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REVIEW ARTICLE

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Clinical use of ketoprofen lysine salt: a reappraisal in adolescents with acute respiratory infections

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Abstract
Upper respiratory infections are widespread, and they are mainly of viral etiology. It has to be remarked that every infection is always associated with an inflammatory response. Inflammation implicates a cascade of bothersome symptoms, including fever, pain (headache, myalgia, and arthralgia), malaise, and respiratory complaints. As a result, anti-inflammatory medications could be beneficial as they act on different pathogenetic pathways. The ketoprofen lysine salt (KLS) has a potent anti-inflammatory activity associated with effective analgesic and antipyretic effects and has a valuable safety profile. However, adolescents present peculiar psychological characteristics that determine their difficulty to be managed. In this regard, an adolescent with a respiratory infection requires a prompt and adequate cure. KLS, thanks to its pharmacologic profile, could be favorably used in this regard. A recent primary-care experience outlined its effectiveness in this issue.

Introduction

Respiratory infections represent one of the most common diseases reported by patients and are among the most frequent causes of visits to doctors' clinics, as recently documented by a systematic review including data from 12 countries across 5 continents.[1] Acute upper respiratory infections (AURI) are the most common and recognize a bacterial or viral cause, although viral forms are the most frequent.[2] Several viruses account for AURI, but the most common are rhinovirus, coronavirus, syncytial virus, influenza, parainfluenza, adenovirus, coxsackievirus, echovirus, paramyxovirus, and enterovirus.[3-8] In addition, viral respiratory infections present a typical seasonality characterized by increased infectivity in cold seasons.[9]

From a clinical point of view, all respiratory viruses may cause an influenza-like illness (ILI).[10] The typical characteristic of an ILI is its viral nature.[11] An ILI (or flu-like syndrome) is an acute manifestation with general and respiratory symptoms. In particular, the definition of ILI

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(common throughout Europe) includes any person who presents a sudden and rapid onset of at least one of the following general symptoms: fever or feverishness, malaise/exhaustion, headache, myalgia, and at least one of the following respiratory symptoms: cough, sore throat, and wheezing.[12] However, milder manifestations are represented by the common cold.[13] Even if these viral infections may also account for the lower respiratory tract, usually, a healthy and immunocompetent subject presents only symptoms concerning the upper airways. Moreover, common cold and ILI are umbrella terms that include different conditions, including rhinitis, sinusitis, pharyngitis, laryngitis, otitis, and tonsillitis.[14]

These respiratory infections, mainly in children and adolescents, significantly burden society from a social and economic perspective.

Management

The management of AURI is based on appropriate diagnosis and quick treatment. The diagnosis is based on clinical features in clinical practice and also encompasses a differential diagnosis.[15] The most common symptoms usually include sneezing, rhinorrhea, nasal congestion, hypo/anosmia, hypo/ageusia, facial pressure, sore throat, cough, headache, discomfort, myalgias, and low-grade fever.[16] Notably, these symptoms usually last less than 10 days.[17] Therefore, the treatment should be timely. However, if symptoms persist longer or worsen, the infection will likely evolve into rhinosinusitis, needing appropriate work-up.[18] Also, it has to be underlined that the cough may last even for more than a month.[19]

Even if these symptoms are self-resolving, they are still particularly annoying. Consequently, doctors prescribe symptomatic relievers as a first-line treatment.[20] The main goal of treatment is, in fact, the prompt reduction of symptom intensity and duration. It is vital to inform patients and parents that antibiotics should not be used unless a bacterial complication occurs.[21] Usually, NSAIDs, nasal lavage, and nonpharmacologic remedies are sufficient to cure rapidly the most acute viral infections.[22]

The COVID-19 lessons

The COVID-19 pandemic required acquiring fundamental notions and consolidating pathophysiological knowledge on respiratory infections.[23] The primary concept we must consider when faced with an infection is that every infectious process is always accompanied by an inflammatory response.[24] As a result, inflammation dampening represents a leading therapeutical target in managing infections.

