SAFETY ISSUES OF CURRENT ANALGESICS: AN UPDATE

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Abstract

Pain represents a complex experience which can be approached by various medicines. Non-opioid and opioid analgesics are the most common drugs used to manage different types of pain. The increased attention nowadays to pain management entailed concomitantly more frequent adverse drug reactions (ADRs) related to analgesic use. Drug-drug interactions can be sometimes responsible for the adverse effects. However, a significant proportion of analgesic ADRs are preventable, which would avoid patient suffering. In order to draw the attention to analgesics risks and to minimize the negative consequences related to their use, the present review comprises a synthesis of the most important safety issues described in the scientific literature. It highlights the potential risks of the most frequently used analgesic medicines: non-opioid (paracetamol, metamizole, non-steroidal anti-inflammatory drugs) and opioid analgesics. Even if there is a wide experience in their use, they continue to capture attention with safety concerns and with potential risks recently revealed. Acknowledging potential safety problems represents the first step for health professionals in assuring a safe and efficient analgesic treatment with minimum risks to patients. Taking into consideration all medical and environmental factors and carefully monitoring the patients are also essential in preventing and early detecting analgesic ADRs.

Keywords: analgesics, adverse drug reactions, drug-drug interactions.

Introduction

Pain is a common condition and has a significant influence on the quality of life [1,2,3]. It was defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [4].

Pain is the main reason nowadays for which patients address healthcare services. The concept of pain relief as a human right has gained more and more ground at a global level to help overcome the barriers against an efficient pain management. Confronted with this trend, health professionals must have the knowledge regarding analgesics to assure an efficient and not least safe pain treatment.

Analgesics are among the most widely used medicines and the primary medicines to treat various types of pain. They mainly include non-opioids (paracetamol, metamizole, non-steroidal anti-inflammatory drugs [NSAIDs]), and opioids (e.g. tramadol, codeine, morphine, oxycodone, meperidine, fentanyl). Adjuvant treatment for pain relief, including other therapeutic classes (anticonvulsants, antidepressants, local anesthetics), can be used; even if they have another primary indication, they prove analgesic efficacy in specific painful conditions.

Unfortunately, even though at this moment there is a wide range of medicines for pain, the management of pain is sometimes inadequate, leading to inappropriate pain control and patient suffering [5,6,7,8]. Even if the safety profile of most of these medicines and the risks for the patients could be predictable, an important number of preventable adverse

drug reactions (ADRs) due to analgesics is still detected [9]. It is clear that analgesics need more attention than they actually receive and that continuous education on proper use and risks of analgesics should be promoted.

Identifying the right type of pain (nociceptive, neuropathic, idiopathic, psychogenic or mixed) and its intensity is necessary for choosing the adequate analgesic treatment [10]. There are important differences in the features of acute and chronic pain as well as the related treatments and their risks to the patients. Acute pain, which is a symptom, if it is not well managed, can lead to chronic pain, which is a disease [11]. Chronic pain persists even if the underlying cause has been treated and can associate over time depression and anxiety, having a significant negative impact on the patients' life [12]. Significantly challenging at present for clinicians is the treatment of highly prevalent chronic non-cancer pain. This condition generally induces chronic analgesic treatment with increased risk of safety issues.

In order to emphasize the main safety concerns in relation to analgesic therapy, the present review comprises a synthesis of the literature regarding the most used analgesics and presents the risks that health professionals should be aware when dispensing or prescribing this class of drugs.

Paracetamol

One of the most frequently used analgesics and also largely available worldwide is paracetamol (acetaminophen). Paracetamol represents the first-line analgesic treatment in children, pregnant women and elderly [13,14,15]. It has an inferior analgesic efficacy in comparison to opioids, which indicates its use in the treatment of various types of mild-to-moderate pain, mostly somatic pain. But it can be associated to opioids, due to its additive effect, to lower demand and increase their tolerability.

