Clinical pharmacology of analgesic medicines in older people: impact of frailty and cognitive impairment

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Pain is highly prevalent in frail older people who often have multiple co-morbidities and multiple medicines. Rational prescribing of analgesics in frail older people is complex due to heterogeneity in drug disposition, comorbid medical conditions, polypharmacy and variability in analgesic response in this population. A critical issue in managing older people with pain is the need for judicious choice of analgesics based on a comprehensive medical and medication history. Care is needed in the selection of analgesic medicine to avoid drug–drug or drug–disease interactions. People living with dementia and cognitive impairment have suboptimal pain relief which in part may be related to altered pharmacodynamics of analgesics and challenges in the systematic assessment of pain intensity in this patient group. In the absence of rigorously controlled trials in frail older people and those with cognitive impairment a pharmacologically-guided approach can be used to optimize pain management which requires a systematic understanding of the pharmacokinetics and pharmacodynamics of analgesics in frail older people with or without changes in cognition.

Introduction

Pain is highly prevalent in older people [1–4] and has significant detrimental effects on function and quality of life [5, 6]. Despite these considerations, large observational studies have demonstrated persistent under-treatment of painful conditions in older people [7, 8]. Although older patients are among the highest users of analgesic medications there is relatively limited clinical evidence to inform the safe and effective use of these medications in the older population, especially those who are frail or cognitively impaired, in part because these patients are systematically excluded from clinical trials [9].

The quality use of analgesic medications is necessary to ensure optimal treatment of pain and to minimize the risk of medication-related adverse effects. This approach starts with the use of non-pharmacological interventions to manage and limit the pain intensity or prevent recurrence of painful episodes. Non-pharmacological interventions

have a role before or as an adjunct to pharmacotherapy. The challenges surrounding analgesic prescribing in older people are further amplified in the presence of frailty and impaired cognition, as there are few data to support evidence-based decisions in such patients. The validity of applying treatment recommendations derived from studies of analgesics in young, healthy subjects to frail, older people is questionable given the marked physiological differences between these groups [10]. An understanding of the pharmacokinetics and pharmacodynamics of analgesics in frail older people is essential for their optimal prescribing and monitoring.

Achieving optimal pain control in older people is a complex and multi-factorial issue but essential given the frail older population have a high demand for effective and safe analgesia. The aim of this review is to examine the clinical pharmacology of analgesics commonly used and recommended in frail older people. A particular emphasis is placed on the complexities of frailty and cognition and

how these may impact on the pharmacokinetics and pharmacodynamics of analgesics in this population. This review focuses on analgesics for non-malignant nociceptive pain and does not specifically focus on cancer pain or neuropathic pain which has been reviewed by others [11–13]. The use of complementary and alternative medicines for chronic pain has been reviewed elsewhere [14].

Pain and comorbidity in older people

Epidemiological studies have estimated that approximately 20% of people in this age group are taking analgesic medicines and the majority are using these medications for greater than 6 months' duration [1, 5]. A survey of over 17 000 Australian adults found that the prevalence of chronic pain peaked in the age range 65–69 years for men and 80–84 years for women and people over the age of 85 years were less likely to receive analgesia than younger subjects [1]. Older people also have the highest rate of surgical procedures [2–4] and are more likely to suffer from musculoskeletal pain and other chronic conditions than their younger counterparts.

One of the most challenging statistics is that between 45% and 80% of older people with pain report that it is inadequately treated [5, 15]. An observational study of 3046 community-dwelling frail older people in Italy found that 40% reported daily pain but only one-quarter of these people received analgesia [16]. The clinical impact of this is highlighted by the growing body of evidence that reveals an association between poorly controlled pain and declining physical function in older people. A large longitudinal study of community-dwelling people over 70 years of age ($n = 754$) demonstrated a significant association between the incidence of restrictive back pain and reduction in lower limb function [17]. Similarly, a study examining the relationship between daily pain and physical function in the oldest old (mean age 85 years) found that those reporting daily pain had significantly lower scores in a physical performance battery and lower grip strength [18]. Declining physical function is predictive of adverse health outcomes that impact on quality of life such as disability [19], loss of independence, anxiety and depression [18, 20]. While these observational studies emphasize the manifestations of untreated pain in relatively non-frail community-based older people, the potential for adverse outcomes is likely to be even greater in frail patients given their vulnerability and lower baseline levels of functioning. The recent MOBILIZE study [21] identified a clear link between chronic pain and the risk of falls. Patients who reported two or more locations of musculoskeletal pain had a greater occurrence of falls and there was a clear link between pain severity and risk of experiencing a fall in older people [21].

