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Construction of a nomogram to facilitate the calculation of equianalgesic doses for opioid rotation

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SUMMARY

In order to make easier the process of dose calculation and to minimize dosage errors, a nomogram was developed, based on current recommendations for opioid dose calculation tools. Using Microsoft Excel 2013, a nomogram was created consisting of 18 parallel lines; some of them marked at 24 equidistant points as a minimum and most of them marked at 87 equidistant points as a maximum, resembling a ruler. The last mark of each line corresponds to the maximum recommended dose for each drug product or the dose equivalent. The nomogram developed for this document enables the equianalgesic dose calculation, at the same time that decreases the risk of making mathematical mistakes. Opioid rotation is an essential medical intervention when looking for efficacy and safety of opioid analgesics in clinical practice. Equianalgesic dose calculation is a complicated process with a high probability of error. The nomogram here described is a new tool able to reduce the complexity of calculation and to decrease the risk for the patient in terms of safety as well taking into account the available scientific evidence and following the measures recommended in the literature.

Key words: Nomogram, opioid, rotation, equianalgesic, doses.

RESUMEN

Con el propósito de facilitar el proceso de cálculo de dosis y minimizar los errores que se cometen en él, se diseñó un nomograma con base en las recomendaciones actuales para los instrumentos de cálculo de dosis de opioides. Se creó un nomograma mediante el programa Microsoft Excel 2013, el cual consiste en 18 líneas paralelas; algunas de ellas marcadas a 24 puntos equidistantes como mínimo y la mayoría de ellas marcadas a 87 puntos equidistantes como máxima dosis recomendada para cada grupo de fármacos o el equivalente de dosis. El nomograma desarrollado para el presente documento facilita el cálculo de dosis equianalgésica, al mismo tiempo que disminuye el riesgo de cometer errores matemáticos. La rotación de opioides es una intervención médica esencial cuando se busca eficacia y seguridad de analgésicos opioides en la práctica clínica. El cálculo de la dosis equianalgésica es un proceso complicado que tiene una elevada probabilidad de error. El nomograma aquí descrito es una herramienta innovadora, capaz de reducir la complejidad del cálculo, de disminuir el riesgo para un paciente (en términos de seguridad) y de tomar en cuenta la evidencia científica disponible, así como las medidas recomendadas en la literatura.

Palabras clave: *Nomograma, opioide, rotación, equianalgésico, dosis.*

INTRODUCTION

Opioid rotation consists in switching from one opioid medication to another and/or changing the route of administration[1-4] to improve the analgesia, to reduce the adverse effects, to respond when changes in the clinical status of a patient occur (i.e. loss of availability of the oral route or onset of a new organic failure), or when it is considered be operatively or economically beneficial[1-7].

It is used in 50% to 80% of patients with cancer pain[1,8,9] because it is effective to improve analgesia in 75% to 95%[1,9,10] and to decrease adverse effects from 50% to 70%[9-11]. However, quality of evidence about its usefulness is low in both cases[10,12].

When performing opioid rotation, it is necessary to carefully select the dose in order to avoid sub-dosage and overdosing because this may lead to adverse effects, withdrawal syndrome or loss of analgesic control[2,3,7,8,13]. To do so, the calculation is usually done using a table of equianalgesic doses which provides comparable analgesia of different opioids[1,3,4,8,12-18]. Nevertheless:

- The original table of equianalgesic doses (published more than 40 years ago) is based on studies designed with a limited methodology, no longer suitable to current clinical situations[3,4].
- The current tables differ in values, and none is based on strong scientific evidence[1,3,4,6-8,10,12,13,19].
- There is significant variability in pharmacokinetic and pharmacodynamic response to opioids[5,7,8,13] (levels of cross tolerance, clinical circumstances, pathologies, changes in drug bioavailability, stages of kidney and liver function, drug-drug interactions, populations, and genetics).
- Up to 39% of the physicians found it difficult to calculate a dose for opioid rotation, 19% to 32% result in incorrect calculations, and 18% simply are not able to make correct calculations.
- Errors decrease but do not disappear at all when computer systems are used[17,18]. That may even increase the incidence of deaths due to overdosing[4,8,13]. Besides, the possibility of making dangerous mistakes in the dose selection is higher when the healthcare personnel is not appropriately trained, poorly designed calculation tools are used, calculation tools are not friendly to use[8,13,19], and the rotation is either made from methadone or to it[8,13].

