapeutic window.

Implications: Rifampicin significantly alters methadone plasma concentrations and necessitates dose adjustments. Daily doses of almost double those used perhaps more commonly in clinical practice are required for optimal plasma concentration and careful consideration of dose reduction strategies would be required during the deinduction phase.

KEYWORDS

Methadone; pharmacokinetics; PBPK; rifampicin; dose optimisation.

1. INTRODUCTION

Opioid use disorder remains an ongoing challenge worldwide, with over 17 million people currently thought to be using heroin (Degenhardt et al., 2016). Some of the latest data for England estimates that 257,476 people aged 15 to 64 are using opiates (Hay et al., 2017). Seventy five percent of those who engage with drug treatment services seek support for opiates and particularly for problems with heroin, according to Public Health England data (Burkinshaw et al., 2017).

The use of oral methadone in opioid substitution treatment (OST) for the management of opioid use disorder is established clinical practice and is supported by a robust evidence base (Lingford-Hughes et al., 2012; National Institute for Clinical Excellence, 2007; World Health Organisation, 2015). Doses are typically initiated at 10-30 mg/day, increasing by up to 5-10 mg/day (to a maximum of 30 mg above the initial dose in the first week), then optimised with incremental changes every few days, aiming for the usual therapeutic range of 60-120 mg/day. When appropriate, doses are reduced at a rate that is tailored to the individual, for example by 5 mg every one to two weeks in the community setting (Public Health England, 2017).

Methadone is an isomeric mixture of R-Methadone and S-Methadone, where R-methadone is thought to be the clinical active moiety with at least 10 times higher affinity for opioid receptors μ (MOR) and δ (DOR) than the S-isomer(Callahan et al., 2004). The elimination of methadone is primarily mediated by hepatic Cytochrome P450 biotransformation, followed by renal excretion. Its *in-vitro* biotransformation is mediated by CYP 2B6, 2C9 and 3A4 (Foster et al., 1999; Gadel et al., 2015). However its clinical biotransformation is primarily mediated through CYP2B6-mediated N-demethylation (Chang et al., 2011; Kharasch, 2017; Kharasch and Stubbert, 2013; Totah et al., 2008).

Given that CYP 2B6 is a highly inducible CYP isozyme (Code et al., 1997; Gadel et al., 2015), this may partly contribute to the wide inter-individual variability in metabolic clearance, which necessitates doses being tailored to individuals over a relatively wide therapeutic range (Rostami-Hodjegan et al., 1999). However, of particular concern is the possibility of patients being treated with concomitant medication that can directly inhibit or induce the CYP 2B6, such as rifampicin, phenytoin, efavirenz and macrolides (Wolff et al., 1993).

Nearly 2 billion people are infected worldwide with tuberculosis (TB) (Glaziou et al., 2009), and within the European region recent reports have suggested an incidence of 32 per 100,000 population (World Health Organization, 2017). People who inject opioids are at increased risk

of being infected with latent *Mycobacterium tuberculosis* (TB) and/or human immunodeficiency virus (HIV) (Centers for Disease Control, 1989), and progression may be accelerated in this group (Antonucci et al., 1995; Markowitz et al., 1997; Selwyn et al., 1989; Selwyn et al., 1992). A recent review has highlighted that the prevalence of TB in people who are using illicit substances can be as high as 59 % (Deiss et al., 2009) and that epidemiological factors that are common in this group (alcohol and tobacco use, homelessness and incarceration) can increase the risk of TB infection (Barclay et al., 1995; Drobniewski et al., 2005; Hudolin, 1975; Nelson et al., 1995). The mainstay treatment for TB treatment is a fixed-dose combination of medication which usually includes rifampicin.

Rifampicin is a highly potent inducer of CYP 2B6 (Faucette et al., 2004; Kenny et al., 2018) and is a common cause of many diverse drug-drug interactions (DDIs) (Pea and Furlanut, 2001; Venkatesan, 1992), particularly when used at common doses for TB treatment (600 mg once daily for 6 months) (World Health Organization, 2010). However, few reports have specifically examined the interaction of rifampicin with methadone from a pharmacokinetic/pharmacodynamics perspective (Dedicoat, 2012; Kreek et al., 1976; Raistrick et al., 1996), and where this was investigated a reduction in methadone plasma concentrations by 35-65% was reported (Baciewicz and Self, 1984; Kreek et al., 1976; Niemi et al., 2003), resulting in a delayed onset and an increased potential for opioid withdrawal symptoms (Niemi et al., 2003).

Given that CYP 2B6 enzyme induction is a time-dependant process (Code et al., 1997; Dedicoat, 2012), the clinical impact of the interaction may not be immediately apparent prior to attainment of a new steady-state enzyme protein/activity levels. Further, given that many patients may be stabilised on maintenance doses of methadone over many years, the (relatively) short period of rifampicin exposure would necessitate careful dose adjustment during the rifampicin-mediated CYP 2B6 induction and de-induction phases of enzyme activity. However, knowledge of how to conduct methadone dose adjustment under these circumstances are currently lacking.

