

A look inside the association codeine-paracetamol: clinical pharmacology supports analgesic efficacy

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Abstract. – Acute and chronic pain often requires a multimodal approach. Combination therapy reduces the number of individual daily administrations and improves patient's compliance with the prescribed analgesic treatment. Despite the association codeine/paracetamol is one of the most widely used central analgesic, the exact mechanism of action, particularly of paracetamol, is still object of pharmacological research. Recent findings showed that paracetamol may act through cerebral cyclo-oxygenase, descending opioidergic inhibitory pathways, serotonin pathway, and the endocannabinoid system; while codeine activity seems to related not only to its conversion to morphine, as previously known, but also by itself and through its metabolites, such as norcodeine (NORC) and codeine-6-glucuronide (C-6-G). The addition of codeine to paracetamol significantly improves the analgesic action and reduces the number needed to treat (NNT) from 5 to 2.3-3.1. Recent warnings about the risk of its metabolism related to CYP450 and its genetic variability in general population should be mainly considered when the association is used in paediatric patients undergoing tonsillectomy and/or adenoidectomy procedures for obstructive sleep apnoea syndrome (OSAS). In adults, the association codeine/paracetamol has been shown to be effective and safe in different settings: acute pain, trauma patients, and chronic nociceptive pain.

Key Words:

Codeine, Paracetamol, Chronic pain, Acute pain, Pharmacokinetics, CYP450, Tolerability.

Introduction

Recent progresses on our knowledge of the pathophysiological mechanisms underlying acute pain and its evolution into chronic pain have highlighted the need for analgesic treatments

characterized by a multimodal approach, that simultaneously uses various methods to control pain^{1,2}.

More specifically, our understanding of the mechanisms by which pain becomes chronic, based primarily on the progress made in the field of neuroplasticity³, have further confirmed the need to use central analgesics, as an alternative to the widely used non-steroidal anti-inflammatory drugs (NSAIDs). The latter, in addition to being burdened by a tolerability profile that makes them incompatible with the majority of patients requiring a prolonged analgesic treatment (elderly subjects with a number of comorbidities, which may increase their susceptibility to the cardiovascular and gastrolesive effects of NSAIDs)^{4,5}, act primarily on peripheral cyclooxygenase and therefore intervene only marginally in the management of chronic pain. Moreover, in accordance with a number of guidelines, they may only be used for short periods, at the lowest efficacious dose and only in conditions of effective inflammatory exacerbation^{6,7}.

Indeed, in the management of acute and chronic pain, in addition to the use of multimodal treatments based on the administration of various drugs with different mechanisms of action, administered in sequence according to specific regimens, it is possible to plan therapies based on the combined action of various compounds administered in a single formulation, when the knowledge of the pharmacokinetic characteristics and the clinical effects of the different combined drugs is complete.

The use of combination therapy brings a number of advantages: it reduces the number of individual daily administrations and improves patient's compliance with the prescribed analgesic treatment.

Paracetamol (or acetaminophen) is the most commonly used agent in combination with opioids (codeine, hydrocodone, tramadol, oxycodone)⁸⁻¹¹ and of these, its combination with codeine represents a milestone in acute and chronic pain treatment, due to its ability to boost analgesic efficacy⁸.

Discovering Paracetamol Pharmacology: a Neverending Story

Paracetamol, recently defined “*a promising ancestor*”¹², is an aniline derivative with analgesic and antipyretic activity. The absence of a peripheral action on prostaglandins makes the compound better tolerated than NSAIDs, whose side effects it does not share, especially the detrimental effect on the gastrointestinal mucosae and the inhibition of platelet activity¹³.

Various hypotheses have been postulated by different authors concerning its mechanism of action, which is still not completely known: it has been seen to have central actions on cerebral cyclo-oxygenase¹⁴, on the descending opioidergic inhibitory pathways and on the serotonin pathways¹⁵, inhibition of peroxydase but not cyclooxygenases, especially myeloperoxidase. This latter mechanism is also thought to cause a reduction in the production of oxidants, which is probably associated with inflammatory conditions, such as atherosclerosis and rheumatic diseases¹⁶.

It is likely that paracetamol exerts its analgesic effect in a complex and multifactorial manner. As highlighted recently, its analgesic activity is due to an interaction with the endocannabinoid system¹⁷. Paracetamol is metabolised, particularly in the liver, to p-aminophenol (p-AP), a compound that is subsequently conjugated with arachidonic acid (AA) in cells containing fatty acid amide hydrolase (FAAH) in the nervous system, including Transient Receptor Potential Vanilloid, member 1 (TRPV1)-expressing neurons: the effect of this conjugation is the synthesis of N-arachidonoylaminophenol (AM404), a TRPV1 activator¹⁸. AM404, a metabolite of paracetamol, inhibits the enzyme that hydrolyses the endocannabinoids (eCB), which prolongs the analgesic action of the eCBs. AM404 therefore activates TRPV1 in the cerebral nuclei and this activation, through the stimulation of the descending bulbospinal inhibitory pathways in the periaqueductal grey, can produce antinociception by regulating the descending antinociceptive pathways, possibly of serotonergic origin, which reduces

nociceptive neurotransmission in the dorsal horn of the spinal cord¹⁹. The pharmacological profile of 4-aminophenol is therefore identical to that previously described for paracetamol, supporting the hypothesis that the hepatic metabolite contributes to the analgesic activity of paracetamol, through the activation of the bulbospinal pathways¹⁹.