Therefore, some authors have consistently expressed the need to have new systems[4,8,13,19] which should be accompanied by practical guidelines pointing out the limitations of any equianalgesic doses calculation system, titrating the dose following an opioid rotation, and implementing measures to minimize the risk of overdosing or sub-dosage[1-7,10,12,13,15,16,19].

Others, emphasizing safety, recommend not to make calculations of equianalgesic doses at all and to titrate from initial low doses throughout a period of several days in all cases[8,13,19]. Nevertheless, this has not demonstrated reducing risks, and it probably requires titration periods which are unnecessarily longer.

Another proposal is developing an equianalgesic dose calculation system easier to use and taking into account the clinical evidence available to date; thus, reducing the risk of dosage errors. In this context, a two-dimensional graphical nomogram was developed aiming to solve mathematical problems in clinical practice following the current recommendations from recent systematic reviews.

METHODS

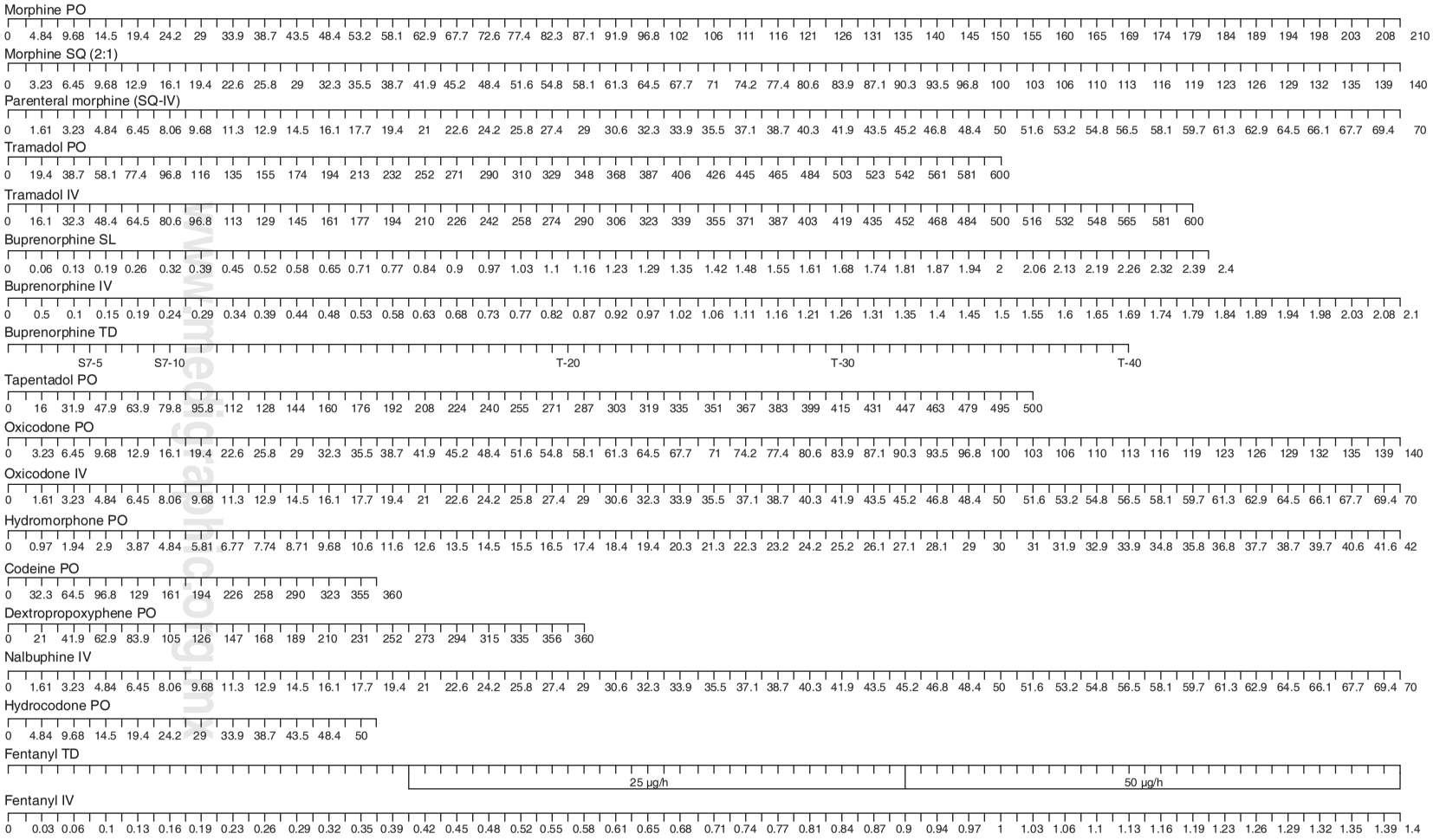
Using Microsoft Excel 2013, a nomogram was created consisting of 18 parallel lines; some of them marked at 24 equidistant points as a minimum and most of them marked at 87 equidistant points as a maximum, resembling a ruler.