The mechanism of action of paracetamol is still debated. The mechanism proposed was the inhibition of prostaglandin synthesis by blocking cyclooxygenase (COX) enzymes COX-1, COX-2 and a variant of COX-1 centrally expressed, COX-3. But to explain the differences with other analgesics, other mechanisms were postulated for paracetamol: central activation of descending serotoninergic pathways, inhibition of the nitric oxide synthase enzyme, involvement of the metabolite N-arachidonoylphenolamine (AM404) which activates the vanilloid subtype 1 receptor (TRPV1), influence on subtype 1 cannabinoid receptors (CB1) and inhibition of the uptake of the endocannabinoid anandamide. Endogenous opioids could also contribute to the antinociceptive effects of paracetamol at a spinal level [16,17].

The gastrointestinal (GI) tolerance and low influence on platelet activity of paracetamol explains the broad use and the favorable safety profile superior to other analgesics,

such as NSAIDs. However, the association of paracetamol with NSAIDs can produce greater GI toxicity than either of the drugs alone [18]. Only a few drug-drug interactions have been described for paracetamol (Table I) [19,20,21].

The dose-dependent **hepatotoxicity** caused by the toxic metabolite of paracetamol, N-acetyl-p-benzoquinone imine, still remains problematic. In the United States and Great Britain, the paracetamol intoxication is the most common cause of acute liver failure [22]. Hepatotoxicity is favored by pre-existing liver disease, malnutrition, anorexia, heavy alcohol intake or in patients treated by hepatic enzyme inducers (rifampicin, phenytoin, carbamazepine, barbiturates) [23,24]. In these cases, the dosage of paracetamol should be reduced and the hepatic enzymes should be monitored; in healthy elderly patients, dosage may not need reduction, but monitoring should be considered. In order to limit the accidental severe liver failure, the US Food and Drug Administration recently recommended restricting the dose of paracetamol prescribed or dispensed to 325 mg per tablet when found in combination medicines [25]. More problematic is the **intravenous paracetamol**, associated with a ten-fold risk of overdose possibly leading to fatal hepatotoxicity due to dose confusion [26,27]. No evidence supports a higher efficacy of repeated intravenous use of paracetamol compared to oral use and therefore, it is recommended for hospital use in the treatment of postoperative pain, only when oral administration is not possible [28].

Intoxication with paracetamol could cause also severe renal failure and the onset can be delayed even 5.9 days after the ingestion [29]. Nevertheless, in the presence of important renal failure, paracetamol should be restricted.

Furthermore, intravenous paracetamol use was related with cases of arterial **hypotension** in reanimation after anesthesia, with a ten-fold higher risk than the one mentioned in the summary of product characteristics (SmPC) [30]. Cases of hypotension have been reported with oral use also [31]. A reduction of both cardiac output and systemic vascular resistance were the mechanisms proposed [32]. In contrast, a randomized, double-blind, placebo-controlled, crossover study demonstrated that a two-week treatment with 1 g paracetamol three times a day, associated with cardiovascular treatment, induced a significant increase in ambulatory blood pressure in patients with coronary artery disease [33].

Various studies showed an association between paracetamol use during pregnancy and an increased risk for the newborn to develop **asthma** in the first months of life. A relation between the consumption of paracetamol in the first years of children's life and a 48% higher risk to develop asthma at six or seven years was also established; the association was discovered to be more significant in genetically susceptible children [34,35,36]. The available data however are not sufficient to discourage paracetamol use in pregnancy and in children [37].

Recently, a meta-analysis of epidemiologic studies found an association between the use of paracetamol or NSAIDs, except aspirin, and an increased risk of developing **kidney cancer.** Higher paracetamol dosage, rather than longer treatment duration, was associated with higher risk. However, further studies are needed to identify possible involved mechanisms [38].