Another recent study showed how AM404 could also induce analgesia by inhibiting the T-type calcium channels Ca(v)3.2, as occurs for other lipoamino acids²⁰.

The interaction with the endocannabinoid system would therefore justify both the analgesic and antipyretic effect of paracetamol. Moreover, the consumption of AA, conjugated with p-AP to form the metabolite AM404, reduces its availability for the production of inflammatory mediators, which explains why paracetamol reduces the cerebral concentration of prostaglandins²¹.

With regard to the relationship between the absorption of paracetamol and its analgesic effect, there are difficulties in interpreting the analgesic and antipyretic responses observed after its administration, as these responses are not directly related to plasma concentration, but rather to those observed in the effect compartment. Effect site concentration does not have real measurable concentrations, however they are roughly equivalent to those present in the cerebrospinal fluid. Target effect compartment concentrations of 5 mg/l for fever and 10 mg/l for pain do not seem unreasonable on the basis of current literature²².

Therefore, although the time to reach therapeutic concentration in the effect site can reflect that of plasma concentration, it is initially subject to a delay, as its maximum concentration is lower than the maximum plasma concentration after a single dose. This delay, which can be quantified as about 1 hour for paracetamol, depends on body size, expressed in weight, and it is lower the smaller the subject²².

In order to accelerate the onset of the effect, the speed can be increased by administering a higher first dose or by improving absorption characteristics²². Absorption can be modified by the formulation and in this sense an increase in the rate of absorption would also increase the onset of the pharmacological action. Indeed, whereas intravenous formulations go directly to the central compartment, tablets and capsules have to be disintegrated and then dissolved, thereby introducing a delay even before duodenal absorp-

tion takes place. The orosoluble formulation has the advantage of rapid disintegration and dissolution, which allows faster absorption than the normal oral formulations, therefore, guaranteeing a faster onset of action²³.

The absorption of paracetamol is also closely related to the product's particular dissociation capacity. Paracetamol has a pKa of 9.5 and, in the alkaline duodenal environment, it is largely non-ionised. Consequently, the absorption of the non-ionised form from the duodenum into systemic circulation is fast: the mean half-life ($T_{1/2}$) for absorption is 6.8 minutes in adult volunteers). By contrast, paracetamol absorption in the stomach is minimal, and in this case the only limiting factor is the emptying of the stomach into the duodenum, and/or the presence of food, which can, therefore slowdown absorption²².

Once it has been absorbed, 90% of paracetamol is metabolised by glucuroconjugation or sulphation. In the liver paracetamol combines rapidly with glutathione to form a non-toxic compound that is eliminated in urine. In the event of an overdose, if glutathione reserves are exhausted, the damage to the liver is not caused by the paracetamol itself, but by the toxic metabolite *N*-acetyl-*p*-benzoquinone imine (NAPQI)²⁴.

To overcome this risk, in case of an overdose, it is necessary to administer *N*-acetylcysteine, a substance that restores the hepatic glutathione reserves. The use of *N*-acetylcysteine drastically reduces hepatotoxicity, when administered 8-10 hours after an overdose. The suggested dose of *N*-Acetylcysteine is 150 milligrams/kg over one hour and subsequently 50 milligrams/kg over 4 hours¹⁵.

Paracetamol toxicity can be the consequence of a single overdose or repeated excessive doses. The maximum recommended therapeutic daily dose for paracetamol is 4 g in adults (3 g in Italy, for the oral formulation only), whereas a single dose over 7.5 g is considered potentially toxic¹⁵.

As the use of analgesics is very common, even small increases in the relative risk of renal dysfunction must be carefully evaluated. As previously published in literature, the study by Rexrode²⁵ provides reassuring evidence of an apparent absence of a close relationship between chronic use of analgesics and chronic renal dysfunction in a large cohort of subjects, in particular those without a prior history of renal insufficiency. The same conclusion was reached in another, even more recent, study²⁶, which showed how the chronic use of paracetamol is not associ-

ated with renal insufficiency, even in subjects using the medicinal product for more than 30 days from the time of monitoring or who have taken a total annual dose of paracetamol greater than 1 kg (corresponding to a daily dose of 3 grams maintained for the whole year).

As far as the risk of gastrointestinal bleeding is concerned, the study by Lewis et al²⁷ confirms the safety of paracetamol. In the absence of non-aspirin nonsteroidal anti-inflammatory drugs (NNSAIDs), there was no evidence of any increase in the risk of upper gastrointestinal tract bleeding at any of the doses of paracetamol used.

Paracetamol, therefore, represents a safe alternative to NSAIDs²⁸, also from the point of view of cardiovascular risk, as confirmed by a study enrolling a total of 2754 subjects treated with paracetamol. Blood pressure was seen to increase in a non-statistically significant way (systolic: +1.6 mmHg, diastolic: +0.5 mmHg) during the treatment with paracetamol in the group whose antihypertensive treatment remained unchanged. The authors concluded that they did not observe any evidence able to confirm the hypothesis that treatment with paracetamol caused a significant rise in blood pressure in a population of patients with treated hypertension²⁹.