The second relevant consequence of the COVID-19 epidemic was the dramatic impact on infection epidemiology. The lockdown, mask use, and social distancing significantly diminished the impact of respiratory infections. The paradigmatic example was the negligible prevalence of bronchiolitis during the early COVID-19 pandemic.[24] However, since the slackening of restrictive measures, there has been a surge in cases of bronchiolitis, which has put a strain on the pediatric hospital network.[25] Similarly, the course of the 2022–2023 seasonal influenza epidemic was characterized by a rapid and early onset, extraordinary incidence, clinical severity, and persistent duration of the epidemic plateau.[26] Consistently, other respiratory infections have spread simultaneously.[27] Therefore, respiratory infections have become increasingly impactful in daily life. A poorly trained immune system contributed significantly to this trend. In addition, using NSAIDs in managing patients with COVID-19 has been recommended as an early strategy at home.[28]

Consequently, careful management of respiratory infections is required today. In this regard, NSAIDs represent an essential therapeutical resource. Furthermore, NSAIDs have fruitful mechanisms of action in contrasting respiratory infections. NSAIDs exert anti-inflammatory, analgesic, and antipyretic effects.[29]

Ketoprofen lysine salt: history and clinical evolution of an NSAID

Nonsteroidal, anti-inflammatory drugs are used to relieve pain (analgesics), reduce inflammation (anti-inflammatory), and lower body temperature in the case of fever (antipyretics). Moreover, NSAIDs are generally used to relieve the symptoms of headaches, painful menstrual cycle (dysmenorrhea), myalgia, colds and flu, arthritis, and other diseases that cause chronic pain.

The most common NSAIDs are diclofenac, ketoprofen, ibuprofen, naproxen, and high-dose aspirin (low-dose aspirin is not considered an NSAID).

The shared mechanism of action exerted by NSAIDs is the blockage of the release of pro-inflammatory mediators, mainly derived from arachidonic metabolism and cytokines. Classically, NSADIs inhibit prostaglandin production by inhibiting the cyclo-oxygenase (COX) enzyme.[30]

Among these molecules, ketoprofen had a particular and unique evolution throughout the years and the countries. In particular, ketoprofen is a highly potent and safe nonsteroidal anti-inflammatory drug of the propionic acid derivative group: 20 times more potent than ibuprofen, 80 times more powerful than phenylbutazone, and 160 times more potent than aspirin in reducing inflammation in a preclinical model.[31,32]

As with all NSAIDs, the physiologic basis of ketoprofen's pharmacodynamic activities is presumed to be an interference with arachidonic acid metabolism. Ketoprofen is one of the most potent inhibitors of COX at concentrations well within the range of therapeutic plasma levels (2 pg/L). The drug was 6 and 12 times more potent than naproxen and indomethacin, respectively, in inhibiting prostaglandin synthesis in isolated guinea pig lung preparations perfused with arachidonic acid.[31] Ibuprofen, phenylbutazone, and aspirin were 800–1500 times less potent than ketoprofen.[32] In addition to its effects on COX, ketoprofen inhibits the lipoxygenase pathway of the arachidonic acid cascade.[33] This pathway produces non-cyclized mono-hydroxy acids (HETE) and leukotrienes.[34] However, only leukotrienes (B_4, C_4, and D_4) increase vascular permeability.[34] Notably, HETE and leukotrienes of leukocyte source promote leukocyte migration and activation.[35] Ketoprofen is also a potent

inhibitor of bradykinin, a relevant mediator involved in pain and inflammatory events.[36]

Several human studies demonstrated that ketoprofen exhibits analgesic, antipyretic, and anti-inflammatory properties through nonspecific COX-1 and COX-2 inhibition.[37] Thought to occur mainly in peripheral sites, recent studies indicate that ketoprofen also appears to have central effects.[38]

The lysine salt of ketoprofen (KLS) represents the evolution of the original ketoprofen molecule; with the aid of pharmaceutical technology, the salification with lysine amino acid gave rise to a new molecule, profoundly different from the original one, more effective and with a reduction in the dosages of use leading to an overall optimal tolerability.

Ketoprofen lysine salt (KLS) has a higher solubility compared to ketoprofen and pharmacokinetic studies demonstrated that its absorption is more rapid and almost complete with a higher peak plasma concentration, 15 minutes versus 60 minutes after intake.[39,40] In addition, KLS has both peripheral and central activity.[41] In the brain, KLS inhibits both nitric oxide (NO) and COX synthase[42] and is rapidly and readily distributed into the central nervous system as it passes the blood–brain barrier within 15 minutes, being highly liposoluble.[43,44] Ketoprofen's liposolubility has been demonstrated to be greater than ibuprofen and other NSAIDs.[45] Moreover, KLS is able to penetrate extensively into the upper airways, making it an optimal solution in the treatment of inflammation in course of pharyngitis, otitis, sinusitis.[46,47] The lysine salt of ketoprofen also demonstrated an analgesic activity two times stronger than ketoprofen.[48]