We have previously applied pharmacokinetic modelling to explore rifampicin-mediated DDI with antimalarial agents and to optimisation antimalarial dosing strategies (Olafuyi et al., 2017a, b). In this study we develop a robust predictive pharmacokinetic model to assess drug interactions between methadone and rifampicin through the application of virtual clinical trials

simulations. Further, the model we proposed is developed from an extensive and robust application of retrospective clinical pharmacokinetics data of methadone use in patients.

The primary aim of this study was to propose clinically appropriate methadone dose adjustment necessary for patients undergoing concomitant rifampicin treatment during methadone maintenance therapy. The objectives of this study were to: (i) develop a robust and validated pharmacokinetic model for R-methadone; (ii) identify a suitable therapeutic window for enantiomeric methadone and (iii) explore the impact of rifampicin on R-methadone pharmacokinetics at different stages of methadone dosing for OST.

2. METHODS

Population based PBPK modelling was conducted using the virtual clinical trials simulator Simcyp (Simcyp Ltd, a Certara company, Sheffield, UK, Version 16). Simulations incorporated mixed genders (50:50) unless otherwise stated. A four-stage workflow approach was applied for the development, validation and simulation of methadone (Figure 1).

The default Simcyp validated adult Healthy Volunteer (HV) population groups were used in simulations for Steps 1-4. The latter population group accounted for ontogenic related changes in physiological/biochemical parameters such as organ volumes, organ perfusion and drug metabolising enzymes (Johnson, 2005, 2008; Small et al., 2017). Further, the Simcyp population groups account for population variability through the inclusion of a variability metric (% coefficient variability) which was established from public health databases such as the US National Health and Nutrition Examination Survey (https://www.cdc.gov/nchs/nhanes/).

2.1 Step 1: Model development and validation

A full description of the model development can be found in Section 1 of the Supplementary Materials. Initial model development considered six clinical studies where R- and S-methadone was dosed as single oral doses of 11 mg (9.9 mg methadone base) (Dale et al., 2004; Kharasch et al., 2012a; Kharasch et al., 2008; Kharasch et al., 2009a; Kharasch et al., 2009b; Totah et al., 2008), and where each study reported enantiomer specific pharmacokinetics. Model refinement was subsequently conducted using a study reported by Bruce *et al.* (2013) (Bruce et al., 2013) in patients stabilised on a maintenance dose of 80-120 mg daily for at least

2 weeks. Model refinement incorporated methadone-mediated auto-induction of CYP 2B6 and CYP 3A4 (Campbell et al., 2013), and are detailed Supplementary Materials Section 1.

Model validation was conducted using: (i) a study reported by Garimella *et al* (2015) (Garimella et al., 2015) where patients were stabilised for at least 28 days on doses of between 40 mg and 120 mg daily; (ii) a study reported by Jamois *et al* (2009) (Jamois et al., 2009) where single daily oral doses of 60-120 mg were used in which patients had been stabilised for 3 months and taking the same dose for at least 2 weeks prior to the study; (iii) refinements to metabolic clearance were assessed against available clinical studies which reported enantiomer specific DDIs between efavirenz and methadone (Kharasch et al., 2012b) and the impact of CYP2B6 polymorphisms on enantiomer specific methadone pharmacokinetics (Kharasch et al., 2015).

In all cases, model simulations were run to match the reported age range, patient number and gender ratio as reported by each study. In the absence of this information, a default trial size of 100 subjects (10x10 design) aged 20-50 years old and with equal numbers of males and females. For genotype validation studies, populations were simulated as entirely wild-type (**1/*1*) or polymorphic (**6/*6*) through modification of the default CYP phenotype frequency within the Simcyp Healthy Volunteer population group. Where multiple doses were administered, a dose escalation strategy was implemented, commencing at 20 mg once daily and escalated in weekly intervals by 20 mg to the required dose, unless otherwise stated. Simulations were run to ensure that the analysis was conducted when the methadone plasma concentration had reached steady-state. In all simulations, the free base form was modelled based upon a salt-to-base conversion ratio of 0.894 (U.S. Department of Justice, 2018). The final enantiomer specific methadone parameters that were applied to all subsequent steps are detailed in Table S1 of the Supplementary Materials. In all subsequent studies, the R-enantiomer was considered.

To ensure optimised methadone dosing, knowledge of a therapeutic window was required. The dose range of 60-120 mg resulted in a reported therapeutic plasma concentration within the range of 80-250 ng/mL for the R-enantiomer and 80-400 ng/mL for the R,S-enantiomer mix (Eap et al., 2000) (Gamaleya et al., 1999). Further, the application of receiver operating characteristics (ROC) was able to identify optimal therapeutic thresholds, with an upper range spanning 200-250 ng/mL for R-methadone and 400-500 ng/mL for R,S-methadone (Hallinan

et al., 2006). Other studies have reported ranges of between 150-700 ng/mL for enantiomeric methadone with doses spanning 3-100 mg daily (Wolff et al., 1991).

Further, it can be difficult to clearly distinguish the overlap between potentially fatal methadone plasma/blood concentrations when the person is in receipt of optimised OST. For example, a report from Australia (Pilgrim et al., 2013) identified a median blood methadone concentration of 500 ng/mL (range: 100-3000 ng/mL) associated with 206 deaths of people using heroin from 2001-2005, although it was not possible to definitively confirm exactly what was consumed prior to death in the context of 'on-top' use compared to what may have been prescribed. Further, Karch and Stephens (2000) (Karch and Stephens, 2000) identified a mean blood concentration of methadone as ≥ 800 ng/mL in 38 patients who were believed to have died from methadone overdose.