Paracetamol is usually recommended even when analgesic drugs are required during oral anticoagulant treatment (OAT), as it does not have a significant effect on primary haemostasis: the use of paracetamol during OAT, even for long periods, did not cause any clinically-relevant changes in INR³⁰.

Finally, paracetamol is also considered the preferred analgesic and antipyretic drug in the paediatric setting, as it does not have any side effect typical of opioids³¹.

Looking Inside Codeine and its Metabolites

Codeine is a weak opioid with a bioavailability of approximately 30-40% after oral administration. To exert its analgesic activity, it must be metabolised in part into morphine and its metabolites (morphine-3-glucuronide and morphine-6-glucuronide) and in part into the metabolites of codeine: norcodeine (NORC) and codeine-6-glucuronide (C-6-G). This process depends on the activity of cytochromes CYP2D6 and CYP3A4, belonging to the large CYP450 family.

In healthy volunteers codeine is metabolized to C-6-G (81.0 ± 9.3%), NORC (2.16 ± 1.44%), morphine (0.50 ± 0.39%), morphine-3-

glucuronide (M-3-G) ($2.10 \pm 1.24\%$), morphine-6-glucuronide (M-6-G) ($0.80 \pm 0.63\%$) and normorphine ($2.44 \pm 2.42\%$)³².

The analgesic effect of codeine is equal to about 1/10 of that induced by morphine, however, recent studies showed that codeine analgesia depends, in addition to the morphine produced by metabolism through CYP2D6, also on codeine itself and its metabolites, such as C-6-G and NORC, which directly contribute to the analgesia induced by the opioid³³.

Lötsch et al³² analysed the extent of the contribution to the analgesic effects of codeine and its metabolites, regardless of the O-demethylation of codeine to morphine, after having reported that codeine has a half-life of 1.47 ± 0.32 hours, that C-6-G has a half-life of 2.75 ± 0.79 hours and that the plasma AUC of C-6-G is about ten times greater than codeine. The authors concluded that the CYP2D6-dependent formation of morphine cannot fully explain the effects of codeine on the central nervous system (CNS) and that C-6-G is the most likely active fraction with a supplementary analgesic activity, with a possible contribution also by NORC.

Despite representing only 2-5% of all P450 liver enzymes, CYP2D6 is responsible for the metabolism of 25% of all drugs used in clinical practice: consequently, the polymorphism of this cytochrome, which is responsible for the metabolism of codeine and formation of its metabolites, can influence the analgesia induced by this drug³³.

The genetic variability in the expression of these cytochromes means that patients can be slow, medium, normal and ultrafast metabolisers, with a significant variation in terms of analgesia and side effects. About 10% of the Caucasian population (one every ten treated patients) belongs to the slow metaboliser category and therefore, in these patients, codeine has a reduced analgesic efficacy. Conversely, fast metabolisers convert codeine rapidly into morphine and other metabolites, and therefore they result more exposed to the risk of side effects³⁴.

The study by Kirchheiner et al³⁵ on the pharmacokinetics of codeine and of its metabolite morphine, in ultrafast metabolisers, characterised by a gene duplication encoded for CYP2D6, showed a $1.5 \times$ increase in exposure to the morphine metabolite compared to normal metabolisers: in other words, for an ultrafast metaboliser (about 3% of the Caucasian population) a 30 mg dose of codeine has the same

effects at a 45 mg dose administered to normal metabolisers (that represent about 50% of the Caucasian population).

The new safer and simpler diagnostic techniques now available should allow a faster diagnosis of metabolic variations. Therefore, once the patient's genotype and phenotype is known, it can be used as a kind of guideline to establish the right dose of codeine, as the CYP genotype can help to identify the best suited drug for the specific patient³⁴.

Like all drugs that undergo direct CYP450-mediated metabolism (among opioids: codeine, tramadol, buprenorphine, oxycodone, fentanyl, methadone), co-administration of codeine and other medicinal products that induce or inhibit CYP2D6 and CYP3A4 cytochromes can cause pharmacological interactions and alter the response to the drug³⁶.

As far as the aforesaid genetic variability of CYP2D6 is concerned, in October 2012 the European Medicines Agency (EMA) launched a review procedure for the benefit/risk profile of products containing codeine, used for paediatric pain relief³⁷, following reports in literature, between 2009 and 2012, of three fatal cases of respiratory depression in children aged 2-5 years, and ultrafast CYP2D6 metabolisers, who had been administered codeine after a tonsillectomy and/or adenoidectomy procedure to treat obstructive sleep apnoea syndrome (OSAS)³⁸⁻³⁹. Although therapeutic doses were used, the combination of an ultrafast metaboliser profile and impaired respiratory condition (OSAS) proved decisive, especially given the fact that in the immediate post-surgical period respiratory conditions can momentarily worsen due to the procedure, which involves the formation of oedema following the removal of the tonsils/adenoids.