Metamizole

Together with paracetamol, metamizole is also a widely used analgesic mostly for the treatment of acute postoperative pain, but only in the countries where it is still available on the market [39,40]. Along with analgesic-antipyretic properties, metamizole has spasmolytic properties and weak anti-inflammatory activity. The compound acts by peripheral and central mechanisms, inhibiting COX enzymes and therefore decreasing the prostaglandin synthesis [41,42]. Other mechanisms of action were associated with the analgesic effects of metamizole: in the peripheral tissue, the activation of neuronal CB1, the activation of the L-arginine- nitric oxide -cGMP pathway and the subsequent opening of K_{ATP} channel which causes direct blockade of hypernociception. At a central level, the activation of cannabinoid receptors was suggested to be involved [43].

Metamizole has been banned for years, or has never been approved in different countries because of the unfavorable benefit-risk profile due to the risk of hematologic events such as **agranulocytosis.** The metabolite 4-aminoantipyrine was the one supposed to be associated with blood dyscrasias which depend on dose, time of exposure and concomitant medication [44,45]. Opinions on metamizole remain however controversial. The incidence of agranulocitosys varies geographically. For example, the risk of agranulocytosis determined within the *International Agranulocytosis and Aplastic Anemia Study* for any exposure in a one-week period was 1.1 per million users [46]. A higher risk was determined in Sweden, one case per 1439, by analyzing sales data and ADRs spontaneously reported [47]. In Poland, the determined rate of agranulocytosis was lower: 0.16 cases per million person-days of use [48]. Agranulocitosys remains after all an unpredictable ADR which could cause fatality, regardless of short-term, long-term or intermittent use. When benefit-risk balance is negative for metamizole, other analgesic alternatives must be considered when treating pain.

Cutaneous conditions frequently manifested as skin rash, urticaria, but also serious effects such as toxic epidermal necrolysis or drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, have been associated with the use of metamizole [49].

Although not reported specifically for metamizole, drug-drug interactions similar to NSAIDs could be expected (Table II). For example, in patients with coronary artery disease, concomitant use of metamizole could abolish the antiplatelet effects of aspirin by reversible binding to platelet COX-1, resulting in steric inhibition of aspirin access to the active site of COX-1 [50,51].

Metamizole induces human hepatic CYP2B6 and CYP3A4, interaction that in patients with long-term therapy could have negative clinical consequences. A phenobarbital-like mechanism of induction was suggested [52]. As an inducer of CYP2B6, metamizole could interact with substrates of this enzyme such as bupropion, cyclophosphamide, efavirenz, ketamine, meperidine, propofol, selegiline, S-mephenytoin [53]. It can also interact with CYP3A4 inhibitors or inducers (aspirin, anticoagulants, antihypertensive drugs, chlorpromazine, cimetidine, cyclosporine, levofloxacin, methotrexate, oleandomycin, selective serotonin reuptake inhibitors (SSRIs), sulfonylureas) [54]. In clinical practice, metamizole was associated with a minor reduction in blood concentration of ciclosporine during the initial period after drug intake [55].

NSAIDs

NSAIDs represent the cornerstone of pain management worldwide, mostly being used for the treatment of inflammatory, acute and chronic pain, alone or in association with other analgesic-antipyretics or opioids. NSAIDs act by inhibiting prostaglandin synthesis, a mechanism of action that explains their analgesic, antipyretic and anti-inflammatory properties. Central inhibition of COX is also involved in their analgesic activity [56,57]. Classic NSAIDs inhibit both isoforms of COX, while coxibs primarily inhibit COX-2. COX-1 is the constitutive isoform, which protects the GI barrier against aggressive factors, maintains vascular homeostasis, activates platelets and stimulates platelets aggregation, modulates renal function, while the inducible COX-2 is

Table I. Drug-drug interactions involving paracetamol.

Drugs associated	Potential consequence	Mechanism
Phenytoin, carbamazepine	Decreased paracetamol efficacy and increased risk of paracetamol hepatotoxicity	Enzyme induction
Acenocoumarol	Potentiation of anticoagulant effect	Inhibition of antivitamins K mechanism/ interference with clotting factor formation
Imatinib	Increased paracetamol levels	Inhibition of uridine 5'-diphospho – glucuronosyltransferases (UGT) – mediated metabolism

mainly responsible for pain and inflammation.