Given that in non-fatality reports, enantiomeric methadone plasma concentration ranges span 80-700 nm/mL, and in fatality cases plasma concentration ranges span >500-800 ng/mL, simulations in subsequent steps defined a therapeutic window with a lower therapeutic limit of 80 ng/mL and upper limit set at 700 ng/mL.

2.3 Step 2: Impact of co-initiation of rifampicin and methadone OST on methadone pharmacokinetics

Building upon Step 1, the DDI between methadone and rifampicin was assessed over 365 days using a scenario wherein 100 subjects (10x10 design) were initiated on R-methadone with a 20 mg daily dose. The initial 20 mg dose was followed by dose escalation, based on weekly 20 mg dose adjustments up to maintenance doses of 60 mg, 90 mg or 120 mg until the end of the study, in line with current UK national guidelines for methadone initiation and monitoring requirements (Public Health England, 2017). In conjunction, rifampicin was orally dosed at 600 mg once daily commencing on day 1 and terminating on day 168. The impact of the resultant DDI on methadone plasma concentrations, and the location of the C_{max} within the therapeutic window was analysed.

2.4 Step 3: Adjusting methadone dose following the termination of rifampicin

Building upon Step 2, the DDI between methadone and rifampicin was simulated over 365 days using a scenario wherein 100 subjects (10x10 design) were initiated on R-methadone with a 20 mg daily dose followed by dose escalation with 20 mg dose adjustments each week up to

maintenance dose of 160 mg. In conjunction, rifampicin was orally dosed at 600 mg once daily commencing on day 1 and terminating on day 168.

In order to identify an appropriate methadone dose reduction strategy upon completion of rifampicin, dose regimen optimisation was carried out to assess the impact of: (i) a shorter dose reduction period (10 mg every four days, versus three days and versus two days) and (ii) the consequence of dose reduction implemented 1 week prior to rifampicin termination.

In all cases, an optimised dose reduction strategy was considered when most subjects achieved a peak methadone plasma concentration within the therapeutic window. For all subsequent steps, the R-enantiomer was considered.

2.5 Step 4: Adjusting methadone dose during the commencement and termination of rifampicin

Building upon Step 3, this step assessed the impact of initiating rifampicin during an existing maintenance phase of methadone OST. Methadone was initiated with a 20 mg daily dose followed by dose escalation with 20 mg dose adjustment each week up to 90 mg daily. On day 84 rifampicin was initiated at a dose of 600 mg for a period of 168 days (terminating on day 252).

During initiation of rifampicin treatment, methadone dose regimen optimisation was considered through increasing the methadone dose by 10 mg every 2 days commencing on (i) day 84 onwards and (ii) commencing prior to rifampicin, from day 74 onwards. Within each dosing regimen, methadone doses were escalated to 160 mg daily.

Immediately after the termination of rifampicin (day 252), methadone dose adjustments were further made to maintain plasma concentrations within the mid-point of the therapeutic window, and utilised the optimised dosing regimen identified in Step 3 for this deinduction phase.

2.6 Predictive Performance

In simulations for Step 1, a prediction to within two-fold (0.5-2-fold) of the mean published clinical data was generally accepted as part of the ‘optimal’ predictive performance (Ginsberg et al., 2004; Prieto Garcia et al., 2018; Tylutki et al., 2018).

2.7 Visual Predictive Checks

Model predictions in step 1 were compared to existing clinical studies using a visual predictive checking (VPC) strategy. This approach was described at the 2012 FDA Pediatric Advisory Committee (US Food and Drug Administration, 2012) (U.S. Food and Drug Administration, 2012). The predictability of the simulations was validated by comparing the predicted 5^{th} and 95^{th} percentiles (along with mean or median) of predicted concentration–time profiles (generated from Simcyp) against the observed data for any validation data sets. Where predicted data points largely overlapped with those from the observed data sets, which should contain (where possible) some measure of spread of observed plasma concentration data (e.g., a standard deviation for each mean concentration point), the prediction was assumed to be valid.

2.8 Data and statistical analysis

The observed data from clinical studies that were used for visual predictive checks were extracted using WebPlotDigitizer v.3.10 (http://arohatgi.info/WebPlotDigitizer/). Where a DDI was simulated, the model performance was principally dictated by the comparison of the AUC ratio or C_{max} ratio (ratio of the AUC or C_{max} in the absence and presence of the inhibitor or inducer). An AUC ratio or C_{max} ratio greater than 1.25 is indicates an inhibition reaction whereas a ratio of less than 0.8 indicates an induction reaction whilst a ratio of between 0.8 – 1.25 indicates no interaction. Where applicable, statistical analysis was conducted using paired t-tests with a $P < 0.05$ indicating statistical significance.