In July 2013, at the end of the review process, the EMA confirmed the favourable benefit-risk profile for codeine in children over 12 years of age and recommended a number of measures to guarantee a better safety profile for medicinal products containing codeine, in particular the contraindication for subjects under 12 years of age and in patients from 0 to 18 years undergoing tonsillectomy and/or adenoidectomy procedures for OSAS and the recommendation not to use codeine in children, aged between 12 and 18 years, with impaired respiratory function. Finally, a limitation was introduced concerning the number of days of therapy, which is particularly necessary in those European countries in which

codeine combination products can be sold without a medical prescription and dedicated above all to the 12-18-year-old age group⁴⁰. More specifically, to avoid the risk of abuse, a condition has been imposed that analgesic drugs containing codeine should not be taken for more than three days without consulting a doctor. In Italy, this would not happen as this type of drug is available only on prescription and under the direct control of a physician. The EMA's recommendations were subsequently assimilated by the Member States, which updated the printed materials of medicinal products containing codeine involved by the review.

Rationale for Codeine-Paracetamol Association

The clinical rationale for an analgesic association is based on the evidence that the analgesic effect obtained is significantly superior to that obtained by the single components, i.e., there must be a synergistic action, with a significant increase in "pain relief".

In the case of the codeine-paracetamol combination, studies showed that the addition of codeine to paracetamol causes a significant improvement in the analgesic action, with an obvious and statistically significant reduction in the number needed to treat (NNT): from 5, the mean NNT reported for paracetamol, to 2.3-3.1 for the codeine-paracetamol combination. In addition, this improvement in the analgesic activity of paracetamol does not affect its excellent tolerability⁴¹.

Combining different analgesics therefore becomes an important option in clinical practice, because it is able both to control a greater number of pain components and to improve the tolerability of the drugs, which guarantees adequate analgesic efficacy at lower doses than obtained by the individual components. In the paracetamol-codeine combination, the pharmacodynamic parameters of the two drugs (Table I) are similar and therefore their pharmacological action is synchronous and has the same duration, thereby guaranteeing maximum synergy.

Combining paracetamol with other analgesics, in particular codeine, therefore finds its rationale in the synergistic action of the two active substances, in order to boost the analgesic effect and minimise the side effects, by reducing the dose of the individual components. However, one point that remains controversial is the optimum dose of the two molecules when proposed in combination. As regards paracetamol alone, a linear relationship has been shown between the plasma concentration and the dose administered per kilogram of body weight and a dose of at least 15 mg/kg is needed to reach therapeutic levels of paracetamol. The plasma concentration threshold to be reached for an efficacious analgesic action has been estimated at approximately 66 mol/L and, therefore, the optimum dose in an adult with an average weight of 60-70 kg is approximately 1.000 mg⁴².

In a recent randomized clinical study⁴³ conducted on over 500 patients in post-dental procedural pain, the 1,000 mg dose of paracetamol was statistically more efficacious than the 650 mg dose in pain management. Regarding side effects, there was no significant difference between the two groups treated with paracetamol and placebo. Even small differences in the posology of paracetamol can therefore be decisive. Specifically, reducing the 1,000 mg dose of paracetamol, when used alone, can cause a reduction in analgesic efficacy.

As regards the optimum dose of paracetamol in combination with codeine, taking into consideration the synergic action, the 500 mg dose can be considered the optimum adult dose, corresponding to about 7 mg/kg. In the case of codeine, on the other hand, in combination with paracetamol, the optimum single dose has been estimated to be 30 mg⁴⁴. This combination therefore makes it possible to best exploit the synergistic action of the two components, by using reduced doses to manage a level of pain that the individual drugs are unable to control alone.

A further reduction in the doses of paracetamol in combination with other agents, as at pre-

Table I. Pharmacokinetic parameters of paracetamol and codeine.

	Plasma half-life (T _{1/2}) (min)	Onset of analgesic activity (min)	Duration of analgesic activity (h)
Paracetamol	150	15-30	6 (4-8)
Codeine	120-180	30	6 (4-8)

sent suggested in the United States (US), with the recommendation to restrict combinations with paracetamol to 325 mg⁴⁵, can lead to a reduction in analgesic efficacy without any direct benefit, apart from avoiding the overdoses that can occur due to the inappropriate concomitant use of multiple products containing paracetamol, which is a very common practice in the US, given the very high availability of free-sale paracetamol and the lack of clarity that characterises the labelling of such drugs. In the US, accidental overdoses are more common, as most over-the-counter drugs also contain, amongst the various compounds, paracetamol (medicines for coughs, cystitis, pain of various origins, flu, fever, etc.). It is therefore common for patients to combine self-prescribed medicines containing paracetamol with drugs prescribed by their general practitioner, again containing paracetamol, without realising it, on account of unclear labels that often use an abbreviation (i.e. APAP for acetaminophen) to indicate the presence of this active ingredient. Co-administration of different drugs containing paracetamol can cause a hazardous accumulative effect in the amount taken⁴⁶. In January 2011, the Food and Drug Administration (FDA) therefore asked manufacturers to restrict to 325 mg the dose of paracetamol present in the associations containing opioids on prescription, within 3 years⁴⁷. Most of the combinations containing more than 325 mg of paracetamol were taken off the market, however in 2014, upon reaching the deadline, the FDA published a circular in which it urged doctors to stop prescribing combination drugs containing more than 325 mg of paracetamol, until manufacturers had taken all non-compliant products off the market⁴⁸.

The situation in Europe is so different that the EMA and Italian Medicines Agency (AIFA) did not feel it necessary to adopt the same measures for the European market.