The marks of each line are aligned with ah the others. Each line corresponds to a different opioid drug and to a specific route of administration. The first mark of each line corresponds to the 0-mg dose and every two marks the equianalgesic dose to all doses aligned with that particular mark is specified (Figure 1).

The calculation of each equianalgesic dose was made according to the selected equianalgesic dose ratio following a rigorous review, but non-systematic, of the current medical literature. The last mark of each line corresponds to the maximum recommended dose for each drug product or the dose equivalent to 210 mg of oral morphine. All lines, marks and doses are carefully aligned; so, when a perpendicular line is traced from any mark upwards or downwards, it will reach the line of a different opioid at the point corresponding to the equianalgesic dose for such drug.

In order to select the equianalgesic dose ratio, a non-systematic literature search was performed throughout two consecutive years (2013-2014). Search was carried out into PubMed, Google and Google Scholar using the following terms: systematic review, guidelines, opioid, opiate, narcotic, morphine, hydromorphone, methadone, fentanyl, oxycodone, tramadol, buprenorphine, tapentadol, codeine, hydrocodone, nalbuphine, dextroproproxyphene, equianalgesic, equianalgesia, dose ratio, potency, potency ratio, and tables.

Literature references of each of the found documents were reviewed and a manual search was performed of those that might provide further relevant information about equianalgesic dose ratios. Likewise, a manual search of textbooks on opioid treatment, pain management, and palliative care was performed. Once the information on different dose ratios



PO = Oral route; SQ = Subcutaneous route; IV = Intravenous route; SL = Sublingual route; TD = Transdermal route.

Figure 1. Nomogram to calculate equianalgesic doses for opioid rotation.

was collected, a selection was done taking into account the frequency at which a ratio recommendation and clinical evidence was repeated, priorizing those supported by high-quality evidence and recommended in practical guidelines issued by renowned medical associations.

RESULTS

Selection of equianalgesic dose ratios

Morphine

The original equianalgesic table suggests that 60 mg of oral morphine are equianalgesic to 10 mg of parenteral morphine; so, a ratio of 6:1 between oral morphine and parenteral morphine (both intravenous and intramuscular) was initially considered. Nevertheless, the recommendation is based on a clinical trial in an acute pain model, in single doses and without previous opioid tolerance[2,3].

In a very consistent manner, the majority of tables most recently developed refer to a ratio of 3:1 between oral morphine and parenteral (subcutaneous and intravenous) morphine[1,2,5,7,12,15,20]. Some references extend the ratio between oral and parenteral morphinefrom 2:1 to 3:1[2,14,21-23].

Most of the guidelines suggest that subcutaneous morphine and intravenous morphine require similar doses at a 1:1 ratio[21]. Moreover, there is evidence that the bioavailability of morphine via subcutaneous route varies from 83% to 100%[24]; so, some clinicians recommend to use higher doses of subcutaneous morphine than intravenous one (2:1 ratio). For purposes of the nomogram, a 3:1 ratio between oral morphine and parenteral (intravenous and subcutaneous) morphine was selected, and an alternative version with a lower ratio, 2:1, for subcutaneous morphine was included.

Oxycod one

With regard to oral oxycodone, the original table specifies that a 20 mg-30 mg dose of oral oxycodone is equivalent to 60 mg of oral morphine, and to 10 mg of parenteral morphine. The ratio between oral oxycodone and oral morphine would be then 1:2-3[3]. Correcting the original table with the currently most accepted ratio between oral morphine and parenteral morphine (3:1), equianalgesia would be 20-30 mg of oral oxycodone to 30 mg of oral morphine with a 1:1-1.5 ratio.