3. Results

3.1 Step 1: Model development and validation

An R- and S- enantiomer methadone file was developed and validated against a range of published clinical studies using the Simcyp Healthy Volunteer population group (See section 2.1). For all single dose and multi-dose studies, the predicted R-methadone and S-methadone plasma concentration-time profiles were successfully predicted to within the observed range for each study and model-predicted t_{max}, C_{max}, and AUC were predicted to within 2-fold of the reported parameters for each study, confirming successful validation. For all subsequent studies, R-methadone was used. Details of all validation results can be found in the Supplementary Materials Section 2.

3.2 Step 2: Impact of co-initiation of rifampicin and methadone OST on methadone pharmacokinetics

To assess the impact of a rifampicin-mediated DDI on methadone pharmacokinetics, three doses of methadone were investigated (60 mg, 90 mg and 120 mg), covering the low, middle and higher end of the established therapeutic dose range (Figure 2).

At the lowest daily dose of 60 mg daily, in the absence of rifampicin (Figure 2A), steady state plasma methadone was attained on day 18 with a mean C_{max} of 230.81 ng/mL ± 99.09 ng/mL (Table 1) (Figure 3). In the presence of rifampicin (Figure 2B), the resultant methadone steady-state mean C_{max} (quantified on day 50) was significantly reduced ($P < 0.0001$) to 85.50 ng/mL ± 43.37 ng/mL with a concomitant decrease in mean AUC from 212.11 ng/mL.d in the absence of rifampicin to 69.11 ng/mL.d in the presence of rifampicin ($AUC_{ratio} = 0.33 \pm 0.1$) (Table 1) (Figure 3).

Increasing the daily dose to 90 mg and 120 mg resulted in a corresponding increase ($P < 0.0001$) in the mean C_{max} to 129.79 ng/mL ± 65.84 ng/mL and 173.02 ng/mL ± 87.72 ng/mL, respectively, in the presence of rifampicin (Table 1) (Figure 3).

Following completion of the rifampicin treatment regimen, the resultant steady-state mean C_{max} and AUC was recovered approximately 21-days post rifampicin completion, day 187, (Figure 2) (Table 1) for all doses (Figure 3).

At steady-state for the 60 mg dose, in the absence of rifampicin, 97 % of subjects possessed a C_{max} within the therapeutic window and 3 % within the sub-therapeutic ranges (See Supplementary Materials Section 3: Table S8). However, in the presence of rifampicin 44 % of subjects possessed a C_{max} within the therapeutic window with 56 % of subjects with a sub-therapeutic C_{max} (See Supplementary Materials Section 3: Table S8). With dose increase to 90 mg and 120 mg, the percentage of subjects possessing a C_{max} within the therapeutic window, in the presence of rifampicin, increased to 81 % and 93 % respectively. However, in the absence of rifampicin, increasing the dose to 90 mg or 120 mg resulted in a concomitant increase in the number of subjects with a supra-therapeutic C_{max}, 2 % and 14 % respectively (See Supplementary Materials Section 3: Table S8).

3.3 Step 3: Adjusting methadone dose following the termination of rifampicin

Step 2 identified that lower daily methadone dose would result in high number of subjects with sub-therapeutic peak methadone concentrations in the presence of rifampicin. This step

therefore simulated the impact of a higher daily dose of 160 mg once daily, with escalation in 20 mg weekly dose intervals (Figure 4)

In the absence of rifampicin (Figure 4A and B), simulated steady state plasma methadone was attained on day 60 with a C_{max} of 616.19 ng/mL ± 261.32 ng/mL (Table 2). In the presence of rifampicin (Figure 4C and D), the resultant simulated methadone steady-state C_{max} (quantified on day 60) was significantly reduced ($P < 0.001$) to 230.56 ng/mL ± 116.73 ng/mL with a concomitant decrease in AUC from 566.10 ng/mL.d in the absence of rifampicin to 186.36 ng/mL.d in the presence of rifampicin (AUC_{ratio} = 0.33 ± 0.10) (Table 2). Following completion of the rifampicin treatment regimen, the resultant C_{max} and AUC were recovered 21-days post rifampicin completion, day 201, (Figure 4E) (Table 2).

At steady-state with a 160 mg daily dose, in the absence of rifampicin, 72 % of subjects possessed a C_{max} within the therapeutic window and 28 % within the supra-therapeutic range. However, in the presence of rifampicin 96 % of subjects possessed a C_{max} within the therapeutic window with only 1 % of subjects within the supra-therapeutic range (See Supplementary Materials Section 3: Table S8).

Following termination of rifampicin, during the 140 mg dose reduction phase, 76 % of subjects possessed a C_{max} within the therapeutic window with 22 % of subjects possessing a supra-therapeutic C_{max} (See Supplementary Materials Section 3: Table S8). However, with a dose of 100 mg, there were still a significant number of subjects (12 %) with peak methadone concentration within the supra-therapeutic range (See Supplementary Materials Section 3: Table S8). Further dose optimisation was therefore considered.

Simulations were conducted to assess a deinduction regimen that would limit the number of subjects with sub- and supra-therapeutic peak methadone concentrations. Trial designs investigated included (i) a 10 mg dose reduction every 4, 3 or 2 days and commencing on the day of rifampicin termination (Figure 5A) and (ii) a dose reduction commencing 1 week prior to rifampicin termination from the optimal dose reduction strategy identified in (i) (Figure 5B).