The difference in the European and the American attitude to paracetamol was also highlighted in a recent French survey on the knowledge and correct application of the recommendations on neuropathic pain, published in 2010 by the French Society of Pain Research and Treatment (Société Française d'Etude et Traitement de la Douleur, SFETD)⁴⁹. More than 50% of the 319 French general practitioners who completed the survey were aware of these recommendations and in recognised cases of neuropathic pain, correctly managed the patient, according to the guidelines of the SFETD. Moreover, in patients

with well diagnosed non-neuropathic pain, general practitioners choose the codeine-paracetamol combination in 77.7% of cases, which confirms the usefulness of this combination for the treatment of non-neuropathic pain.

Codeine-Paracetamol Association in Clinical Practice

The combination of drugs belonging to different classes (a non-anti-inflammatory central analgesic and an opioid), therefore characterised by different mechanisms of action, can offer the opportunity of optimising efficacy and tolerability, using lower doses of each medicinal product to achieve the same degree of pain relief⁴¹.

In the update to a previous Cochrane review published in 2000⁵⁰, in 2009, Toms et al. evaluated the efficacy and safety of paracetamol combined with codeine, using recent data⁴¹. The paracetamol-codeine combination provided clinically useful pain relief levels in at least 50% of patients with moderate-to-severe postoperative pain, compared to less than 20% in patients receiving placebo. Moreover, the use of a combination of the two drugs extends the duration of analgesia by approximately one hour compared to the dose of paracetamol alone⁴¹.

In a recent review⁸, the codeine-paracetamol combination was considered efficacious in the treatment of various types of pain, thanks to the synergistic action of the two molecules. Despite the scientific evidence cannot be considered conclusive, due to the non-uniformity of the trials, some of which were very old, the authors conclude in favour of the non-inferiority of the paracetamol-codeine combination compared with NSAIDs in the treatment of different types of pain. They also stressed that NSAIDs have a greater incidence of potentially harmful side effects, and suggest using this combination in the management of moderate-to-severe pain, particularly in elderly patients, in those with severe cardiovascular risks or in those on primary or secondary prevention treatment for stroke or acute coronary syndrome.

Another recent study⁵¹ analyzed the effects of a global rehabilitation programme on 44 patients with osteoarthritis awaiting total joint replacement. The addition of paracetamol to the rehabilitation programme at the maximum daily dose of 3 g/day statistically reduces the intensity of pain. In addition, in case of failure with paracetamol alone, the authors suggested the

use of a 500/30 mg paracetamol-codeine combination, as this treatment has been shown to be particularly efficacious when compared to paracetamol alone⁵¹.

Another group of patients particularly complex to be managed is that of polytrauma victims, in which it is essential to treat both acute and chronic pain appropriately. The association codeine/paracetamol has been shown to be a valid alternative to NSAIDs, such as ketorolac, especially in patients with a documented haemorrhage or with a high haemorrhagic risk⁵². Indeed, although NSAIDs are the agents most frequently used in these patients, their use can be associated with an increased risk of haemorrhage. Italian Intersociety Recommendations on pain management in the emergency setting suggested to use paracetamol for its opioid sparing properties and for reduction of opioid related adverse events. The combination paracetamol-codeine 500/30 mg, repeatable every 6 hours, is suggested for moderate pain (numeric rating scale 4-6)⁵³.

A recent prospective, double-blind clinical trial⁵⁴ evaluated a cohort of over 170 patients with acute post-traumatic limb pain, discharged from the emergency department, randomized to be treated with a hydrocodone-paracetamol combination (5 mg/500 mg) or with codeine-paracetamol (30 mg/300 mg). The study outcomes were improvement in pain two hours after taking one of the 2 medicinal products, onset of side effects and the degree of patient satisfaction. Both combinations reduced pain by about 50%. The hydrocodone-paracetamol combination did not show any statistically significant superiority in either the control of pain or overall patient satisfaction, with similar side effects in both groups. The authors concluded that this data should encourage physicians to give more consideration to the use of the paracetamol/codeine combination in this setting of patients with acute pain.

Conclusions

More than a century after its advent, paracetamol remains the most widely-used analgesic agent. Despite its lengthy history, its beneficial analgesic and antipyretic effects, as well as its secondary effects, still represent the subject of a great number of publications, as the mechanisms responsible for these effects are still not completely clear.

A PubMed search showed that there was an increase from just 1 paper indexed in 1957 to 243/year in 1982, i.e. 25 years later, before leaping to 828/year 25 years later in 2007 and 1076 publications/year in 2013.

Recent studies reveal a new approach to paracetamol: a pro-drug that needs to be bio-transformed in order to exert its analgesic effect. Different neurophysiological systems appear to be involved in the mechanism of action of paracetamol, from the serotonergic to the opioidergic systems, to which we can also add, based on current knowledge, the cannabinoidergic and vanilloidergic system. Paracetamol is currently recommended as the preferred analgesic in various conditions, as it is considered safe and efficacious for the management of mild pain and because it can be used for lengthy periods of time, even in elderly patients, in whom the cardiovascular, renal and gastrointestinal risks associated with the chronic use of NSAIDs is well known.

It has also been shown that in cases of inadequate analgesia with paracetamol alone, the use of formulations constituted by a combination with a mild opioid such as codeine is efficacious. Indeed, thanks to the synergistic action of the individual active ingredients, this combination significantly increases the analgesic effect, without increasing side effects and its ease of management makes it a good option for the continued home treatment of post-traumatic or other acute and chronic pain.