Frailty is now recognized as a condition or phenotype that is predictive of adverse health outcomes [22–25]. The

frailty 'syndrome' has been variously described in terms of an excessive reduction of lean body mass, sarcopenia, chronic under-nourishment, a reduction in walking performance and mobility and poor endurance associated with a perception of exhaustion and fatigue [24, 25]. Frail older people are characterized as having a high susceptibility to disease, impending decline in physical function and a high risk of death. What is apparent is that frailty is a complex, multifactorial and dynamic state characterized by decreased energetic and homeostatic reserve and an increased vulnerability to stressors [24, 25]. Blyth *et al.* [26] investigated the relationship between pain, frailty and co-morbidity in 1705 community-dwelling men (older than 70 years) and found a close link between intrusive pain and comorbid burden in frail older men.

The clear association between comorbidity (including frailty and functional impairment) and pain presents a challenge to optimal analgesic selection to achieve pain control [27, 28]. Care is needed in the selection of analgesic medicine to avoid drug–drug or drug–disease interactions [29].

Pain management in frail older people – an evidence gap

The impact of age and age-associated changes in body composition and organ function as a determinant of response to medicines is well described [10, 22, 23]. Older patient populations are more heterogeneous in terms of physiology and morbidity, resulting in a less predictable response to medications [10, 22]. Frailty further increases this heterogeneity [10, 24] but its effects on pharmacokinetics and pharmacodynamics of drugs and metabolites are relatively poorly elucidated. Current treatment guidelines almost ubiquitously advocate a 'start low and go slow' approach to analgesic dosing in older patients, particularly in the treatment of frail older patients [5, 15, 30]. Hanlon *et al.* highlights that this 'risk management' dosing strategy is often misinterpreted as 'start low, stay low' [31] compounding the risk of inadequate analgesia.

A review of 83 clinical trials involving greater than 10 000 subjects treated with simple analgesics found that only 2.3% of subjects were aged over 65 years and none was over the age of 85 years [32]. Bayer *et al.* [9] who reviewed 155 trials of relevance to older people concluded that this issue is not limited to analgesics as they found only five trials had a justifiable upper age limit. Indeed, in 85 of the studies reviewed, the upper age limit was deemed unnecessary and in some cases actually conflicted with the aims of the study. The validity of clinical recommendations arising from a study is questionable when an atypical population has been represented. Despite a growing body of literature examining the implications and consequences of frailty for a range of medical outcomes [24, 25], frail older people have been significantly under-

represented in clinical trials, including those designed to investigate optimal pain management strategies. It must be acknowledged that the inclusion of frail older people in clinical trials is challenging. The heterogeneity that ageing and frailty inevitably introduce into a population results in the need for large sample sizes to ensure adequate power [33]. There can also be ethical obstacles to recruiting older people to trials, particularly when communication difficulties arise or when invasive procedures are involved, although researchers have demonstrated that it is possible to recruit successfully frail older patients into clinical trials [34].

Analgesic medicines also have the potential to provide a burden of potential harm to older people. An analysis of hospital record data for people over 60 years of age in Australia found that analgesics were responsible for approximately 17% of the 37 296 hospital admissions attributed to adverse drug reactions [35]. If relevant information about the pharmacokinetics and pharmacodynamics of analgesics in older people was available to inform optimal drug and dose selection, many of these adverse effects would be predictable (and preventable), rather than idiosyncratic [10, 35]. While it is understood that frail older people have an increased susceptibility to the adverse effects of analgesics [36], analgesic medicines can still be used safely and effectively in this patient cohort.

Clinical pharmacology principles challenge the suitability of the 'start low and go slow' approach to analgesic dosing in frail older people [10, 22]. The use of inappropriate dosing strategies, resulting from a limited understanding of the clinical pharmacology of analgesics in frail or cognitively impaired older people, has the potential to under-treat not only pain but also to result in adverse events (as reviewed by the American Geriatrics Society) [5, 15]. The optimal use of simple analgesics can reduce the need to escalate drug selection to stronger opioid analgesics, which come with their own spectrum of adverse events in the older patient [36]. A number of observational studies have demonstrated chronic under-treatment of pain in the older patient, and this in itself calls into question the suitability of the 'start low and go slow' approach [7, 8, 37]. A study investigating the development of delirium in hip fracture surgery found severe pain and the use of low doses of opioids to be correlated significantly with progression to delirium. There was no significant association found between the use of higher doses of opioids and development of delirium in either cognitively intact or cognitively impaired patients [38]. These results suggest that under-treatment of pain has at least as great a propensity to harm as the use of opioids. Evidence of the routine under-treatment of pain in frail older patients, coupled with the increased incidence of preventable adverse effects of analgesics, builds a strong case for the need to investigate systematically frailty as a predictor of response to these drugs.