NSAIDs are considered nonspecific analgesic drugs, used mainly for their anti-inflammatory effect. But the coexisting analgesic effect makes them indispensable in the management of inflammatory pain in rheumatic diseases, such as osteoarthritis or rheumatoid arthritis [58,59]. Being used widely and frequently, NSAIDs are often associated with ADRs. Especially the geriatric population is predisposed to treatment complications [60,61]. The main safety concerns when using NSAIDs are GI, renal, cardiovascular, hematologic effects, hepatic and allergic reactions [62]. The occurrence of drug-drug interactions could be the cause of certain NSAIDs ADRs (Table II) [63,64,65,66].

GI complications related to NSAIDs are promoted when risk factors are present, for instance past medical history of peptic ulcer or GI complications, older age, anticoagulation treatment, corticosteroid use, high-dose NSAID or multiple NSAIDs used simultaneously (including an NSAID plus low-dose aspirin) [67]. Blockage of COX-1 is responsible for the GI ADRs (dyspepsia, abdominal pain, nausea, vomiting, heartburn, hemorrhage, ulceration, perforation or obstruction) [68]. COX-2 specific inhibitors have lower GI risk than traditional NSAIDs; of the latter, ibuprofen has the lowest potential for GI side effects, while ketoprofen, piroxicam and naproxen have shown the highest risk [69,70].

The geriatric population is predisposed also to **renal toxicity** related to NSAID use. The compounds could inhibit the prostaglandins that maintain the glomerular filtration rate in volume depleted states, thus possibly leading to various renal conditions including acute renal failure [71]. Concomitant use of NSAIDs with diuretics, angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor II blockers (ARBs) - usually common in patients with heart failure, hypertension and inflammatory disease or chronic pain - is associated with an increased risk of acute kidney injury, especially at the beginning of the treatment. The risk is lower for the double therapy, NSAIDs and diuretics or any of ACEIs and ARBs [72].

NSAIDs have been associated with an increased risk of cardiovascular effects in long-term use, such as arterial **thrombotic effects** (myocardial infarct, stroke) and atrial or ventricular tachy-arrhythmias [73]. While rofecoxib was removed from the market in 2004 because of an increased risk of myocardial infarct, the risks are still debated for the existing COX-2 inhibitors whose use was recently restricted in Europe in patients with ischemic heart disease and/or cerebrovascular disease and in patients with peripheral arterial disease. A meta-analysis of NSAIDs trials showed that the cardiovascular risk of high-dose diclofenac and possibly of ibuprofen was similar to COX-2 specific inhibitors, while a high-dose of naproxen was associated with a minor risk [74,75]. It is important to consider these potential risks when using NSAIDs, especially in patients with cardiovascular diseases.

In case of concomitant use of alcohol or anticoagulants, in elderly patients or in the presence of liver disease or coagulopathies, NSAIDs could lead to **prolongation of bleeding time** and significant risk of hemorrhage by altering vascular homeostasis [76].

Recently, it was suggested that NSAIDs use could be problematic in patients at risk for **delayed fracture healing**; blockage of COX-2 could cause inhibition of the endochondral ossification pathway, thereby NSAIDs could have an influence on bone healing [77,78].

NSAIDs are among the medicines most frequently associated with **hypersensitivity reactions**. Cross-reactions can occur for compounds with similar chemical structure, therefore NSAIDs from the same chemical class should not be used after a hypersensitivity reaction, unless allergy tests are performed. Clinical manifestations include respiratory signs (bronchoconstriction), cutaneous disease (wheals, urticaria, angioedema), anaphylaxis, delayed hypersensitivity reactions (exanthema, fixed drug eruption, toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, contact and photocontact dermatitis, maculopapular eruptions) or

Table II. Drug-drug interactions involving NSAIDs.