Recent scientific progresses led to subdivide patients according to their ability to metabolise codeine, bringing to light the specific analgesic role of the metabolites of this agent, and not merely the part that is transformed into morphine.

Therefore, fixed-dose analgesic combinations, in this case paracetamol/codeine, offer patent advantages in different types of patients and different clinical settings, when molecules with complementary mechanisms of action are chosen, when the appropriate doses of the single components are identified, in order to limit side effects, to simplify the overall regimen, and to increase patient compliance.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

- 1) PERGOLIZZI J, AHLBECK K, ALDINGTON D, ALON E, COLUZZI F, DAHAN A, HUYGEN F, KOCOT-K PSKA M, MANGAS AC, MAVROCORDATOS P, MORLION B, MÜLLER-SCHWEFE G, NICOLAOU A, PÉREZ HERNÁNDEZ C, SICHÈRE P, SCHÄFER M, VARRASSI G. The development of chronic pain: physiological CHANGE necessitates a multidisciplinary approach to treatment. *Curr Med Res Opin* 2013; 29: 1127-1135.
- 2) COLUZZI F, BERTI M. Change pain: changing the approach to chronic pain. *Minerva Med* 2011; 102: 289-307.
- 3) WOOLF CJ. Pain: Moving from Symptom Control toward Mechanism-Specific Pharmacologic Management. *Ann Intern Med* 2004; 140: 441-451.
- 4) KRESS HG, AHLBECK K, ALDINGTON D, ALON E, COACCOLI S, COLUZZI F, HUYGEN F, JAKSCH W, KALSO E, KOCOT-K PSKA M, MANGAS AC, MARGARIT FERRI C, MORLION B, MÜLLER-SCHWEFE G, NICOLAOU A, PÉREZ HERNÁNDEZ C, PERGOLIZZI J, SCHÄFER M, SICHÈRE P. Managing chronic pain in elderly patients requires a CHANGE of approach. *Curr Med Res Opin* 2014; 30: 1153-1164.
- 5) MATTIA C, COLUZZI F. COX-2 inhibitors: pharmacological data and adverse effects. *Minerva Anestesiol* 2005; 71: 461-470.
- 6) HOCHBERG MC1, ALTMAN RD, APRIL KT, BENKHALTI M, GUYATT G, MCGOWAN J, TOWHEED T, WELCH V, WELLS G, TUGWELL P; AMERICAN COLLEGE OF RHEUMATOLOGY. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)* 2012; 64: 465-474.
- 7) ZHANG W, DOHERTY M, ARDEN N, BANNWARTH B, BJLSMA J, GUNTHER KP, HAUSELMANN HJ, HERRERO-BEAMONT G, JORDAN K, KAKLAMANIS P, LEEB B, LEQUESNE M, LOHMANDER S, MAZIERES B, MARTIN-MOLA E, PAVELKA K, PENDLETON A, PUNZI L, SWOBODA B, VARATOJO R, VERBRUGGEN G, ZIMMERMANN-GORSKA I, DOUGADOS M. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2005; 64: 669-681.
- 8) FRANCESCHI F, IACOMINI P, MARSILIANI D, CORDISCHI C, ANTONINI EF, ALESI A, GIACOBELLI D, ZUCALÀ G. Safety and efficacy of the combination acetaminophen-codeine in the treatment of pain of different origin. *Eur Rev Med Pharmacol Sci* 2013; 17: 2129-2135.
- 9) SINGLA A, SLOAN P. Pharmacokinetic evaluation of hydrocodone/acetaminophen for pain management. *J Opioid Manag* 2013; 9: 71-80.
- 10) MATTIA C, COLUZZI F, SARZI PUTTINI P, VIGANÒ R. Paracetamol/Tramadol association: the easy solution for mild-moderate pain. *Minerva Med* 2008; 99: 369-390.
- 11) RAFFA RB, PERGOLIZZI JV, SEGARNICK DJ, TALLARIDA RJ. Oxycodone combinations for pain relief. *Drugs Today (Barc)* 2010; 46: 379-398.
- 12) MALLET C, BARRIÈRE DA, ESCHALIER A. Le Paracétamol; un ancêtre plein d'avenir. *Thérapie* 2012; 67: 277-281.
- 13) MATTIA C, COLUZZI F. What anesthesiologists should know about paracetamol (acetaminophen). *Minerva Anestesiol* 2009; 75: 644-653.
- 14) ARONOFF DM, OATES JA, BOUTAUD O. New insights into the mechanism of action of acetaminophen: Its clinical pharmacologic characteristics reflect its inhibition of the two prostaglandin H2 synthases. *Clin Pharmacol Ther* 2006; 79: 9-19.
- 15) BERTOLINI A, FERRARI A, OTTANI A, GUERZONI S, TACCHI R, LEONE S. Paracetamol: new vistas of an old drug. *CNS Drug Rev* 2006; 12: 250-275.
- 16) GRAHAM GG, DAVIES MJ, DAY RO, MOHAMUDALLY A, SCOTT KF. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. *Inflammopharmacology* 2013; 21: 201-232.
- 17) OTTANI A, LEONE S, SANDRINI M, FERRARI A, BERTOLINI A. The analgesic activity of paracetamol is prevented by the blockade of cannabinoid CB1 receptors. *Eur J Pharmacol* 2006; 531: 280-281.
- 18) MALLET C, BARRIÈRE DA, ERMUND A, JÖNSSON BA, ESCHALIER A, ZYGMUNT PM, HÖGESTÄTT ED. TRPV1 in brain is involved in acetaminophen-induced antinociception. *PLoS One* 2010; 5: pii: e12748.
- 19) BARRIÈRE DA, MALLET C, BLOMGREN A, SIMONSEN C, DAULHAC L, LIBERT F, CHAPUY E, ETIENNE M, HÖGESTÄTT ED, ZYGMUNT PM, ESCHALIER A. Fatty acid amide hydrolase-dependent generation of antinociceptive drug metabolites acting on TRPV1 in the brain. *PLoS One* 2013; 8: e70690.
- 20) KERCKHOVE N, MALLET C, FRANÇOIS A, BOUDES M, CHEMIN J, VOETS T, BOURINET E, ALLOUI A, ESCHALIER A. Ca(v)3.2 calcium channels: the key protagonist in the supraspinal effect of paracetamol. *Pain* 2014; 155: 764-772.
- 21) ZYGMUNT PM, CHUANG H, MOVAHED P, JULIUS D, HÖGESTÄTT ED. The anandamide transport inhibitor AM404 activates vanilloid receptors. *Eur J Pharmacol* 2000; 396: 39-42.
- 22) GIBB IA, ANDERSON BJ. Paracetamol (acetaminophen) pharmacodynamics: interpreting the plasmaconcentration. *Arch Dis Child* 2008; 93: 241-247.
- 23) BANDARI S, MITTAPALLI RK, GANNU R, RAO YM. Orodispersible tablets: An overview. *Asian J Pharm* 2008; 2: 2-11.
- 24) PATTEN CJ, THOMAS PE, GUY RL, LEE M, GONZALEZ FJ, GUENGERICH FP, YANG CS. Cytochrome P450 enzymes involved in acetaminophen activation by rat and human liver microsomes and their kinetics. *Chem Res Toxicol* 1993; 6: 511-518.