Frailty as a predictor of response to medicines

The effects of ageing on the pharmacokinetics and pharmacodynamics of medications are widespread and variable and have been reviewed extensively [10, 22, 23, 39–41]. While it is clear that renal function declines with age, the effects of chronological age and associated changes in body composition on the distribution and metabolism of drugs are inconsistent and poorly elucidated [42]. Chronological age is a poor determinant of pharmacological response. In light of this, a limited number of studies have examined the effect of frailty as an independent predictor of the pharmacokinetic behaviour of selected drugs [43–45]. The interpretation of these studies is further complicated by the inconsistent manner in which frailty as a phenotype has been defined, assessed and classified. The pharmacodynamics of analgesics may also be altered in older people as age-related changes in pain processing, including suprathreshold pain responses, may make it difficult for older people to modulate or effectively respond to nociceptive input [46].

Age associated changes are not always clinically significant and thus do not universally result in dose regimen alterations [10]. In contrast, frailty is characterized by chronic under-nourishment and sarcopenia [24, 25, 28, 47] and while this could theoretically impact on the distribution of some drugs, there have been no specific studies to assess resultant changes in pharmacokinetic parameters or the clinical significance of this. Inflammation and frailty have been associated [48, 49] which in turn has the potential to down regulate drug metabolism and transporter pathways [50, 51] further complicating the impact of frailty on the clinical pharmacology of analgesics.

The widely held belief that oxidative metabolism universally declines with age and frailty, partially underpins the 'start low and go slow' dosing doctrine. Schwartz [45] investigated the hypothesis that frailty, independent of age, maybe an important factor in determining drug elimination capacity by using the erythromycin breath test as a marker of metabolic activity. The study concluded that old and very old (>80 years) people maintain the ability to metabolize some drugs via selected metabolic pathways and that frail people do not universally display reduced drug clearance via these pathways or perhaps have down-regulation of transport processes [45]. However, erythromycin is an imperfect marker of CYP3A4 activity as it is also a substrate for the drug efflux transporter, p-glycoprotein [52]. The review by Butler & Begg [42] made a clear link between the impact of the age-associated decline in albumin concentrations and changes in the unbound fraction on the hepatic clearance for drugs with a low hepatic extraction ratio. These authors confirmed that unbound hepatic clearance (a key determinant of maintenance dose rate) for the majority of medicines declines in older people. Wynne *et al.* [44] used metoclopramide to assess the

impact of frailty on conjugative metabolism (sulfation) and concluded that, while the activity of this pathway is preserved in fit older subjects, it is significantly decreased in frail older subjects. The same group also investigated the effects of frailty on paracetamol glucuronidation, finding that frailty had a bigger influence on this pathway than age [43]. Esterase activity has been shown to be diminished in frail older people and is negatively correlated with markers of inflammation [49]. Taken together, these results suggest frailty has a global effect on a number of drug metabolizing pathways.

While pharmacokinetic information is very valuable for informing dose regimen design in a patient group, this information must be interpreted along with information about pharmacodynamics. Chronological age has been suggested as an important predictor of analgesic response [53, 54] but studies have not investigated the impact of frailty as an independent predictor of pharmacodynamic response. Without this information, the clinical significance of the effects of frailty on analgesics will remain elusive.

Cognition as a predictor of response to analgesic medications

A significant cohort of the frail older population are cognitively impaired [55]. There is evidence that people with Alzheimer's disease are administered fewer analgesics and report less pain than cognitively intact people [7, 56]. A number of studies has investigated pain rating and functional MRI brain responses following mechanical pressure stimulation in patients with Alzheimer's disease and age-matched controls [56, 57]. These studies found no diminution of pain perception or processing associated with Alzheimer's disease, raising concerns about the adequacy of pain management in this highly dependent and vulnerable patient group. Interestingly, Benedetti *et al.* [57] investigated the placebo response using both open and hidden lignocaine application prior to venepuncture. At baseline, subjects with mild Alzheimer's disease (mean Mini Mental State Examination score = 24) reported a mean reduction in pain rating score of $63.2 \pm 14\%$ when lignocaine was openly applied, but only a $22.7 \pm 18.2\%$ mean reduction when lignocaine application was hidden ($P < 0.001$). This difference indicated the open application resulted in a meaningful placebo-response. However, at 1 year's follow up, when the patient's cognitive state had declined (mean MMSE = 15.6), a much smaller difference in pain reduction was seen with open administration (40.7 ± 21.3 compared with $23 \pm 15.1\%$, $P < 0.001$). This study suggests that older people with dementia and impaired prefrontal functioning may have a reduced placebo response to analgesics [57] providing the further possibility that typical doses of analgesics may be less effective in this patient group than in the general population.

Taken together these findings reflect a growing body of evidence concerning the impact of cognitive impairment on pain perception and analgesic pharmacodynamics. The findings of these studies again challenge the 'start low and go slow' approach to analgesic dosing and suggest a more comprehensive understanding of the clinical pharmacology of analgesics in this population is needed to inform optimal dosing strategies. The recent development and validation of innovative tools for assessing pain in cognitively impaired patients [58–61] means it is now possible to investigate systematically the clinical pharmacology of analgesics in this cohort. Importantly, pain can be controlled adequately with approach selection and utilization of analgesic medicines and non-pharmacological strategies with careful consideration of pain intensity, frailty, disability and cognitive status [5].