One of the main improvements of the salification process with the amino acid lysine was the possibility to reduce the effective daily dosage (DDD) versus ketoprofen. This is of particular significance in terms of safety and tolerability, the improved solubility as well as bioavailability of ketoprofen lysine salt, and the reduced dosage has the particular advantage of reducing the gastrointestinal toxicity of the molecule demonstrating a better gastrointestinal safety profile when used at the recommended dosages. Recent and elegant ex vivo studies have provided clear evidence of its negligible effects on the gastric mucosa; in particular, it has been demonstrated that L-lysine in the ketoprofen molecule has a potent antioxidant effect stimulating the production of endogenous gastro-protective proteins and pointing out the strong synergic effect between L-lysine and ketoprofen. Recent studies of the same working group demonstrated that ketoprofen per se is responsible for a safer response of the gastric epithelium compared to ibuprofen.[49]

For this reason, KLS safety profile is particularly favorable and, as a result, has better gastrointestinal tolerability than ketoprofen acid and ibuprofen.[50] There is robust evidence that KLS has better and longer analgesic control with greater and faster pain relief than other NSAIDs, with the highest ratio between anti-inflammatory and analgesic effects.[44,51,52]

In the pediatric setting, ketoprofen is used widely in managing children and adolescents with inflammatory and musculoskeletal conditions, pain, and fever.[53] Pharmacokinetic and pharmacodynamic studies conducted in children showed that the ketoprofen profile was similar to adults.

The absolute bioavailability of oral ketoprofen (S-enantiomer), 12.5–50 mg, is approximately 70–80%.[54] Moreover, there is no difference in the bioavailability of a single intramuscular and oral ketoprofen dose.[54]

A series of pediatric studies explored its efficacy in children with fever; the results showed that ketoprofen (administered at a dose of 0.5 mg/kg) was as effective as acetaminophen (15 mg/kg) and ibuprofen (5 mg/kg) as recently reviewed.[55]

Pediatric studies on the management of postsurgical pain reported a relevant analgesic effect in various surgery models, as recently reviewed.[56] In particular, five pediatric studies investigated opioid-sparing and analgesic activity. The results showed that ketoprofen significantly reduced the opioid need as the rescue fentanyl. In addition, a 3-week follow-up study measured the analgesic effects in children after tonsillectomy.[57] This study confirmed sufficient pain control if associated with paracetamol or paracetamol-codeine.

These studies confirmed the outcomes of a systematic review and meta-analysis comparing ketoprofen vs. ibuprofen and diclofenac in patients with pain.[58] This study included 13 randomized controlled studies, recruiting 898 patients. The results demonstrated that oral ketoprofen was significantly better than ibuprofen and diclofenac in improving moderate-to-severe pain, joint function, and general condition.

A unique 4-week study explored the anti-inflammatory and analgesic activity in children with juvenile rheumatoid arthritis,[59] demonstrating a significant reduction of joint pain associated with functional recovery.

Regarding the safety profile, ketoprofen rarely induces relevant adverse events in childhood, usually self-resolving and mild/moderate.[60] However, most evidence from the literature concerns a healthy pediatric population. As a result, children with severe illness or comorbidities (mainly hypovolemia, hypotension, electrolyte disturbance, heart failure, and renal disease) require adequate attention and dosage titration. Finally, an essential issue in childhood is palatability and the ease of intake. In this regard, the current formulations guarantee optimal acceptability and, consequently, high therapy adherence.

Ketoprofen and respiratory infections

Based on our best knowledge, only one primary-care study compared a single dose of KLS with a single dose of paracetamol or placebo in 97 children (age range 6–12 years) with pharyngotonsillitis.[61] The study demonstrated that a single dose of ketoprofen lysine salt or paracetamol safely improves sore throat symptoms.

The lysine salt of ketoprofen has proven, in clinical practice, to be effective in pain and fever in the symptomatic treatment of AURI. These events are, in fact, the main features of respiratory infections. As we have seen, all infectious processes are accompanied by an inflammatory reaction that causes symptoms and signs to appear. Fever, in the first place, is the consequence of releasing

mediators that activate the thermoregulation centers. In addition, pain is expressed in acute respiratory infections through the occurrence of headache, myalgia, arthralgia, and widespread bone pain. Therefore, controlling these three pathophysiological events with a single drug is an important therapeutic strategy.

Once again, the COVID-19 pandemic helped renew interest in using NDAIDs for early infection control, precisely by counteracting the inflammatory reaction. After an initial therapeutic bewilderment at the pandemic's beginning, the viral agent is unknown; there was soon a move toward using NSAID molecules for early home treatment. At the beginning of the outbreak, there were skepticism and concern about the use of NSAIDs in patients with COVID-19. This behavior is derived from a lack of experience regarding this new viral disease. In this regard, the Italian Society of Pharmacology evaluated the literature evidence concerning the role of COX in the inflammatory process and the effects of NSAIDs in patients with infections.[62] As a result, the document concluded that NSAIDs should be used cautiously and under medical control. However, after this initial period, NSAIDs have been widely used in clinical practice, as recommended by regulatory agencies.[63] Therefore, their benefits are evident in managing patients with acute viral infection.[64,65]

A very recent review pointed out the potential role of KLS in the strategy of COVID-19 treatment.[66] In the context of NSAIDs, ketoprofen lysine salt has some distinctive pharmacological features that can be used in the early management of mild/moderate forms of COVID-19, such as analgesic, anti-inflammatory, antipyretic, and antiplatelet effects.[67,68]

Considering the overall pharmacological aspects, KLS could be a valuable candidate for managing patients with acute respiratory infections.