Some authors have recommended rotation between oral oxycodone and oral morphine at a 1:1 ratio leading to effective and safe analgesia in a series of cases[7,25]. The vast majority of the tables and practical guidelines; however, recommend to consider oral oxycodone as a more potent drug than oral morphine, even though the recommended relative potency ratio between oral oxycodone and oral morphine varies from 1:1.1 to 1:2.3[1,2,5,7,12,14,15,20,22,23,25-28]. These recommendations are based on clinical studies, and variations in ratio may be explained in terms of bioavailability. Many of the guidelines and systematic reviews recommend to use a 1:1.5 ratio between oral oxycodone and oral morphine[5-7,14,20,25-28]. For this nomogram, we chose a 1:1.5 ratio between oral oxycodone and oral morphine.

The oral bioavailability of oxycodone is about 50% to 60%[3,29]. According to several equianalgesia tables based on systematic reviews, an equianalgesic dose ratio from 1.5:1 to 2:1 was established between oral oxycodone and parenteral oxycodone[1,2]. In a number of clinical studies it has been shown that the relative potency ratio between parenteral oxycodone and oral morphine varies from 0.7:1 to 4.1:1[3,7,20]. A study comparing different doses by means of patient controlled analgesia (PCA) demonstrated that the potency between parenteral morphine and parenteral oxycodone is very similar (ratio of 1:1)[3,20]. Moreover, a 2:1 ratio between oral and parenteral oxycodone, and a 3:1 ratio between oral and parenteral morphine are mathematically consistent with a ratio of 1:1 between parenteral oxycodone and morphine. Due to these reasons, a 1:1 ratio between parenteral morphine and oxycodone was chosen.

Fentanyl

In the nomogram, lines for intravenous fentanyl and for transdermal fentanyl were included. The original equianalgesic dose table recommends an equianalgesic ratio of 1:100-200 between 50-00 μg of intravenous fentanyl and 10 mg of parenteral morphine and corresponding to a ratio of 1:300-600 between parenteral fentanyl and oral morphine[3]. However, most recent evidence highlights the fact that parenteral fentanyl (intravenous and subcutaneous) is only about 80 times more potent than parenteral morphine[2]. In some opioid rotation studies, 1:60 and 1:70 ratios[7,30-32] have been used in a number of patients. In consequence, several tables and practical guidelines recommend to modify the original table in order to include 1:80-100 ratios between parenteral morphine and parenteral fentanyl[2,3,7,30-32].

Although the evidence available for equianalgesic dose calculation of parenteral fentanyl (intravenous and subcutaneous) is relatively scarce, there are studies which suggest the possibility that most of the information collected about equianalgesia of transdermal fentanyl may be extrapolated. Hence, in a study of 20 patients with terminal cancer it was found that the dose of intravenous fentanyl, titrated by means of patient controlled analgesia (PCA), corresponded to a 1:1 ratio to that released by a fentanyl transdermal device[33]. Thus, different authors have recommended an equianalgesia ratio of 1:1 between intravenous, subcutaneous and transdermal fentanyl[15,22,23,32,33].

Most of the equianalgesic doses studies for transdermal fentanyl do establish conversion ratios with respect to oral morphine. Manufacturers of fentanyl transdermal devices recommend an average ratio of 1:150 between transdermal fentanyl and oral morphine (90 mg/day of oral morphine equivalent to a device delivering 25 μg/h, that is, 0.6 mg/day), corresponding to a 1:50 ratio between transdermal fentanyl and parenteral morphine (assuming a ratio of 3:1 between oral morphine and parenteral morphine). However, due to the fact that the devices are manufactured in fixed doses, extended ranges of oral morphine are usually recommended, which should be rotated to one same fixed dose of the transdermal device. So, the officially recommended ratio actually varies from 1:75 to 225[2,14,32,34]. Nevertheless, it has been observed that such recommendation results in too low doses in 50% to 58% of the patients, and only 40% of patients receive an adequate dose. Therefore, most of the patients usually get a dose of transdermal fentanyl that could have been calculated by using a 1:70-100 ratio between transdermal fentanyl and oral morphine instead[14,35]. It has been shown that a 1:100 ratio results in rotations with good response, and such ratio is usually recommended by a number of the reviewed authors[1,2,6,12,15,36,37]. Some authors have even proposed clinical algorithms using a ratio of 2 mg/day of oral morphine to 1 μg/h of transdermal fentanyl (1:83 ratio)[38].