All proposed dose reduction approaches resulted in a significant percentage of subjects remaining within the sub- and supra-therapeutic regions (data not shown) (Figure 5A). However, a reduction of dose 10 mg every 2 days, commencing one week prior to rifampicin termination (Figure 5B), resulted in a minimal 'peak' in C_{max} observed for dose reduction initiated post-rifampicin termination on day 168 (Figure 5A), with a mean C_{max} of 531.64 ng/mL ± 239 ng/mL on day 168 (Table 3). Furthermore, with this optimal strategy, on day 168,

93 % of subjects attained a steady-state C_{max} within the therapeutic window with no subjects within the supra-therapeutic regions (See Supplementary Materials Section 3: Table S8).

3.4 Step 4: Adjusting methadone dose during the commencement and termination of rifampicin

Based upon results obtained in Step 3, dose optimisation was conducted to identify a suitable dose escalation and reduction regiment during rifampicin treatment. Following incremental 20 mg weekly dose escalation (Figure 6A) to achieve a final daily dose of 90 mg, in the absence of rifampicin (Figure 6B), simulated steady state plasma methadone was attained on day 33 with a mean C_{max} (as quantified on day 80) of 359.85 ng/mL ± 152.48 ng/mL (Table 4). During this phase 97 % of subjects achieved a C_{max} within the therapeutic window, with 2 % within the supra-therapeutic region (See Supplementary Materials Section 3: Table S8).

Rifampicin was initiated on day 84. However, the impact of a dose escalation in methadone was considered by increasing dose by 10 mg every 2 days commencing on day 84 onwards and increasing to 160 mg daily (Figure 6D). Further, the impact of commencing this dose escalation prior to commencement of rifampicin was considered by a similar dose escalation commencing on day 74 (Figure 6D).When commencing dose escalation prior to rifampicin initiation, methadone plasma concentrations peaked within the supra-therapeutic regions (Figure 6D) on day 84. Therefore, methadone dose-escalation prior to the commencement of rifampicin was not considered as part of the optimal dosing regimen design and dose escalation was commenced on the day of rifampicin initiation (Figure 6D). Under these conditions, simulated methadone plasma concentrations decreased over 7 days until a new steady state concentration had been attained on day 97. On day 100, methadone C_{max} had significantly reduced ($P < 0.001$) to 234.36 ng/mL ± 120.03 ng/mL with a resultant AUC ratio of 0.34 ± 0.10 and C_{max} ratio of 0.39 ± 0.10 (Supplementary Materials Section 4: Table S9). During this phase 94 % of subjects attained a C_{max} within the therapeutic window (in the presence of rifampicin) (See Supplementary Materials Section 3: Table S8). Further, during this steady-state period, the highest individual C_{max} reported during the rifampicin treatment phase was 577 ng/mL (Supplementary materials Section 4: Table S9). Rifampicin treatment terminated on day 252. However, dose reduction took place 1 week prior to this commencing on day 245, reducing by 10 mg in 2 day intervals to 90 mg daily (Figure 6E). On day 252, the impact of this dose reduction prior to stopping rifampicin resulted in a decrease in C_{max} to 176.9 ng/mL ± 92.47 ng/mL (Supplementary materials Section 4: Table S10), with the lowest individual C_{max} of 50.06 ng/mL (Supplementary materials Section 4: Table S10). However, at the end of

the study period, methadone plasma concentration had recovered to similar levels as those reported on Day 80 (Table 4). During this dose reduction phase, on day 252 the number of subjects achieving a C_{max} within the therapeutic window was 95 % with 1 % demonstrating supra-therapeutic concentrations (See Supplementary Materials Section 3: Table S8).

4. DISCUSSION

Oral methadone is a widely used medication for OST both nationally and internationally (Herget, 2005; Public Health England, 2017). To ensure successful treatment outcomes, dose optimisation is critical in ensuring both sub-therapeutic (withdrawal symptoms/cravings) and supra-therapeutic (overdose/toxicity) effects are limited. The understanding of methadone pharmacokinetics is limited but wide inter- and intra-individual variability exists (Boulton et al., 2001). Such variability is important to consider, given that only 1 in 5 individuals receiving OST have optimised doses and some may require even higher doses (>200 mg daily) to achieve stabilisation (D'Aunno et al., 2014; Kreek et al., 2010). Part of this variability may be attributed to individual patient polymorphisms at methadone metabolism enzymes, particularly for CYP 2B6 (Mouly et al., 2015). Additionally, clinically relevant DDIs may occur with concomitant medication such as rifampicin, which is typically used for managing TB, which people who inject opioids are at high risk of contracting (Begre et al., 2002; Ferrari et al., 2004). As a potent CYP 2B6 inducer, rifampicin can pose particular difficulties when attempting to optimise methadone doses when initiating or terminating rifampicin (Kreek et al., 1976).

This study implemented an exemplar dosing approach in line with current UK guidelines (Public Health England, 2017), with the goal of attempting to better characterise the potential impact of rifampicin on methadone plasma concentrations in order to better understand the necessary methadone dose adjustment requirements (e.g. ‘how soon?’ and ‘how quick?’), through the application of pharmacokinetic modelling and simulated virtual clinical trials. We adopted a work-flow based modelling approach with robust model development and refinement using retrospective clinical studies reporting methadone pharmacokinetics. Thereafter, the question of the development of clinically appropriate methadone dose adjustments in rifampicin-mediated DDIs was investigated using virtual clinical trials simulations.