Drugs associated	Potential consequence	Mechanism
Methotrexate	An increased risk of hematologic and GI toxicity	Decrease in the clearance of methotrexate, removal of methotrexate from the binding proteins
Other NSAIDs (ibuprofen, naproxen, nimesulide, flufenamic acid, celecoxib, with the exception of diclofenac and ketorolac)	Decreased antiplatelet activity of aspirin	Competition for COX-1 binding site
Antihypertensive drugs (ACEIs, diuretics, beta-blockers, ARBs)	Decreased efficacy of antihypertensive drugs	Decreased renal prostaglandin production
Acenocoumarol	Increased risk of bleeding	Inhibition of platelet function
SSRIs	Increased risk of bleeding	Impair of haemostatic function
Diuretics and ACEIs or ARBs	An increased risk of acute kidney injure, especially in volume-depleted patients	Decrease in glomerular filtration
Lithium	Increased risk of lithium toxicity	Decrease in lithium clearance

mixed reactions [79,80].

Nimesulide is associated with an increased risk of **liver toxicity** compared to other NSAIDs, which restricted its long-term symptomatic use in chronic conditions such as osteoarthritis. Signals of hepatotoxicity related to the use of nimesulide were analyzed before, but the European Medicines Agency (EMA) concluded in 2011 that for patients with acute pain and primary dysmenorrhoea the benefit/risk ratio remained positive and that the compound remained available on the market with imposed restrictions [81].

Opioids

The use of opioids has significantly increased during the last decades and concomitantly the ADRs related are more frequent [82]. Opioids were used in the past mostly for the treatment of cancer related pain, acute surgical and posttraumatic pains, but since the interest for adequate chronic pain management has increased, their use was extended along with the increase in opioid prescribing [83]. Concomitantly, the risk for **opioid dependence**, leading to abuse and misuse, has increased, which could be an impediment in adequately approaching pain by healthcare professionals.

Opioids are found on the last two steps of the pain ladder established by World Health Organization in 1986, with three steps of analgesia to be chosen according to the intensity of pain. The fact on which attention must be drawn is the type of pain for which the ladder was elaborated, that is cancer pain in adults. The trend is now to inappropriately extrapolate the therapeutic recommendations of the ladder to other types of pain which could lead to inefficient analgesia and serious ADRs. There is an ongoing research in updating and adjusting this pain scale to specific pain conditions such as rheumatic pain or in special pathological situations such as renal insufficiency, in order to avoid therapeutic failure and safety concerns [84,85,86].

Opioids remain the strongest analgesics available, used for the treatment of moderate to severe, acute or chronic, cancer or non-cancer pain. They act by binding to opioid receptors, μ receptor being the most important, suppressing neurotransmission in the central nervous system (CNS). Opioid analgesia is explained by both inhibition of nociceptive ascending transmission and activation of descending pain control pathways [87]. Beside opioid-related mechanism, some opioids such as tramadol could influence the uptake of serotonin and norepinephrine and therefore increase the risk of other adverse effects and drug-drug interactions [88]. **Tolerance**, a common complication of opioid treatment, causes loss of treatment effectiveness forcing the increase of dosage, which simultaneously entails a greater risk for ADRs [89]. Increased pain sensitivity, also known as hyperalgesia, can appear during opioid treatment, despite increasing dosage of opioids or steady state of disease. The approach of

hyperalgesia consists in reducing opioid dosage or adding N-methyl-D-aspartate receptor modulators [90].

Most commonly, opioid ADRs include constipation, sedation, nausea and vomiting, respiratory depression, urinary retention, and pruritus. Drug-drug interactions potentially leading to ADRs have been described when using opioids (Table no. III) [91,92,93]. **Constipation** is the adverse effect for which tolerance unfortunately does not develop and which can lead to unpleasant GI effects. The opioid receptors present in the digestive tract mediate this effect. Usually, the opioid treatment is associated with laxatives such as lactulose or with new peripherally acting compounds (methylnaltrexone, alvimopan) that could counteract opioid-induced constipation [94].