Based on this review, it may be concluded that the relative potency of fentanyl with regard to morphine was overestimated in the beginning, and more recent studies have been progressively reduced the conversion ratio. The official conversion ratio is 1:150 between transdermal fentanyl and oral morphine, and 1:50 in regards to parenteral morphine. This ratio will be appropriate in 40% of the patients, but in the remaining patients a subsequent titration will be necessary. This percentage could be reduced changing to a 1:100 ratio with regard to oral morphine (1:33 to parenteral morphine), and even more if changing to a 1:70-80 ratio (1:23-27 to parenteral morphine). However, overdosing risk is increased when switching to transdermal fentanyl.

Therefore, emphasizing the need of safe opioid rotations and the importance of monitoring the titration, it was decided to use the ratios recommended by the manufacturer (1:150 with regard to oral morphine and 1:50 to parenteral morphine) in this nomogram.

Hydromorphone

The original equianalgesic dose table suggests that 60 mg of oral morphine is equivalent to 7.5 mg of oral hydromorphone; that is, a 1:8 ratio between hydromorphone and morphine[28]. However, different tables created subsequently uses different ratios ranging from 1:4 to the original 1:8[1-3,15,22,23,34,39,40].

A number of more recent clinical studies have used narrower ranges of ratios between 1:4.9 and 1:5.7, with a central trend towards a ratio of 1:5 between oral hydromorphone and oral morphine[2,5,6,14,22,23,28,34,39,41]. This 1.5 ratio has proven to be effective and safe[6,39-42].

Based on the enormous consistency among recent recommendations and the good quality of evidence supporting it, a 1.5 ratio between oral hydromorphone and oral morphine was chosen for the nomogram.

Tapentadol

Tapentadol is an opioid drug of recent clinical appearance. Hence, it has not yet been included in many of the equianalgesic dose calculation tables, including the original one[3]. A 1:2.5 ratio was one of the first ratios recommended for the calculation of equianalgesic doses between oral morphine and oral tapentadol. However, this recommendation was based on experimental studies in animals[43-45].

In subsequent clinical studies, it was observed that the ratio was closer to 1:3. For example, a phase IIIb study found a 1:2.9 ratio with regard to oral morphine and a 1:4.3 ratio to oral oxycodone (as relevant to the ratio of 1:1.5 between oral oxycodone and oral morphine)[46]. A study of opioid rotation from and to tapentadol in cancer patients found that a 1:3.3 ratio resulted in effective and safe rotations[47]. Based on these considerations, a conversion ratio of 1:3.3 between oral morphine and oral tapentadol was chosen for the nomogram.

Hydrocodone

The relative potency of hydrocodone in relation to other opioids has not been studied appropriately and is rather based on clinical practice and empirical knowledge[14,15]. Hydrocodone is not included in the original equianalgesic dose table and many other tables do not incorporate it either[3]. In those tables where it is included, a 1:1 ratio with oral morphine is always considered. In these tables, pairs of equianalgesic doses, such as 20-30 mg of oral morphine equivalent to 20-30 of oral hydrocodone[2], 30 mg of oral morphine equivalent to 30-45 mg of oral hydromorphone[15], or 30 mg of oral morphine equianalgesic to 30 mg of oral hydromorphone, may be observed. In spite of important limitations of the available evidence, the recommendations are sufficiently consistent to determine a 1:1 ratio in regards to oral morphine to be used in the nomogram.

Codeine

As with hydrocodone, the data for the calculation of equianalgesic doses are originated rather from empirical knowledge than from good quality evidence and the original table does not include them either[2,3,14,22,23,28]. In tables included in good quality systematic reviews and guidelines, an equivalence of

200 mg of oral codeine to 30 mg of oral morphine is consistently considered corresponding to a 1:6.7 ratio between morphine and codeine[2,14].

In some of the tables published for local operational purposes, an equivalence of 7.5 mg of oral morphine to 60 mg of oral codeine is also mentioned; that is say, an extended ratio of 1:8[22,23,38]. In spite of the limited quality of evidence, due to the higher methodological quality of reviews recommending it, the ratio of 1:6.7 between oral morphine and oral codeine was preferred for the construction of this nomogram.