- 25) REXRODE KM, BURING JE, GLYNN RJ, STAMPFER MJ, YOUNGMAN LD, GAZIANO JM. Analgesic use and renal function in men. *JAMA* 2001; 286: 315-321.
- 26) KELKAR M, CLEVES MA, FOSTER HR, HOGAN WR, JAMES LP, MARTIN BC. Acute and chronic acetaminophen use and renal disease: a case-control study using pharmacy and medical claims. *J Manag Care Pharm* 2012; 18: 234-246.
- 27) LEWIS SC, LANGMAN MJ, LAPORTE JR, MATTHEWS JN, RAWLINS MD, WIHOLM BE. Dose-response relationships between individual nonaspirin nonsteroidal anti-inflammatory drugs (NANSAIDs) and serious upper gastrointestinal bleeding: a meta-analysis based on individual patient data. *Br J Clin Pharmacol* 2002; 54: 320-326.
- 28) HINZ B, BRUNE K. Paracetamol and cyclooxygenase inhibition: is there a cause for concern? *Ann Rheum Dis* 2012; 71: 20-25.
- 29) DAWSON J, FULTON R, McINNES GT, MORTON R, MORRISON D, PADMANABHAN S, HEWITT J, MEREDITH P, MUIR S, DOMINICZAK AF, WALTERS MR. Acetaminophen use and change in blood pressure in a hypertensive population. *J Hypertens* 2013; 31: 1485-1489.
- 30) GADISSEUR AP, VAN DER MEER FJ, ROSENDAAL FR. Sustained intake of paracetamol (acetaminophen) during oral anticoagulant therapy with coumarins does not cause clinically important INR changes: a randomized double-blind clinical trial. *J Thromb Haemost* 2003; 1: 714-717.
- 31) CHIARETTI A, PIERRI F, VALENTINI P, RUSSO I, GARGIULO L, RICCARDI R. Current practice and recent advances in pediatric pain management. *Eur Revi Med Pharmacol Sci* 2013; 17(Suppl 1): 112-126.
- 32) LÖTSCH J, SKARKE C, SCHMIDT H, ROHRBACHER M, HOFMANN U, SCHWAB M, GEISSLINGER G. Evidence for morphine-independent central nervous opioid effects after administration of codeine: contribution of other codeine metabolites. *Clin Pharmacol Ther* 2006; 79: 35-48.
- 33) LEPPERT W. CYP2D6 in the metabolism of opioids for mild to moderate pain. *Pharmacology* 2011; 87: 274-285.
- 34) SAMER CF, LORENZINI KI, ROLLASON V, DAALI Y, DESMEULES JA. Applications of CYP450 testing in the clinical setting. *Mol Diagn Ther* 2013; 17: 165-184.
- 35) KIRCHHEINER J, SCHMIDT H, TZVETKOV M, KEULEN JT, LÖTSCH J, ROOTS I, BROCKMÖLLER J. Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. *Pharmacogenomics* 2007; 7: 257-265.
- 36) LISI DM. Drug-Drug Interactions Involving Pain Medications. http://www.uspharmacist.com/continuing_education/ceviewtest/lessonid/109799/ Accessed 20 August 2014
- 37) EMA/385716/2013 28th June 2013
- 38) CISZKOWSKI C, MADADI P. Codeine, Ultrarapid-Metabolism Genotype, and Postoperative Death. *N Engl J Med* 2009; 361: 827-828.
- 39) KELLY LE, RIEDER M, VAN DEN ANKER J, MALKIN B, ROSS C, NEELY MN. More Codeine Fatalities After Tonsillectomy in North American Children. *Pediatrics* 2012; 129: e1343.
- 40) MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA) Drug Safety Update 2013; Vol 6 Issue 12, July: A1.
- 41) TOMS L, DERRY S, MOORE RA, McQUAY HJ. Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults. *Cochrane Database Syst Rev* 2009; (1): CD001547.
- 42) BRETT CN, BARNETT SG, PEARSON J. Postoperative plasma paracetamol levels following oral or intravenous paracetamol administration: a double-blind randomised controlled trial. *Anaesth Intensive Care* 2012; 40: 166-171.
- 43) QI DS, MAY LG, ZIMMERMAN B, PENG P, ATILASOY E, BROWN JD, COOPER SA. A randomized, double-blind, placebo-controlled study of acetaminophen 1000 mg versus acetaminophen 650 mg for the treatment of postsurgical dental pain. *Clin Ther* 2012; 34: 2247-2258.e3.
- 44) QUIDING H, PERSSON G, AHLSTRÖM U, BÄNGENS S, HELLEM S, JOHANSSON G, JÖNSSON E, NORDH PG. Paracetamol plus supplementary doses of codeine. An analgesic study of repeated doses. *Eur J Clin Pharmacol* 1982; 23: 315-319.
- 45) SCUDDER L, HERTZ S. Acetaminophen, Opioids, and Safety [Internet]. *Medscape* 2014 Feb 05 [cited 2014 May 20]. Available from: <http://www.medscape.com/viewarticle/820039>.
- 46) DIMITROPOULOS E, AMBIZAS EM. Acetaminophen Toxicity: What Pharmacists Need to Know. <http://www.uspharmacist.com/content/t/pain%20management/c/47337/> Accessed 20 August 2014.
- 47) FDA 13 Jan 2011 FDA Drug Safety Communication: Prescription Acetaminophen Products to be Limited to 325 mg Per Dosage Unit; Boxed Warning Will Highlight Potential for Severe Liver Failure. <http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm239955.htm> Accessed 25 August 2014
- 48) FDA 14 Jan 2014 Acetaminophen Prescription Combination Drug Products with more than 325 mg: FDA Statement - Recommendation to Discontinue Prescribing and Dispensing. <http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm381650.htm> Accessed 25 August 2014
- 49) MARTINEZ V, ATTAL N, VANZO B, VICAUT E, GAUTIER JM, BOUHASSIRA D, LANTÉRI-MINET M. Adherence of French GPs to Chronic Neuropathic Pain Clinical Guidelines: Results of a Cross-Sectional, Randomized, "e" Case-Vignette Survey. *PLoS One* 2014; 9: e93855.
- 50) MOORE A, COLLINS S, CARROLL D, McQUAY H, EDWARDS J. Single dose paracetamol (acetaminophen), with and without codeine, for postop-