4.1 Step 1: Model development and validation

In Step 1, we adapted an existing Simcyp derived model for methadone and conducted robust validation tasks: 6 single dose studies, 3 multi-dose studies, 1 DDI study and 1 DDI study with consideration of CYP 2B6 single nucleotide polymorphism (SNPs). In all simulations, the predicted R-methadone and S-methadone plasma concentration-time profiles were within the range reported within each clinical study with associated predictions of C_{max}, t_{max} and AUC to within 2-fold of that reported for all studies (See Supplementary Materials Sections 1 and 2).

4.2 Step 2: Impact of co-initiation of rifampicin and methadone OST on methadone pharmacokinetics

Rifampicin is known to induce CYP 2B6 and therefore this step explored the impact of this DDI at methadone daily dose ranges of 60 mg, 90 mg and 120 mg. In all cases, the impact of rifampicin was evident during the 168 day treatment period, with lower simulated steady-state peak plasma C_{max} and AUC (and both demonstrating dose dependant increases) in the presence of rifampicin (Table 1). A similar reduction in methadone plasma concentrations by 35-65% has been reported in other studies (Baciewicz and Self, 1984; Kreek et al., 1976; Niemi et al., 2003), and where the consequence of this change was reported to be a delayed onset of methadone action and an increased potential for opioid withdrawal symptoms (Niemi et al., 2003). This was confirmed, in our simulations, by the number of subjects with simulated peak methadone concentrations below the therapeutic window in the presence of rifampicin (56 %) when compared to the absence of rifampicin (3 %) at the lowest dose of 60 mg daily (See Supplementary Materials Section 3: Table S8). A dose increase to 120 mg daily resulted in 93 % of subjects within the therapeutic window (Figure 2B). However, there still remained 7 % of subjects with sub-therapeutic methadone levels. Therefore, a clear dose increase in such situations would directly benefit the majority of subjects whilst not significantly increasing the number of subjects with potentially toxic effects (See Supplementary Materials Section 3: Table S8).At the termination of rifampicin, methadone plasma concentrations recovered within 25 days (Figure 2B), a process mediated by CYP 2B6 deinduction. Despite the relatively short half-life of rifampicin (3-4 hours), the regulation of the expression of CYP 2B6 protein (and subsequently degradation rates) are time-dependant processes and is therefore likely to be the primary cause for the time-dependant deinduction. For example, in a previous study examining DDI between rifampicin and midazolam, the clearance of midazolam took 2-4 week to recover to baseline, with the authors estimating the deinduction half-life in this case to be approximately 7-8 days (Reitman et al., 2011). Other studies have also reported a similar time-scale. For example, rifampicin-induced reduction of propranolol attained steady-state

concentrations within 10 days and returned to baseline within 20 days (Branch and Herman, 1984). Similarly, the return to baseline for prednisolone, following rifampicin induction, took 14 days (Lee et al., 1993).

4.3 Step 3: Adjusting methadone dose following the termination of rifampicin

As demonstrated in section 4.2, following the termination of rifampicin, the deinduction of CYP 2B6 is a time-dependent process. This step therefore focussed on approaches to dose-optimise during this deinduction phase. Having established the importance of increasing daily doses during rifampicin treatment phases, the maintenance dose was increased to 160 mg daily during the 168 day rifampicin phase.

In the absence of rifampicin, this resulted in a mean simulated C_{max} of 616.19 ng/mL ± 261.32 ng/mL, with the largest individual C_{max} of 1365.14 ng/mL, placing this significantly outside of the therapeutic window (Table 2) (Figure 4A). This was further confirmed with 28 % of subjects possessing a C_{max} outside of the upper therapeutic window (See Supplementary Materials Section 3: Table S8). In the presence of rifampicin, the mean C_{max} of 230.56 ng/mL ± 116.73 ng/mL was within the therapeutic window and resulted in 96 % of subjects residing within this window range with only 3 % of subjects with sub-therapeutic concentrations (See Supplementary Materials Section 3: Table S8)(Figure 4B and 4C), confirming that the dose selected during this rifampicin treatment phase was suitable to ensure that most subjects would achieve methadone plasma concentration within the therapeutic window. It was, however, noted that during the deinduction phase, a 140 mg dose resulted in a significantly larger proportion, 22%, of subjects possessing peak methadone plasma concentrations outside of the therapeutic window (See Supplementary Materials Section 3: Table S8)(Figure 4D), so further dose optimisation around this deinduction phase was conducted (Figure 5A). This resulted in the identification of a dose decrease of 10 mg every 2 days (to 90 mg) commencing at least 1 week prior to rifampicin termination (Figure 5B), which ensured that the majority of subjects (93 %) were within the therapeutic window range with no patients demonstrating supra-therapeutic concentrations.