Buprenorphine

Conversion ratios were investigated to construct lines in the nomogram for buprenorphine administered by parenteral and sublingual route, and through transdermal devices.

In some countries, buprenorphine has been available since the 1960's in its parenteral and sublingual form. Nevertheless, clinical evidence about its relative potency has been scarce. The recent development of systems for transdermal delivery has largely increased the number of studies conducted with buprenorphine[48].

In most of the papers where equianalgesic doses of transdermal buprenorphine were investigated, it was compared to oral morphine. The recommended ratio varies from 1:75 to 1:115 (between transdermal buprenorphine and oral morphine)[48,49]. In all cases, ratios were calculated based on the amount of buprenorphine that was actually administered per day, and not the amount contained within the device.

During the first years of development of the device, a 1:75 ratio (0.8 mg/day of transdermal buprenorphine equivalent to 60 mg of oral morphine) was recommended, although it was determined based on preclinical studies and initial approaches[2,36,37,50,51]. Subsequent studies, however, showed that this ratio could lead to doses higher than those required upon switching to a transdermal buprenorphine device[50]. Thus, a 1:100 ratio between buprenorphine and oral morphine has been consistently recommended[14,22,23,50,52]. More recently, some authors state that such ratio might be as high as 1:110-115[51,53,54].

Just as with transdermal fentanyl[33], it would be expected that the amount actually administered of transdermal buprenorphine keep a ratio of 1:1 with buprenorphine administered via the parenteral route. Although there are no studies available directly comparing this ratio, if it was true, it would be expected that assuming a 3:1 ratio between oral morphine and parenteral morphine, and a 1:100 ratio between transdermal buprenorphine and oral morphine, the ratio between parenteral buprenorphine and parenteral is 1:33.

This mathematical hypothesis has been confirmed in several clinical studies demonstrating an equivalence between 0.3 mg of parenteral buprenorphine (intravenous or intramuscular route) and 10 mg of parenteral morphine[3,14,55,56]. On the other hand, there is very limited evidence about the relative potency of sublingual buprenorphine, although there is one study that directly compared the effects of sublingual buprenorphine versus its parenteral formulation showing that 0.4 mg of sublingual buprenorphine are equivalent to 0.3 mg of parenteral buprenorphine (intravenous and intramuscular route) corresponding to a 1:0.75 ratio between both formulations[14,57].

For the nomogram purposes, a 1:1 ratio between parenteral buprenorphine and the amount actually administered of transdermal buprenorphine was selected. In addition, a 1:100 ratio between transdermal/parenteral buprenorphine and oral morphine (given a 1:33 ratio between parenteral buprenorphine and morphine) was considered. Likewise, a 1:0.75 ratio between sublingual buprenorphine and parenteral buprenorphine, and one of 1:75 between sublingual buprenorphine and oral morphine were chosen.

Nalbuphine

Just as with codeine and hydrocodone, the existing evidence regarding the calculation of equianalgesic doses of nalbuphine is very limited, and it is another opioid not included in the original equianalgesic dose table. In the few clinical studies that have been conducted[3], it was found that its potency ranges from a 1:0.8 ratio to a 1:1 ratio with regard to parenteral morphine. And the scarce tables including hydrocodone consistently used a 1:1 ratio in relation to parenteral morphine. Therefore, such ratio is used in the nomogram.

Tramadol

Tramadol is available for oral and parenteral administration route. In a very consistent manner it has been found that the relative potency of parenteral morphine with regard to parenteral tramadol is 1:10 to 1:11, and the most repeated and used recommendation is 1:10[14,22,23,58,59]. Some tables recommend this same 1:10 ratio when converting doses between oral morphine and oral tramadol. The bioavailability of oral tramadol (80% to 100%); however, is much higher than that of oral morphine (30% to 50%)[6], so maintaining the 1:10 ratio would be paradoxical.