Clinical pharmacology of analgesics in frail older people

Rational prescribing of analgesics in frail older people is complex due to heterogeneity in drug disposition, comorbid medical conditions, age-related changes in body composition, polypharmacy and variability in analgesic response in this population [10, 27, 29]. In general terms, the pharmacologically-guided approach to optimizing pain management requires a systematic understanding of the pharmacokinetics and pharmacodynamics of analgesics in the target population to inform drug and dose regimen selection. The implementation of the dose regimen then requires careful monitoring of efficacy and safety with dose titration. In the absence of rigorously controlled trials in frail older people, an understanding of the changes in these parameters enables greater confidence in prescribing. The following sections review the evidence of the effects of age and frailty on the pharmacokinetics and pharmacodynamics of paracetamol and selected opioids.

While a number of analgesic medicines may be commonly used in older people, some analgesics pose an unacceptable risk to frail older people who may also be cognitively impaired due to the risk of potential medicine related harms. Non-steroidal anti-inflammatory drugs (both selective and non-selective NSAIDs) are generally accepted as posing a risk of life-threatening gastrointestinal bleeding and significant adverse effects on renal function in the frail older patient [5]. Due to the risk of drug–drug and disease–drug interactions in frail older people NSAIDs are not reviewed here but have been considered by others [62, 63]. Pethidine has an active metabolite that has the potential to accumulate in older people with renal impairment [64]. Dextropropoxyphene has a long half-life in older people and has been associated with a significant risk of side effects in older people [65]. Despite their wide use the weak opioid agents codeine and tramadol have a

limited role in frail older people, especially those with cognitive impairment, due to the risk of significant drug–drug and drug–disease interactions as well as considerable variability in response and adverse effects [66, 67]. Both codeine and tramadol are metabolized by CYP2D6 to active metabolites such that pharmacogenetic determinants or drug interactions have the potential to shift significantly the harm to benefit ratio for these medicines in this patient population [68, 69]. A number of these analgesics carry an unacceptable risk of falls and fracture in older people which highlights the need to limit their use [70, 71].

Paracetamol

Paracetamol is a simple analgesic recommended as the drug of choice for the management of mild to moderate pain and in combination with opioid analgesics in more severe pain [5]. Paracetamol is a safe and effective analgesic in the management of post-operative pain and other acutely painful conditions [72]. Additionally, paracetamol has a key role in the management of persistent pain and can have a significant opioid-sparing effect in chronic conditions [5, 15, 72–75]. Of particular significance to older people is the use of paracetamol in the management of osteoarthritis where it is recommended as first-line treatment [74, 75].

The pharmacokinetics of paracetamol in healthy young adults has been well characterized [76, 77]. A number of studies have investigated the pharmacokinetics of paracetamol in healthy older adults, reporting variable effects of age [78–82]. Paracetamol is rapidly and completely absorbed from the gastrointestinal tract and neither the rate nor the extent of absorption appears to be age-dependent [78]. The volume of distribution of paracetamol in healthy young adults has been reported as between 0.8 l kg^{-1} and 1 l kg^{-1} , and decreases in volume of distribution have been associated with increasing age and female sex [77–79], which is consistent with the drug's hydrophilic nature and age-associated changes in body composition. Wynne *et al.* [43] reported no significant difference in volume of distribution between healthy and frail older people.

The elimination pathways of paracetamol have been studied extensively [83, 84]. A number of studies has identified a reduction in paracetamol clearance in older people [42, 43, 78–80]. Two studies have specifically investigated the impact of frailty on the elimination of paracetamol in older people. The first included 29 fit older people (mean age 77 ± 8 years) and 26 frail older subjects (mean age 84 ± 7 years) and compared the pharmacokinetics of a single dose of 1000 mg in the two groups [85]. Subjects were classed as frail if they were unable to live independently. Frailty was associated with a statistically significant decrease in total clearance ($17.7 \pm 6.7 \text{ l h}^{-1}$ in the fit older vs. $13.4 \pm 5.2 \text{ l h}^{-1}$ in the frail older people, $P < 0.01$) and increase in elimination half-life ($2.7 \pm 0.5 \text{ h}$ in the fit older person vs. $3.4 \pm 1.2 \text{ h}$ in the frail older person, $P < 0.01$). The

clinical significance of this difference is uncertain, but the increased variability seen in the frail group indicates that the pharmacokinetics of paracetamol are likely to be less predictable in this population.

