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Renal impairment: a challenge for opioid treatment?
The role of buprenorphine

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Impairment of renal function is common among elderly patients due to an age-related decline in renal excretory function. In addition, many diseases such as hypertension and diabetes mellitus are associated with an accelerated decline in renal function. Renal dysfunction affects the metabolism of compounds and thus has important therapeutic consequences for drug safety. For pain patients who have reduced renal function such as those in palliative care, most opioids used for chronic pain treatment should be administered at reduced dosages, with increased dosage intervals, or not at all because of the risk of accumulation of the parent compound or its metabolites. For instance, for morphine or codeine, active metabolites are formed in the liver and cleared by the kidney and may therefore accumulate in cases of renal dysfunction. In contrast, buprenorphine can be administered at normal doses in patients with renal dysfunction because it is mainly excreted through the liver. In patients undergoing regular haemodialysis treatment, removal of an opioid during dialysis varies between individuals based upon a number of factors including the dialysis technique used. Morphine appears to be difficult to process in haemodialysis patients due to possible 'rebound' of metabolites between dialysis sessions. By contrast, the pharmacokinetics of buprenorphine are unchanged in haemodialysis patients, which means that there is no need for dose-reduction with this drug. Thus, in patients with reduced renal function, chronic renal insufficiency and haemodialysis, buprenorphine appears to be a safe choice when opioid treatment is initiated. Palliative Medicine 2006; 20: s17–s23

Key words: active metabolite; buprenorphine; Cockcroft-Gault formula; creatinine-blind range; creatinine clearance; elderly; haemodialysis; morphine; renal impairment

Introduction

The risk for cancer rises with increasing age. It has been estimated that up to 70% of all cancer cases will be diagnosed in patients aged 65 years or older within the next 20 years, a value which may well increase. As the rate of morbidity increases with age, so does persistent pain, resulting in the elderly having a greater requirement for appropriate analgesic treatment. In the last years of life the prevalence of moderate-to-severe pain is very high. For instance, ~85% of palliative care patients suffer from malignant disease and ~70% from non-malignant disease, either of which make pain treatment with opioids such as morphine a necessity.

When considering palliative care and pain treatment in elderly patients, the liver and the kidneys require special attention because organ function is gradually reduced with increasing age, even in healthy individuals. The glomerular filtration rate (GFR), the measure of the kidneys’ ability to filter and remove waste products, decreases by 1 mL/min per consecutive year from the age of 30–40 years onwards in healthy individuals, with the result that a healthy 80-year-old person typically has 35–50% of the renal excretory capacity of a 20 year old. In addition, the ageing kidney is at high risk of eventual failure from acquired renal disease.

Many chemotherapeutic agents induce renal and/or liver function impairment or require special dosage considerations (both in number and size of dosage) in renal and/or liver dysfunction. This has been shown to be true, for example, for methotrexate, carboplatin, cisplatin, topotecan and other drugs, whether in the palliative care setting or in the elderly population in general. Elderly patients are also most likely to be prescribed opioids, and because they are more fragile and have diminished body functioning, this population is more vulnerable to opioid-induced adverse events. Thus, the use of opioids as the mainstay of pain treatment in the palliative care setting requires careful consideration in respect to drug choice, dosage, dosage intervals and risk of adverse events. For instance, in patients with liver...
dysfunction, a dose adjustment is recommended for use of all opioids.

Interestingly, renal dysfunction in the elderly is very common but often remains undetected and unrecognized, even though it is clinically significant. Published data have shown that upon discharge of patients from geriatric wards, renal impairment is not often referred to as a diagnosis. This was demonstrated in a study by Wong and Jones, where 42% of patients who had a creatinine clearance of 10–20% of normal were recorded as not being diagnosed with impaired renal function in the discharge documentation of a UK hospital. More importantly, two-thirds of patients who had a calculated creatinine clearance of <10 mL/min had received a discharge prescription for drugs that were actually contraindicated in renal function impairment.