The 1:10 ratio between oral morphine and oral tramadol has only been found in studies that were not designed for this purpose, but to compare groups of patients with one or the other drug product without performing an opioid rotation. In opioid rotation studies, the final ratios were found rather between 1:3.8 and 1:5.3[60,61]. With regard to this range, which is more appropriate considering the differences in bioavailability, there are many tables recommending a 1:5 ratio between oral morphine and oral tramadol, but they come from not clinical

studies[22,23,28]. On the other hand, there are clinical studies on opioid rotation supporting the use of a 1:4 ratio[14,62]. Due to this evidence, we used a 1:10 ratio between parenteral morphine and parenteral tramadol, and a 1:4 ratio between oral morphine and oral tramadol. Therefore, a 1:1.2 ratio between parenteral tramadol and oral tramadol is assumed.

Dextropropoxyphene

Dextropropoxyphene is an old drug initially used based on efficacy and safety studies of poor quality[63,64]. At present, due to its poor benefit-risk balance, it is recommended not to use this drug[2]. Only few equianalgesic dose tables include it, and these usually consider that a 130 a 200 mg dose of dextropropoxyphene is equivalent to 30 mg of oral morphine and 200 mg of oral codeine[63-66]. The clinical studies comparing its efficacy with other drug products consider that 65 mg of dextropropoxyphene is equianalgesic to 65 mg of codeine[63,64,66]. Given that the most accepted equianalgesic dose ratio between codeine and oral morphine is 200 mg to 30 mg, for this nomogram we consider that dextropropoxyphene is equianalgesic to codeine and, thus, maintains the same ratio (1:6.7 between oral morphine and oral dextropropoxyphene).

Creation of the nomogram

The final version of the nomogram is shown in figure 1. The selected equianalgesic dose ratios are listed in table I. A nine-step instructive was developed in order to guide the user when using the nomogram to calculate opioid equianalgesic doses (Table II).

Selection of safety recommendations and use instructions

Most of the authors have recommended that any opioid rotation system shall be accompanied by practical guidelines emphasizing the limitations of any equianalgesic dose calculation system, the need of titrating the dose following any opioid rotation, and the implementation of measures to decrease to the utmost potential risks of overdosing or subdosage[1-7,10,12,13,15,16,19]. It is also suggested to always include such recommendations in a clear manner in any calculation tool in order to increase safety and usefulness[7]. Thus, this nomogram includes some important recommendations on safety. One of the most repeated and emphasized aspects is that every user of an equianalgesic dose calculation system shall bear in mind that all of them are only heuristic guidelines and may not consider individual biological variability or clinical characteristics such as age, level of organic function, predisposition to adverse effects or pharmacogenetic and physiopathological differences[1,3,5,7,14].

Therefore, upon functioning as a heuristic tool, the calculated equianalgesic doses may provide results with different levels of efficacy and safety. High doses increase the possibility of having an appropriate efficacy, but also the risk of

Table I. Equianalgesic dose ratios selected for the nomogram creation.

Oral morphine	3:1	Parenteral morphine
Oral morphine	2:1	Subcutaneous morphine
Oral oxycodone	1:1.5	Oral morphine
Parenteral oxycodone	1:1	Parenteral morphine
Oral oxycodone	2:1	Parenteral oxycodone
Parenteral fentanyl	1:1	Transdermal fentanyl (released dose)
Parenteral/transdermal fentanyl	1:150	Oral morphine
Parenteral/transdermal fentanyl	1:50	Parenteral morphine
Oral hydromorphone	1:50	Oral morphine
Oral morphine	1:3.3	Oral tapentadol
Oral hydrocodone	1:1	Oral morphine
Parenteral buprenorphine	1:1	Transdermal buprenorphine (released dose)
Parenteral/transdermal buprenorphine	1:100	Oral morphine
Parenteral/transdermal buprenorphine	1:33	Parenteral morphine
Sublingual buprenorphine	1:0.75	Parenteral/transdermal buprenorphine
Sublingual buprenorphine	1:75	Oral morphine
Parenteral nalbuphine	1:1	Parenteral morphine
Parenteral morphine	1:10	Parenteral tramadol
Oral morphine	1:4	Oral tramadol
Parenteral tramadol	1:1.2	Oral tramadol
Oral morphine	1:6.7	Oral codeine
Oral morphine	1:6.7	Oral dextropropoxyphene
Oral codeine	1:1	Oral dextropropoxyphene

Table II. Nomogram usage instructions and safety recommendations.