The major pathways of paracetamol metabolism in the liver involve conjugation to glucuronide and sulphate metabolites [43]. The association between frailty and the hepatic conjugation of paracetamol has been examined by Wynne *et al.* [43]. Total clearance (per kg) was significantly reduced in a healthy older group ($n = 20$, mean age 73 ± 1 years) and frail older group ($n = 9$, mean age 82 ± 2 years) when compared with a healthy young cohort ($n = 19$; mean age 25 ± 1 years). Additionally, the frail group demonstrated significantly reduced total clearance when compared to the healthy older group, an observation that was preserved when corrected for age. Interestingly, when expressed per litre of liver volume, the clearance of paracetamol in the healthy young and older subjects was not statistically different but the frail older group still demonstrated reduced clearance when compared with either healthy group. This suggests that the intrinsic conjugative activity of the liver maybe preserved in healthy older people but may be compromised in frail older people. The effects of frailty on specific conjugative pathways were further clarified in this study, with clearance to paracetamol glucuronide significantly reduced, while clearance to paracetamol sulfate appeared unaffected [43]. The clinical significance of these changes are unclear given the wide safety margin of paracetamol, the small sample of frail older subjects in this study ($n = 9$), the possible confounding effects of diet and the fact that no explicit frailty classification system was used in the study. Further investigation into the link between pharmacodynamic response and the observed pharmacokinetic changes is required in the frail older population.

Oxidative metabolism, catalysed by CYP2E1 and CYP3A4, constitutes a minor biotransformation pathway for paracetamol but results in the formation of the highly reactive metabolite, N-acetyl-p-benzoquinoneimine (NAPQI) [83, 84, 86]. Under normal conditions NAPQI is detoxified by conjugation with glutathione and subsequently renally excreted [86]. However, if the rate of production of NAPQI exceeds the rate of glutathione conjugation, hepatic centrilobular necrosis can ensue [86]. A number of factors that increase the risk of hepatotoxicity have been identified, including chronic alcoholism, dosing in excess of 4 g day^{-1} , pre-existing liver disease, concomitant use of microsomal enzyme inducers and malnourishment [83, 87, 88]. Given the physiological changes characteristic of frailty, in particular malnourishment, frail older people may be more susceptible to the adverse effects of paracetamol than their healthy counterparts. Interestingly, a recent prospective observational study by Mitchell *et al.* [89] found that frail older people were less susceptible to the changes in markers of hepatic function when compared with non-frail patients receiving

paracetamol in the hospital setting. This suggests that frail older people may be less likely to generate the NAPQI metabolite via oxidative metabolism pathways, a view consistent with other studies of the age-associated changes in drug metabolism [42].

Despite paracetamol dosing guidelines that recommend a dose reduction in the treatment of older patients, no studies have systematically studied the relationship between age or frailty and paracetamol pharmacodynamics. Of particular interest is the dose–response relationship of paracetamol in patients with dementia. There has been increasing interest in the use of routine paracetamol in patients with dementia, even in the absence of overt signs of pain. A randomized, placebo-controlled study of 25 nursing home residents with moderate to severe dementia found regular administration of paracetamol (three times daily) resulted in increased social interaction, work-like behaviour and self-talk [90]. It appears that the regular administration of paracetamol can reduce the sequelae of untreated pain and improve functioning in patients with dementia, although an optimal dose has not yet been ascertained. Further studies correlating pharmacokinetic and pharmacodynamic data will be useful in informing safe and effective dosing regimens for paracetamol in older people living with dementia.

Opioid analgesics

Opioid analgesics have been used in the treatment of moderate to severe pain for many years and their clinical effectiveness and potential harm are well established [64]. However, rational prescribing of opioids in the treatment of frail older people remains challenging [5, 8, 91]. Opioid analgesic may offer little therapeutic value in selected clinical presentations of persistent and chronic pain (such as chronic low back pain) as these medicines may reduce function further and increase disability. Age is a significant predictor of opioid-related harm, with patients over 60 years of age having a two- to eight-fold increased risk of respiratory depression [36] and falls and fractures [6, 71]. It is likely that the reduced homeostatic reserve that characterizes frailty will further increase susceptibility to the adverse effects of opioids. However, there is limited understanding of the impact of frailty on opioid-related outcomes. While there are now clear guidelines about the limited role of some opioids, such as pethidine and propoxyphene, in the treatment of older people, the use of other opioid analgesics is increasing in the frail older population [92–95]. In the absence of high level evidence for the safety and efficacy of opioids in frail older people, a detailed understanding of the pharmacokinetic–pharmacodynamic relationships of these drugs is needed to optimize their use.