Prurit is one of the most common adverse effects of opioids, more frequent with parenteral route than oral. Opioid-induced prurit is primarily mediated by mu-opioid receptors, serotonin receptors and to a lesser extent by histamine; thereby, first-line treatment should include low-dose nalbuphine, low-dose naloxone, and ondansetron; antihistamines are less efficient [95].

Drowsiness and **sedation**, nausea and vomiting, could appear when using opioids, usually in dosage transition states. Sedation represents the best early clinical indicator of **respiratory depression**. The main factors that contribute to respiratory depression, possibly life threatening and even fatal, are renal impairment, sensory deafferentation and pharmacokinetic drug interactions involving antifungal agents, antibiotics, antidepressants, or chemotherapy [96].

Immunosuppression leading to significant infections has been demonstrated for opioids in experimental studies; clinical studies however do not provide yet clear evidence for the association of infections with opioid use [97].

Patients on long-term opioid treatment could experience hypogonadism caused by the central suppression of hypothalamic secretion of gonadotropin-releasing hormone. Patient monitoring, both in male and female, is necessary to detect **opioid endocrinopathy** [98]. Sex hormones have been associated with cardiovascular risk factors such as atherosclerotic processes, adverse lipid profiles and insulin resistance; in relation to this, a case-control study found a slightly increased risk for **myocardial infarction** in presence of current use of any opioids and cumulative use of eleven or more prescriptions [99].

Opioids tend to cause **hyperglycemia** by decreasing the insulin secretion through the sympathetic nervous system [100]. In contrast, tramadol was found to cause **hypoglycemia**, especially in patients with diabetes; cases were detected inclusively for non-diabetes patients. Renal insufficiency or advanced age could promote hypoglycemia induced by tramadol. Central serotoninergic and opioidergic components were suggested to cause glycemia changes [101].

Table III. Drug-drug interactions involving opioids.

Drugs associated	Potential consequence	Mechanism
CNS depressants (benzodiazepines, barbiturates)	Respiratory depression	Significant depression of CNS
Clarithromycin, ritonavir, ketoconazole, itraconazole, troleandomycin, nelfinavir, nefazodone	Increased risk of fentanyl toxicity	Inhibition of CYP3A4 metabolizing pathway
SSRIs (fluoxetine, sertraline, paroxetine)	Reduced analgesia for tramadol and codeine	Inhibition of CYP2D6 metabolizing pathway
P-glycoprotein inhibitors (amiodarone, captopril, ranolazine, verapamil, clarithromycin, cyclosporine, itraconazole, ritonavir, ticagrelor)	Increased morphine exposure	Unknown
MAOIs (phenelzine, tranylcypramine, isocarboxazid, selegiline)	Serotonin-like syndrome when meperidine is associated8.	Accumulation of the potential neurotoxic meperidine metabolite which cannot be inactivated anymore by MAO
SSRIs, MAOIs	Increased risk of serotonin syndrome when tramadol is associated (hypertension, hyperthermia, myoclonus, mental status changes)	Additive reuptake of monoamines

"Stress cardiomyopathy", also known as **Takotsubo cardiomyopathy** (transient left ventricular dysfunction, usually triggered by intense emotional or physical stress), could appear when withdrawing opioids. Professionals could consider clonidine to prevent serious cardiac complications after sudden discontinuation of a long-term therapy with opioids [102].

Conclusions

The choice of analgesic when treating pain sometimes represents a challenge for health professionals. This review represents a useful tool when establishing the most appropriate analgesic treatment; it highlights the main and most important risks of analgesics. But being aware of the potential risks of the drugs should not be an impediment for health professionals to initiate an analgesic therapy when considered needed. The patient remains at the center of care, and treatment decisions must take into account all medical and environmental factors that might influence the safety and efficacy of drugs. Non-opioid and opioid analgesics remain among the most widely used drugs worldwide and it is thus important for health professionals to pay more attention to their use. It goes without saying that the patients should be closely evaluated and monitored during treatment, especially when risk factors are present. Careful monitoring still remains the main way of early detecting safety issues related to analgesics.

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