Instructions

This nomogram may be used to calculate equianalgesic doses in opioid rotation when switching from another opioid and/or from a different route of administration or when using the same opioid drug but switching to a different route of administration. To use it, make sure the steps below are followed:

1. Calculate the total opioid dose received by the patient within 24 hours
2. Identify in the nomogram the line corresponding to the original opioid and the route of administration
3. Find the daily dose received by the patient on the selected line
4. Trace a perpendicular line intersecting the lines of the remaining opioids upwards and downwards from the mark found for the daily dose
5. Identify in the nomogram the line corresponding to the opioid and route of administration to which it will be switched or rotated. The equianalgesic dose corresponds to the point in which this line is intersected by the perpendicular line traced in the previous step
6. For reasons of safety, based on the identified equianalgesic dose, **always** apply a 20%-50% decrease. Usually, a 30% decrease is needed, but reductions up to 50% may be required in elderly or medically fragile patients
7. The calculated equianalgesic dose corresponds to the total daily dose to be administered. It has to be distributed in adequate doses throughout 24 hours taking into account the pharmacokinetics of the chosen opioid
8. It is very unlikely that the first selected dose is the ideal one. Thus, after having initiated the treatment with the selected dose, monitor the efficacy of treatment and the presence of adverse effects. Increase or reduce the dose accordingly to find the optimal dosage
9. The dose calculated by this method is only an approximate guideline. You should **always** use your medical judgment and clinical experience for determining the daily dose and its posology. Take especially into account age, race, co-morbidities of the patient, and the presence of kidney or liver failure

decreasing safety. Lower doses are more secure, but are less likely to be effective.

The optimal result of an opioid rotation is choosing a dose that is effective and safe at the same time. When this combination may not be achieved, the second best alternative is a dose that is less effective, but safe. The idea of improving efficacy in exchange of reduced safety is not acceptable[14]. However, it is also important to avoid using too low doses leading to poor efficacy or withdrawal syndrome[3].

Due to this reasoning, it is always preferred to act slightly conservative when choosing a dose for opioid rotation. The objective is to reach the optimal dose between sub-dosage and overdosing. This may be achieved by means of a systematic decrease of the calculated dose[1-5,7,14]. Another reason to try this systematic decrease when calculating the dose of a rotation is the fact that cross tolerance among different opioid drugs due to heterologous sensitization is usually lower than that caused by homologous sensitization[1].

Different published practical guidelines recommend applying a 25%-50% reduction when using a tool to calculate an equianalgesic dose. The most usual reduction is 30%, with major decrease in elderly, non-Caucasian and weakened patients[1,2,4,5,7,14,15,22,23].

Likewise, experts have repeatedly recommended to clearly indicate that these tools do not replace the medical experience and judgment, and it is always important to adjust the dose according to the unique circumstances of each patient, especially related to possible pharmacokinetic variations secondary to organic failures (as in renal and hepatic insufficiency)[1,5,7,14]. Once chosen, it is critical to monitor the efficacy and safety of the starting dose in order to implement a titration process. Hence, the calculation of an initial equianalgesic dose is only the first step of a titration process aiming to find the optimal dose[1,5,7,14].

DISCUSSION

The nomogram herein described makes easier the process of equianalgesic dose estimation and reduces the risk of mathematical error. Nevertheless, due to the low-quality of the evidence currently available, the huge individual variability among patients, and the variation among results, risk of error in calculation cannot be totally avoidable. Thus, any estimation of opioid equianalgesic dose may be potentially erroneous. Likewise, choosing a ratio may imply a personal bias, considering that there is no ratio unanimously accepted as the best one.

Therefore this nomogram, or any other method, must always include a clear notice explaining that such tool should be used as an initial heuristic guideline when looking for an appropriate dose in opioid rotation, and further titration and monitoring processes should always be in place.

CONCLUSIONS

Opioid rotation is an essential medical intervention when looking for efficacy and safety of opioid analgesics in clinical practice. When switching to a new opioid, it is necessary to find a dose providing an adequate efficacy along with an acceptable level of safety. This is often achieved by the calculation of equianalgesic doses. Equianalgesic dose calculation is a complicated process with a high probability of error.

In this paper, we propose a nomogram as a new tool able to reduce the complexity of calculation and to decrease the risk for the patient in terms of safety as well taking into account the available scientific evidence and following the measures recommended in the literature.

In the future, it will be important to determine by means of well-designed clinical studies whether the different tools or guidelines currently available meet such recommendations.

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