The issue of adolescents

Adolescence represents a critical period of life. Adolescents undergo a mental maturation process that takes them from childhood to adulthood.[69] This transition takes place in stages, sometimes creating a feeling of inadequacy concerning the stimuli from the outside world. In addition, the adolescent has to make his/her way of relating to others (parents, family members, friends, schoolmates, and adults), which is often conflictual.[70] This uneasiness sometimes turns into a sense of invincibility and sometimes into extreme fragility.

Moreover, when confronted with the illness, the adolescent often tends to minimize the severity of the symptoms and not take treatment. Being ill is inconceivable, and the important thing is not to be stigmatized by peers. Furthermore, the COVID-19 pandemic has contributed to a deterioration in the quality of life of adolescents.[71] In this context, it is essential to manage the adolescent with an acute respiratory infection appropriately to ensure prompt and rapid recovery of his or her psycho-physical condition. In this context, NSAIDs can enable fast and adequate symptom control. Therefore, the formulation of NSAIDs is also essential.

Ketoprofen lysine salt in adolescents with respiratory infections: a primary-care experience

Recently, a group of primary-care pediatricians collected cases concerning using KLS in adolescents with acute upper airway infection [manuscript submitted]. This practical experience included 61 adolescents (age range 12–15 years), who were monitored through telemedicine. Parents or adolescents reported axillary temperature and the perception of symptom severity assessed by visual analog scale daily. The symptoms were rhinorrhea, nasal obstruction, sore throat, malaise, headache, earache, myalgia, and cough. The retrospective analysis showed that KLS quickly and impressively reduced the number of adolescents with fever and the perception of symptom severity (Figure 1 and 2).

Conclusive remarks

The adolescent with respiratory infection requires timely and thorough management. Even if most respiratory infections are mild/moderate and self-limiting, prompt control of symptoms is desirable. In this regard, KLS could quickly relieve fever and pain (headache, myalgia, arthralgia, and malaise) through rapid control of inflammation and an overall very good safety profile. In addition, the oral

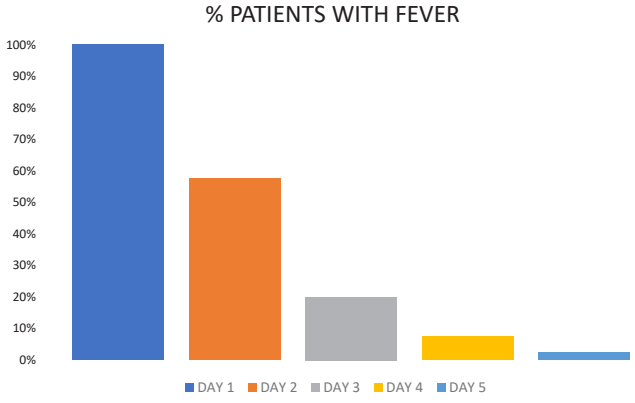

Figure 1 Number of adolescents with fever, evaluated daily.

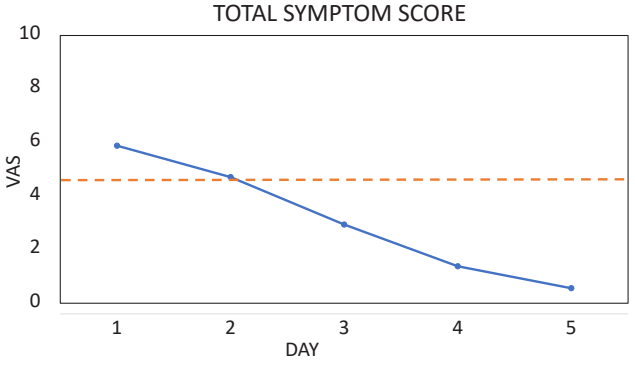

Figure 2 Mean of visual analog score for total symptom score (sum of the single symptom scores), evaluated daily.

administration of soluble powder guarantees high acceptability and adherence. Further studies could investigate whether KLS has any advantages over other NSAIDs in terms of reducing hospitalization rates, decreasing the risk of complications, and facilitating earlier return to work or school in acute upper respiratory tract infections.

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