Morphine Morphine is the most widely used opioid throughout the world and the standard against which other analgesics are judged. It is available for administra-

tion by many routes, oral, parenteral, rectal, buccal, and thus is a versatile analgesic for moderate to severe pain that is useful in many settings. The pharmacokinetic characteristics of morphine have been extensively studied over a number of years and a range of patient factors have been identified as potential predictors of pharmacokinetic response [96]. While a strong relationship exists between morphine dose and serum concentrations of the parent and its active metabolites (including morphine-6-glucuronide), covariates such as age, weight and sex only appear to account for a very small proportion of the observed inter-individual variability [97]. There is now a greater understanding of the role of genetic variation in the human μ -opioid receptor gene and how this contributes to variability in response to morphine (and other opioids) [97–100]. Older age is associated with an increased sensitivity to morphine [64] a number of studies has investigated age-related changes in the pharmacokinetic parameters of morphine [101, 102].

Morphine is extensively metabolized, chiefly by the liver, with only 10% of the dose excreted unchanged in the urine [96]. Glucuronidation is the major biotransformation pathway for morphine, resulting in the production of two active metabolites: morphine-3-glucuronide and morphine-6-glucuronide [103]. Morphine-6-glucuronide has a high affinity for the μ -receptor, penetrates the blood–brain barrier and has approximately twice the analgesic potency of morphine when given intravenously [104]. Morphine-3-glucuronide also penetrates the blood–brain barrier but has lower μ -receptor affinity. It is thought to be responsible for the neurotoxic effects of morphine [105, 106]. Renal function is an important consideration in older people with pain receiving morphine as both glucuronide metabolites are renally excreted and may accumulate in people with renal impairment [107] leading to a significant risk of adverse outcomes. Furthermore, frailty has been associated with impaired conjugation [43, 44], and the investigation of morphine: metabolite ratios in frail older subjects may expand the understanding of the clinical pharmacology of morphine in this population. Clearly effects of age on the pharmacokinetics of morphine do not fully explain the observation that older people are more sensitive to the therapeutic and adverse effects of morphine and dose adjustment and careful monitoring are essential requirements when using this important opioid analgesic.

Oxycodone Oxycodone is a semi-synthetic opioid agonist that is formulated for parenteral, rectal and intranasal use and as controlled- and immediate-release oral tablets and an oral liquid dose form [108]. In common with many opioids, oxycodone has an established role in the short-term treatment of acute pain [109]. In recent years a number of studies have been conducted to investigate the safety and efficacy of longer-term oxycodone use in the treatment of chronic nociceptive and neuropathic pain

[109–114]. While these studies have included a reasonable proportion of older people (over 65 years), information about the efficacy and tolerability of oxycodone in the oldest old and frail is limited.

A number of studies have described the pharmacokinetic behaviour of oxycodone in young adults [115–120]. The pharmacokinetic parameters of oxycodone in young subjects suggest that it is a suitable opioid for use in older people, particularly because of its relatively short half-life. Approximately 9% of an oral dose is excreted as unchanged drug in urine [120] and, compared with other opioids, oxycodone appears to have a predictable dose–response relationship [121, 122].

The major metabolic pathway is CYP3A4-catalysed N-demethylation to noroxycodone [123]. A secondary metabolic pathway for oxycodone is CYP2D6-mediated O-demethylation to oxymorphone [123, 124]. A study in young volunteers found that inhibition of CYP2D6 resulted in a compensatory increase in CYP3A4-mediated metabolism [124]. While CYP2D6 inhibition tended to increase in oxycodone exposure there was no significant change in pharmacodynamic response confirming the observation that although the metabolites of oxycodone are pharmacologically active, it is the parent drug that is responsible for the analgesic effects after a dose of oxycodone.

Oxycodone is a commonly used [95] and recommended [30] opioid in hospitalized older people because of relatively fewer ‘pharmacological complexities’ such as dose adjustment with renal impairment and few drug–drug interactions. As yet, no studies have examined frailty as a predictor of pharmacokinetic or pharmacodynamic response to oxycodone, although a single study has found no significant alterations in response to oxycodone in healthy older people (age range 65–79 years) compared with young people [122]. The most comprehensive study of the clinical pharmacology of oxycodone in older people was conducted by Liukas *et al.* [125]. These researchers investigated the pharmacokinetics of oxycodone and its metabolites noroxycodone, oxymorphone and noroxymorphone in four cohorts of patients aged 20–40, 60–70, 70–80, and 80–90 years ($n = 10$ in each group). This study found that older patients (aged 70–90 years) had a significantly higher exposure to oxycodone (ranging from 50–80%). These authors also explored the impact of CYP2D6 genotype in these patients. CYP2D6 genotype has a major effect on the pharmacokinetics of oxycodone metabolites and the authors suggest that poor and intermediate CYP2D6 metabolizers are expected to need less oxycodone for equal effect than extensive metabolizers [125]. However, age, genotype and concomitant medications that affect CYP enzymes all contribute to the variability in oxycodone pharmacokinetics (and probably pharmacodynamics) which further highlights the need to adjust oxycodone doses according to response in older people.