- erative pain. *Cochrane Database Syst Rev* 2000; (2): CD001547.
- 51) CASALE R, DAMIANI C, ROSATI V, ATZENI F, SARZI-PUTTINI P, NICA AS. Efficacy of a comprehensive rehabilitation programme combined with pharmacological treatment in reducing pain in a group of OA patients on a waiting list for total joint replacement. *Clin Exp Rheumatol* 2012; 30: 233-239.
- 52) FRANCESCHI F, BUCCELLETTI F, MARSILIANI D, CARROCCIA A, GIUPPONI B, DE MARCO G, GILARDI E, MERRA G, MANCINI F, POTENZA A, GIANNUZZI R, CALCINARO S, MARINI M, GENTILONI SILVERI N. Acetaminophen plus codeine compared to ketorolac in polytrauma patients. *Eur Rev Med Pharmacol Sci* 2010; 14: 629-634.
- 53) SAVOIA G, COLUZZI F, DI MARIA C, AMBROSIO F, DELLA CORTE F, OGGIONI R, MESSINA A, COSTANTINI A, LAUNO C, MATTIA C, PAOLETTI F, LO PRESTI C, BERTINI L, PEDUTO A, DE IACO F, SCHIRALDI F, BUSSANI F, DE VITO L, GIAGNORIO G, MARINANGELI F, COACCIOLI S, AURILIO C, VALENTI F, BONETTI C, PIROLI A, PALADINI A, CICCOSZI A, MATARAZZO T, MARRARO G, PAOLICCHI A, MARTINO A, DE BLASIO E, CERCHIARI E, RADESCHI G. Italian Intersociety Recommendations (SIAARTI, SIMEU, SIS 118, AISD, SIARED, SICUT, IRC) on Pain Management in the Emergency Setting. *Minerva Anesthesiol* 2014 May 22. [Epub ahead of print]
- 54) CHANG AK, BIJUR PE, MUNJAL KG, GALLAGHER JE. Randomized Clinical Trial of Hydrocodone/Acetaminophen Versus Codeine/Acetaminophen in the Treatment of Acute Extremity Pain After Emergency Department Discharge. *Acad Emerg Med* 2014; 21: 227-235.