Whilst very few direct studies have explored this pharmacokinetic interaction, rifampicin has been well characterised as a potent CYP 2B6 inducer (Bolt, 2004) and has also been identified as a clinical inducer by the US FDA (U.S. Food and Drug Administration, 2018). Further, a number of case reports have shown rifampicin to cause opioid withdrawal symptoms in patients taking methadone. A case report described a 40-year female taking methadone, who exhibited

opioid withdrawal symptoms when starting rifampicin for tuberculosis. This caused her to not comply with her rifampicin regimen. On recommencement of her rifampicin, her methadone dose was titrated from a stabilising dose of 50 mg (prior to TB infection) to 150 mg once daily in an inpatient setting (Raistrick et al., 1996). A further case report described withdrawal symptoms 5 days after starting rifampicin for TB (Bending and Skacel, 1977), with the patients symptoms alleviated following a methadone dose increase to 60 mg one daily. A study by Kreek *et al* (1976) (Kreek et al., 1976) reported that of the 87 patients on methadone who had also been taking a course of rifampicin (600 mg to 900 mg daily), 30 % demonstrated signs of withdrawal symptoms with reported methadone plasma concentrations that were 33-68 % lower during rifampicin treatment. Further, these withdrawal symptoms were absent in the remaining patients, whose TB was treated without rifampicin (Kreek et al., 1976). In another study, Kharasch *et al.* (2004) demonstrated that rifampicin decreases methadone C_{max} by 30 % with an approximate 4-fold increase in clearance (Kharasch et al., 2004). Of note, however, is that this effect is not limited to methadone: similar reports have demonstrated that rifampicin co-administration with buprenorphine reduces the AUC of buprenorphine by 25 % (Hagelberg et al., 2016).

Rapid dose reductions of methadone are not usually recommended unless facilitated by adjunct medication used for managing withdrawal signs and symptoms. However, our proposed schedule of dose reduction counteracts the impact of a return of CYP 2B6 levels to baseline, which would otherwise require a rapid reduction in methadone, particularly given the 25 days 'recovery' period for CYP 2B6 expression. Without reductions, individuals may achieve significantly larger C_{max} within supra-therapeutic regions which may be fatal. A slow decrease on a weekly basis would take at least 5-7 days to achieve a new steady-state concentration and therefore, a slow dose reduction (assuming a weekly basis) would be expected to take at least 1 month before standard dose ranges (60-120 mg) are achieved. In clinical practice, it is proposed that individuals receive frequent reviews and are assessed for both sub and supra-therapeutic effects and ideally using an objective rating scale such as the Clinical Opioid Withdrawal Scale (COWS) (Wesson and Ling, 2003).

4.4 Step 4: Adjusting methadone dose during the commencement and termination of rifampicin

Based upon the proposed optimal dosing adjustment, Step 4 attempted to incorporate a dose escalation and dose reduction before and after rifampicin treatment. In order to ensure that subjects were generally maintained within the therapeutic window prior to rifampicin,

methadone doses were increased by 20 mg each week to 90 mg daily. During the commencement of rifampicin, we examined the possibility of implementing methadone dose escalation on day 74 with 10 mg increments every 2 days (Figure 6), however this resulted in a noticeable 'peak' in the methadone plasma concentrations in the absence of rifampicin (during days 75-84) (Figure 6D). However, methadone dose increases at the same time as the commencement of rifampicin resulted in 94 % of subjects having a peak methadone plasma concentration within the therapeutic window (See Supplementary Materials Section 3: Table S8), indicating optimal dosing.

During the induction process, rifampicin treatment significantly ($P < 0.001$) increases the oral clearance of methadone from 13.4 L/h in the absence of rifampicin (Supplementary Materials Section 5 Figure S7) to 31.2 L/h following commencement of rifampicin (Supplementary Materials Section 5 Figure S7). Similar reports have identified an approximate 3-fold increase in methadone clearance with concomitant rifampicin (Kreek et al., 1976; Rostami-Hodjegan et al., 1999). The induction and deinduction effects were time-dependant (Supplementary Materials Section 6 Figure S8), lasting approximately 25 days. Further, the calculated methadone deinduction half-life was 7.2 days (Supplementary Materials Section 7). This may explain why a dose-adjustment prior to rifampicin commencement was not required, as the dose adjustments on day 84 onwards were sufficient to counteract the increased oral clearance of methadone following rifampicin induction (Yang et al., 2008).

In summary, methadone dose correction is required during initiation and cessation of rifampicin to directly counteract CYP 2B6 induction. The half-life of methadone and the induction time process requires consideration prior to the design of a dosing regimen to counteract the enhanced clearance of the methadone in the presence of rifampicin. Our studies demonstrated that a daily dose of 90 mg is acceptable to ensure the majority of the subjects were within the therapeutic window in the absence of rifampicin. However, during rifampicin treatment, a dose escalation to 160 mg daily may counteract the enhanced metabolic clearance of methadone and help to ensure that individuals achieve peak methadone plasma concentrations within the therapeutic window. It should be noted that although the proposed dosing regimen (during steady-state) could be conducted in a community setting, daily assessments alongside supervised consumption, or an inpatient setting may be preferable, especially if significantly high doses of methadone are thought to be required.

Although the clinical impact of rifampicin on methadone has been well established, the data presented within this study provide, for the first time, a pragmatic approach to optimise dosing of methadone in patients presented with TB. Nevertheless the work presented requires further investigation in clinical practice to confirm our findings, however our proposed dosing range for methadone is similar to those reported previously in clinical case reports (Kreek et al., 1976; Raistrick et al., 1996).