Fentanyl Fentanyl is a potent and highly lipophilic semi-synthetic opioid agonist that rapidly penetrates the blood–brain barrier, resulting in prompt onset of analgesia [126]. Due to a high first pass effect, fentanyl is unsuitable for oral administration [127] and is formulated for administration via parenteral, transdermal and buccal routes. Fentanyl has long been used as an anaesthetic agent and in the treatment of cancer pain [128] and in recent years has received increasing attention as a treatment option for acute and chronic non-malignant pain [129]. A meta-analysis comparing transdermal fentanyl and slow-release oral morphine found that, overall, fentanyl was as effective as morphine in reducing average pain and produced a significantly greater reduction in ‘right now’ pain ratings than morphine in patients with chronic non-malignant pain [130]. Subgroup analyses revealed that this reduction was less marked in patients over 60 years and in patients with low body mass indices, suggesting investigation of the pharmacokinetic–pharmacodynamic relationship of fentanyl in the frail older population is needed.

Following an intravenous bolus dose, the actions of fentanyl are rapidly terminated by redistribution from the central nervous system into more poorly-perfused tissues [126]. Fentanyl undergoes extensive oxidative metabolism to norfentanyl, an inactive metabolite, which is subsequently renally excreted [131]. This metabolism is mediated by CYP3A4 and is the primary means of termination of effect when fentanyl is given longer term, for example by intravenous infusion or transdermal patch [131]. The highly lipophilic nature of fentanyl results in a relatively large volume of distribution, reported to be between 1.3 l kg^{-1} and 4 l kg^{-1} [126, 132, 134]. Given the known alterations in body composition that accompany ageing and frailty, it is predicted that fentanyl will display a larger volume of distribution and longer half-life in older people. Additionally, fentanyl has a high hepatic extraction ratio and age-related decreases in liver blood flow would be expected to result in a lower hepatic clearance. Nonetheless, existing evidence is conflicting [133, 134]. A study comparing the pharmacokinetics of an intravenous bolus dose of fentanyl in four older females (mean age 67 ± 2 years) and five young females demonstrated no difference in volume of distribution between the two groups but a significantly longer elimination half-life in the older subjects ($4.41 \pm 0.37 \text{ h}$ in young vs. $15.75 \pm 1.07 \text{ h}$ in older people; $P < 0.005$) [133]. The researchers concluded that the clearance of fentanyl is impaired in older people. However, these findings are limited by study design as the calculated half-life of fentanyl was outside the duration of blood sampling and the small sample size may have introduced significant type 2 error. In contrast, a study of seven young and seven older (71–82 years) patients found a similar clearance and elimination half-life for intravenous fentanyl in the two study groups, but a significantly lower volume of distribution in the older group ($2.3 \pm 0.8 \text{ l kg}^{-1}$ in the young vs. $1.4 \pm 0.4 \text{ l kg}^{-1}$ in the elderly, $P < 0.05$) [132]. It was postulated

that this may be due to decreased perfusion of tissues in older people, counteracting the effect of increased adiposity. Ariano *et al.* [132] compared the pharmacokinetics of a single dose of intravenous fentanyl in young healthy volunteers and older healthy volunteers (mean age 66 ± 3 years). While no statistically significant differences were found between the groups in terms of volume of distribution or clearance, the older group was observed to display a higher degree of inter-subject variability. When considered together, these studies highlight the uncertainty surrounding the effect of age on the pharmacokinetic parameters of fentanyl. It is likely that the variability that age confers on these parameters would be augmented in the presence of frailty. Specifically, the characteristic sarcopenia and undernourishment of frailty [16] could have significant effects on the disposition of fentanyl.

Fentanyl is formulated as a transdermal therapeutic system (TTS) patch, consisting of a backing, drug reservoir matrix, rate-limiting membrane and drug-in-adhesive [135]. On initial application of the patch a depot of fentanyl forms in the cutaneous layers of the skin, with subsequent absorption into the circulation. This process causes a delay in onset of analgesia and results in a prolongation of effect after the removal of the patch [136]. Consequently, removing a patch does not immediately terminate the analgesic or adverse effects of fentanyl which has important implications for the timely titration of the optimal dose rate. The administration of fentanyl via the transdermal route offers a number of advantages in the treatment of chronic pain. Steady drug concentrations can be achieved in a non-invasive manner and barriers to oral administration, such as low oral bioavailability, swallowing difficulties and vomiting, can be overcome [136]. Despite the stable pharmacokinetic profile of transdermal fentanyl a high degree of inter-patient variability in concentration–time profiles has been reported [137, 138]. An understanding of the patient factors that affect this relationship is essential for determining a safe and efficacious dose in an individual. As older people have an increased susceptibility to the adverse effects of opioids [36], a knowledge of the impact of ageing and frailty on the pharmacokinetics of transdermal fentanyl is particularly important.