### Serum creatinine and ‘creatinine-blind range’ in renal function

Measuring creatinine clearance in a patient is both laborious and time-consuming. It requires a 24-hour urine collection to be made and an additional blood sample to be drawn at the mid-interval of urine collection. Technicians need to measure and record urine volume and make a calculation. It is for this reason that in many instances clinicians prefer to estimate renal function by using serum creatinine concentration rather than calculating creatinine clearance, even though the latter is more accurate.

Creatinine is a non-protein waste product of creatine phosphate metabolism by skeletal muscle tissue, and its production is continuous and proportional to muscle mass. Secretion of creatinine is also dependent on the ingestion of meat products, which causes creatine to be converted to creatinine. The creatinine level can be altered by muscle mass changes (increase in elderly), liver disease (decreased muscle mass and creatine decrease), malnutrition (decrease), large protein meat intake (increase), exercising (increase) and renal failure (increase). Moreover, drugs can increase creatinine, as can ketoacidosis. The use of serum creatinine as a measure of kidney functioning is a very insensitive marker of mild renal function impairment. This is demonstrated in Figure 1(B), where serum creatinine concentration appears to be stable over the age range. It is only when the creatinine clearance declines to below 50% of the initial healthy value (~100 mL/min) that the serum creatinine concentration begins to rise noticeably. Thus, the ‘creatinine-blind range’, where a decrease in renal function occurs that is not observable solely from monitoring serum creatinine, has to be taken into account to provide a better assessment of a patient’s renal status.

### Assessment of renal function is more accurate using creatinine clearance

To accurately gauge the creatinine clearance and thus the patient’s renal status, serum creatinine concentration is only one factor. Other factors such as sex, age and body mass are equally important and are used in a formula developed by Cockcroft and Gault several decades ago to accurately calculate creatinine clearance. In order to compensate for physiological and metabolic differences between the sexes, 15% needs to be subtracted from the obtained value of creatinine clearance when making the calculation for female patients.

The Cockcroft–Gault formula

$$\text{CL}_{\text{Creat}} \text{ (mL/min)} = \frac{140 - \text{age (years)} \times \text{body mass (kg)}}{72 \times \text{serum creatinine (μmol/L)}}$$

where $\text{CL}_{\text{Creat}}$ is creatinine clearance.

As an alternative to the formula developed by Cockcroft and Gault, a series of formulas have been developed from data generated in the Modification of Diet in Renal Disease (MDRD) Study. The most widely used of these formulas has the advantage that only serum creatinine and age are needed to estimate the GFR. As this formula requires more sophisticated mathematics than the Cockcroft–Gault formula, it has been suggested that the MDRD formula be included in laboratory software, thereby enabling estimated creatinine clearance to be routinely printed into lab reports.

The modified MDRD formula

$$\text{eGFR} \text{ (mL/min/1.73 m}^2\text{)} = 186 \times \text{serum creatinine (mg/dl)}^{-1.154} \times \text{age}^{-0.203}$$

where eGFR is the estimated glomerular filtration rate (×0.742 in women; ×1.210 in blacks; ×body surface/1.73 for calculation of individual GFR).

The use of these formulas to calculate creatinine clearance when there is no 24-hour urine sample available assumes stable renal function. The calculation is unreliable at extremes of renal function (very high and very low GFR), and is unlikely to be accurate when normal body composition is disturbed, such as with marked oedema, obesity, pregnancy and severe muscle wasting.

### Differences in drug accumulation are dependent on age

Renal function is an important factor in the metabolism and pharmacokinetic profile of any drug and generally deteriorates with age. For example, if the metabolism of a drug with a half-life of 6 hours is considered in a young patient with a healthy renal function (GFR of ~100 mL/
min), a steady-state plasma drug concentration, which can be eliminated without accumulation, is rapidly achieved (Figure 2). However, if the patient is elderly, the GFR may deteriorate to \( \frac{50}{C_2} \text{mL/min} \), which is common in older individuals and can lead to a quite different pharmacokinetic profile being present. In this scenario, accumulation of the drug would occur and the half-life (\( t_{1/2} \)) would increase from 6 to 24 hours. Thus, complete clearance would not be possible before the next dose was administered. As the drug remains in the body longer, this may be an important factor in the cause of drug-related adverse events.