This is important considering the epidemiological complexities associated with 'real' OST patient cohorts, and particularly as our modelling approaches assume good adherence. Whilst data on adherence is relatively sparse, a medication adherence study over 8 years in China for patients enrolled on methadone-maintenance therapy identified a drop-out rate of 52 % (Zhou et al., 2017). Therefore, the impact of poor adherence, particularly when individuals' life circumstances are more chaotic, may need to be considered in the context of the simulated results presented within this study for both methadone and, more importantly, rifampicin.

It should also be noted that patients taking methadone, particularly long-term, often present with co-morbidities resulting from the individuals' life circumstances and may require a range of pharmacological interventions with other psychotropic drugs, antibiotics, anticonvulsants and antiretroviral drugs, all of which can elicit a range of pharmacokinetic interactions (Ferrari et al., 2004). However, such co-morbidities can alter physiological processes required for methadone pharmacokinetics, for example through hepatic impairment as a result of hepatitis which may result in portal shunting and a net reduction in hepatic metabolism of methadone (Davis, 2007), or a decrease in plasma protein product resulting in an increase in free (unbound) concentration (Verbeeck, 2008). Further studies should consider the impact of additional clinical covariates on the dose adjustment requirements for similar types of DDIs in patients whom present with organ function impairment.

Furthermore, although we have provided an exemplar approach to methadone dose adjustment throughout rifampicin treatment, the quantitative outcome of our approach may initially not be easily transferrable to other non-invasive sampling methods, e.g. urine analysis. Nevertheless, utilising robust validation approaches focussed on plasma methadone levels, we have proposed the application of mechanistic pharmacokinetic modelling (through virtual clinical trial) as an approach to pragmatically assess the need for methadone dose adjustments during rifampicin treatment. This approach has the advantage of providing directly accessible clinical guidance

to address the questions 'how soon should a dose adjustment be made?' and 'at what frequency should this be done?'. Nevertheless, future studies should consider confirming the dosing adjustments we propose through the use of urine analysis in clinical studies.

Further, from a clinical perspective, the dose adjustment simulated during the initiation and cessation of rifampicin would require careful consideration during OST prescribing reviews, with healthcare professionals remaining vigilant during the induction and deinduction phases. Specialist treatment services should be involved in assertively engaging individuals with TB treatment and proactively encouraging adherence. When methadone dosing changes are warranted due to the addition of rifampicin, patients may be reluctant to change or concerned with change. Additionally, they may struggle to understand the need for important OST changes. These patients require careful counselling about the anticipated dose changes. Pharmacists who dispense methadone may also be able to counsel patients through changes (Public Health England, 2017). Finally, although this study focused on methadone, the potential impact of rifampicin on other OST agents such as buprenorphine is warranted (Rothman et al., 2000).

5. CONCLUSION

The use of rifampicin for the management of TB is common. People who inject substances are at increased risk of contracting TB and may be prescribed methadone as OST. We demonstrated an approach to conduct methadone dose correction to 160 mg, during rifampicin co-administration, in order to counter the increased methadone hepatic elimination associated CYP 2B6 induction. This study will add to the knowledge supporting prescribers in dose adjustment necessary for treating opioid addiction when faced with patients taking concomitant pharmacological inducers of methadone.

Conflict of interest statement

Conflicts of interest: none.

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LIST OF FIGURES

Figure 5: The impact of dose optimisation during the deinduction phase

R-methadone was orally administered and dose escalated by 20 mg each week to a final daily dose of 160 mg to day 168. Rifampicin was dosed from day 1-168 at 600 mg once daily. (A) The impact of methadone dose reduction on plasma concentration profiles from day 168 onwards with a 10 mg every 2 (green), 3 (red) or 4 (yellow) day reduction or 10 mg every 2 days commencing 1 week prior to termination of rifampicin; (B) the proposed optimal dose reduction strategy (10 mg decrease every 2 days) commenicng 1 week prior to termination of rifampicin. (n=100). Thick solid lines represent median predicted plasma concentration-time profile. For (A), the upper most feint lines represent the 95^{th} percentile for each dose optimisation strategy (5^{th} percentiles are not shown for these). The lower-most feint line represents the 5^{th} percentile for the 'two day redction at 1 week prior' dosing strategy. For (B) the median and 95^{th} and 5^{th} percentiles are illsutrated. The shaded area represents the range of the therapeutic window.

Figure 6: The impact of methadone dose-escalation and dose-reduction to counter a rifampicin-mediated DDI: rifampicin initiation during methadone maintenance.

R-methadone was orally administered and dose escalated by 20 mg each week to a final daily dose of 100 mg the absence (A and B) of rifampicin. Rifampicin was initiated on day 84 at a 600 mg once daily dose and the methadone dose was increased to 160 mg daily (Figure C and D). Rifampicin was subsequently terminated on day 252 and methadone dose was reduced to 90 mg once daily from days 252-365 (E). (n=100). Solid lines represent median predicted plasma concentration-time profiles with dotted lines representing 5^{th} and 95^{th} percentile range (Black: absence of rifampicin; Blue: presence of rifampicin). The shaded area represents the range of the therapeutic window.