Permeation of a drug through the skin is influenced by many factors such as application site, skin temperature, sweat gland function and skin integrity. The inclusion of a rate-limiting membrane in the fentanyl patch means that only extreme changes in any of these factors are likely to affect its absorption [135, 138]. It is more likely that inter-individual differences in clearance are responsible for the observed pharmacokinetic variability. While the impact of frailty on CYP3A4 metabolism is still poorly understood, its influence on the clearance of fentanyl will remain unclear. Additionally, fentanyl is a substrate of p-glycoprotein [139] and the effects of frailty associated inflammation on this transporter have not yet been investigated.

No study has specifically investigated the influence of frailty on the pharmacokinetics or pharmacodynamics of TTS fentanyl, although one study has specifically investigated the impact of age [140]. Ten young and nine older (age range 64–82 years) patients undergoing intra-abdominal surgery received a $50 \mu\text{g h}^{-1}$ patch 2 h pre-operatively. While no significant differences were seen between the groups in terms of the C_{max} , t_{max} or AUC of fentanyl, the time for plasma concentrations to double was significantly longer in the elderly (4.2 ± 0.6 h in the young vs. 11.1 ± 1.9 h in the elderly, $P < 0.005$). Additionally, although not statistically different, the elderly group had a longer mean elimination half-life following removal of the patch (21.2 ± 2.8 h in the young vs. 30.5 ± 6.4 h in the older people) and this is potentially clinically significant due to the increased incidence of adverse effects in older patients. The findings of this study are limited by its small sample size.

Fentanyl is a potent opioid agonist and as such transdermal fentanyl should not be used in patients who are opioid naïve due the risk of excessive pharmacological effects and toxicity [30]. Furthermore, transdermal fentanyl is not recommended for use in acute settings due to the delayed onset of action and risk of respiratory depression [136] and these results are not necessarily applicable to patients treated continuously with transdermal fentanyl for persistent or chronic pain who have previously received oral opioid analgesics. Despite the warnings long-acting opioids (such as transdermal fentanyl) continue to be used to initiate opioid analgesia in frail older people [141] which poses an unacceptable risk. Evidently there is a need for the systematic investigation of the pharmacokinetic and pharmacodynamic properties of transdermal fentanyl in frail older patients and those who are cognitively undergoing treatment for persistent pain.

Buprenorphine The mixed opioid agonist/antagonist (partial μ -opioid receptor agonist and a κ -opioid receptor antagonist) has been increasingly used in the age care setting due to the availability of a transdermal delivery system that provides sustained analgesia over an extended period [30, 142]. This is despite the relatively limited information available on the clinical pharmacology of this analgesic in frail older people. One challenge that is yet to be fully explored is the pharmacological compatibility of using 'breakthrough' pain relief with immediate release opioid agonists (such as morphine and oxycodone) which may (theoretically) be antagonized by buprenorphine limiting the clinical utility of this combination. However, a number of studies have highlighted that the use of morphine and other opioids for the management of breakthrough pain is safe and effective for people receiving transdermal buprenorphine [142].

Buprenorphine is metabolized in part by CYP3A4 [143]. Few *in vivo* drug–drug interactions have been detected and *in vitro* studies support this observation [144, 145].

Inhibitors or inducers of CYP 3A4 are not expected to cause significant alteration of buprenorphine metabolism or effects [30]. No significant difference in the pharmacokinetics of transdermal buprenorphine in patients with renal impairment [146, 147] have been observed and age did not have a significant effect on buprenorphine pharmacokinetics after transdermal administration [142].

Conclusions

Pain is a significant health problem in the older population, as evidenced by its prevalence, apparent under-treatment and association with declining physical function. The choice of analgesic and dose regimen requires careful consideration of comorbid medical conditions and concomitant medicines in frail older people. The pharmacological management of pain is complicated by a lack of clinical investigations conducted in older populations, particularly the frail and cognitively impaired patient. It is apparent that frailty may be predictive of an individual's pharmacokinetic and pharmacodynamic response to analgesic medications but, as yet, there are few data examining this. Clearly, further research is needed into the pharmacokinetic and pharmacodynamic properties of analgesics in frail older people and those with cognitive impairment to inform rational prescribing in this group. A key issue is the systematic and consistent assessment and definition of frailty status in these studies to allow comparison and interpretation. Research to understand the role of non-pharmacological interventions as an adjunct to pharmacotherapy is also needed. This is an active area of research and these suggestions align with recent expert consensus on opioid pharmacotherapy research priorities [148, 149]. Until more comprehensive clinical data are available in this vulnerable population a rational strategy for achieving optimal pain control should involve closely monitored analgesic dose titration in frail older people with careful attention to potential harms and pain intensity [149].

Competing interests

There are no competing interests to declare.

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