**Drug accumulation also depends on metabolism**

Drugs accumulated and any resultant adverse events are not only dependent on the age and physiology of the patient but also on how individual drugs are metabolized. Even when comparing drugs from the same class there are differences in metabolism, as can be demonstrated by considering the opioids morphine and buprenorphine. Morphine is metabolized in the liver to the glucuronide metabolites morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), both of which are excreted via the kidneys into the urine (Figure 3). Importantly, M6G is an active metabolite that, when urinary excretion fails in renal impairment, accumulates in the body with the potential to cause severe adverse events.\(^{14}\) \(^{16}\) In contrast, buprenorphine is metabolized in the liver to metabolites that pass into the bile and are, to a major extent, excreted unchanged in the faeces. The major metabolite is the weakly active compound norbuprenorphine, which constitutes \( \approx 30\% \) of total buprenorphine metabolism. It is for this very reason that these metabolites are excreted via the bile that no accumulation occurs in patients with renal dysfunction. Thus, renally impaired patients, contraindicated for morphine because of the potential for adverse events due to
accumulated metabolites, can be safely administered buprenorphine.

**Accumulation of M6G is dependent on renal function**

The ratio of M6G to morphine in the plasma is closely correlated to creatinine clearance calculated using the Cockroft–Gault formula, as has been confirmed in a study by Peterson et al. The results of this study underline the fact that accumulation of M6G is dependent on renal function. This relationship explains the observation that morphine dosage requirements are generally reduced in patients with renal impairment, and is the reason for dosage recommendations having been derived according to GFR. For instance, renally impaired patients who have a GFR of 20–50, 10–20 or <10 mL/min require that their morphine dosages be reduced to 75, 50 and 25% of the normal dosage, respectively. Renal impairment has a serious impact on the clearance of most opioids used in the clinical setting.

**Dosage modifications and recommendations for opioids**

M6G is increased in patients with renal dysfunction who are treated with morphine, which provides the reason for recommending dosage reduction in this group. In contrast, no such accumulation of norbuprenorphine occurs in patients with renal dysfunction who are treated with buprenorphine, and, thus, there is no need for dosage modification. For other opioids, there are varying degrees of accumulation of the parent drugs or their active metabolites, which has led to dosage reduction being recommended in the approved labelling and prescribing information documentation (Table 1).
culminate in apnoea. A recent study by Filitz et al., investigated long-term treatment with transdermal buprenorphine in 10 renally impaired patients (mean body weight 65±9 kg) who had renal dysfunction sufficiently severe to warrant chronic haemodialysis therapy. On sampling blood before and after a haemodialysis session, the concentration of buprenorphine (and norbuprenorphine) was little different, indicating that there was very little accumulation (Figure 5). Although the concentration of each component after dialysis was fractionally higher, this was considered to be due to volume depletion during the haemodialysis process and not due to accumulation. There were no episodes of unconsciousness recorded on buprenorphine treatment.

In patients undergoing regular haemodialysis treatment, elimination of the opioid varies between individuals based upon several factors: molecular weight, water solubility, volume of distribution, protein binding of the substance, flow rate of the dialysis solution and the patient’s blood, technical characteristics of the dialyzer such as surface area, pore size and geometry of the membrane, and the dialysis technique used. Morphine appears to be a difficult drug to use in haemodialysis patients because of possible ‘rebound’ of metabolites between haemodialysis sessions. Serious adverse events have also been reported for codeine because of accumulation of active metabolites. Fentanyl is not dialyzable but adsorption of this drug to the dialyzer membrane may cause problems in some cases. For buprenorphine, the pharmacokinetics are unchanged in haemodialysis patients as compared with controls, and thus do not require dosage modifications. Based on these data, no restrictions of use have been issued for buprenorphine in haemodialysis, peritoneal dialysis, or predialytic renally impaired patients. However, despite extensive pharmacokinetic data as discussed in detail below, safety data on buprenorphine in these patient groups have remained much more sparse.

Another study that showed the benefit of using buprenorphine in vulnerable populations, by Filitz et al., was conducted in 82 patients, divided into two groups, who were treated with transdermal buprenorphine for 28 days. One group consisted of patients aged ≥65 years (n=30; median age = 74.3 years), while the other group contained patients aged <65 years (n=52; median age = 51.0 years). The mean serum creatinine concentration was similar in both groups (1.17 and 1.23 mg/dL, respectively), while the mean estimated creatinine clearance was considerably lower in the ≥65-year group even though the concentration of creatinine in plasma was

### Table 1

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Comparative change in half-life</th>
<th>Comparative change in half-life of metabolites</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>+</td>
<td>+ +</td>
<td>Dosage ↓</td>
</tr>
<tr>
<td>Buprenorphine (transdermal)</td>
<td>+</td>
<td>+ +</td>
<td>Dosage unchanged</td>
</tr>
<tr>
<td>Fentanyl (transdermal)</td>
<td>+</td>
<td>+</td>
<td>Dosage ↓</td>
</tr>
<tr>
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<td>+ +</td>
<td>+</td>
<td>Dosage ↓</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>+ +</td>
<td>+</td>
<td>Dosage ↓</td>
</tr>
<tr>
<td>Tramadol</td>
<td>+</td>
<td>+</td>
<td>Dosage ↓</td>
</tr>
</tbody>
</table>

Figure 4

**Insidious intoxication after morphine treatment in renal failure.** *Modified from: Angst et al.* with permission.
stable (estimated creatinine clearance in the \( \geq 65 \)-year group, \( 55.2 \pm 3.5 \) mL/min, compared with \( 87.6 \pm 5.5 \) in the <65-year group; \( P < 0.05 \)). Respectively, between groups containing younger or older individuals, there was no statistical difference in accumulation of plasma norbuprenorphine (0.15 versus 0.13 ng/mL; \( P = 0.494 \)) or plasma buprenorphine (0.40 versus 0.31 ng/mL; \( P = 0.954 \)). For all patients, both younger and older, the mean plasma concentration was \( \sim 0.35 \) ng/mL for buprenorphine and \( \sim 0.15 \) ng/mL for norbuprenorphine. This study has demonstrated that accumulation of buprenorphine or norbuprenorphine is not age-dependent.

Comedication can affect renal function

The complexity of pain therapy is further increased by comedication, much of which can directly affect renal function, and should be considered when estimating the correct dosage of a drug. To illustrate this, a study recently conducted by our investigators in which 24 healthy young women were treated with a single dose of the non-steroidal anti-inflammatory drugs (NSAIDs) meloxicam or ibuprofen, and from whom 24-hour urine samples were collected before and after drug administration showed that urine volume output during this period decreased by almost 50\%. Moreover, if these volunteers had been elderly women with various comorbidities, the influence on renal function estimation and on the ability to excrete metabolites via the kidney, even in those who had their renal failure compensated beforehand with other drugs, most probably would have been even more severely hampered. Besides NSAIDs, diuretics and angiotensin-converting enzyme inhibitors are important classes of drugs that affect renal function and need consideration.

Conclusions

Assessment of renal function plays an important and often unrecognized role when treating palliative care patients with opioids. Serum creatinine is an insensitive marker of mild impairment of renal function that manifests as an increased concentration only in the more advanced stages of renal dysfunction. Calculating the creatinine clearance using the Cockcroft–Gault formula, however, provides an easy and sufficiently reliable estimate of renal function to facilitate any dosage adjustment required to minimize accumulation of the parent drug or its active metabolites. Without dose adjustment, severe adverse events have been reported in renally impaired patients receiving morphine due to the accumulation of M6G. This contrasts to buprenorphine for which no dose adjustment is required in this population, and no restrictions apply for its use in dialysis patients. In the literature, serious adverse events, including respiratory depression and other centrally mediated effects, have been reported when variable pharmacokinetics between opioids in renal dysfunction were disregarded. Knowledge of the renal elimination fraction of a drug is fundamentally important for ensuring the safety of analgesic therapy with opioids, especially in vulnerable patients, such as the elderly patients in general, or in particular cancer patients in palliative care.

References


