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Review Article

The Secrets of Clodronate: An Old Drug with a New Soul

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Abstract

Clodronate belongs to a class of drugs (bisphosphonates - BPs) that began to be studied in the late 1960s due to their high affinity for bone hydroxyapatite, to which they bind stably while inhibiting osteoclastic bone resorption. Although BPs share similar chemical structures, they exhibit markedly different pharmacodynamic behaviors and systemic tolerability profiles, both in terms of their primary activity and safety. Studies conducted over the years on these interesting compounds-characterized by poor oral absorption and rapid renal excretion without undergoing metabolic transformation-have revealed their potential applications in various pathological conditions beyond their main anti-osteoclastic action. In this regard, Clodronate stands out among bisphosphonates for its broad spectrum of demonstrated activities and excellent tolerability.

Keywords: *Clodronate; Bisphosphonate; VNUT; Purinergic Receptors; Immunity*

Introduction

Clodronate (dichloromethylene-bisphosphonate, CLO) belongs to a class of compounds first investigated in the late 1960s. The innovative and defining pharmacodynamic characteristic of bisphosphonates (BPs) lies in their ability to inhibit excessive bone resorption resulting from increased osteoclastic activity. Early *in vitro* findings were followed by animal studies in the early 1970s and, subsequently, by preliminary clinical investigations. These data were presented at the First International Symposium on Bisphosphonates held in Rome in 1979, where initial results on the two most studied BPs etidronate and clodronate were reported. This event marked a turning point, triggering significant interest and research activity worldwide.

Subsequent studies helped clarify the pharmacological properties of this drug class and led to the synthesis of new analogues designed to improve and expand upon the original compounds. CLO began to stand out for its distinctive characteristics. Despite this, by the late 1980s, attention shifted toward newer BPs featuring amino groups in their molecular structure, which conferred a significantly stronger

anti-osteoclastic activity. Alendronate and Neridronate (Italian patents, 1980-1981) were among the first of this new generation and were soon approved for the treatment of bone-related diseases. In the following years other N-BPs have been synthesized and marketed for similar therapeutic application (Figure 1).

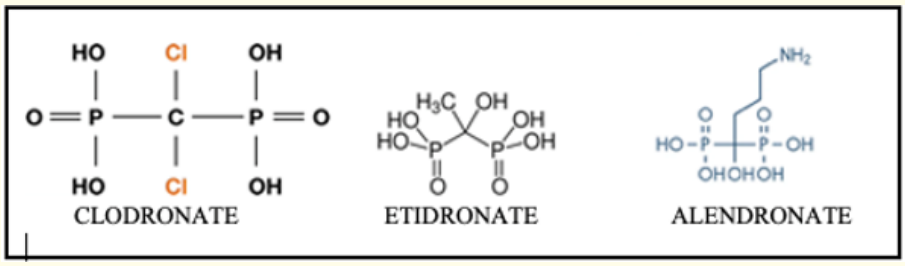

Figure 1: *Chemical formulas of clodronate, neridronate and alendronate.*

The surge of experimental and clinical research driven by strong commercial interest gradually overshadowed CLO, despite its early approval by the Italian Ministry of Health in the 1980s for the treatment of tumor-induced osteolysis while studies were underway for its future application in osteoporosis. By the late 1990s and early 2000s, competition among approved BPs for Osteoporosis treatment pushed CLO further into the background. However, large-scale clinical trials continued to demonstrate that its efficacy in treating Osteoporosis was comparable to that of newer amino-bisphosphonates (N-BPs) [1]. Meanwhile, CLO also revealed therapeutic potential in osteoarticular diseases through mechanisms not shared by other BPs. The distinctiveness of CLO is evident even from a basic analysis of its chemical structure: CLO lacks both the central hydroxyl group and a side chain features present in other BPs and does not contain amino groups.

Clodronate: Pharmacodynamic and mechanism of action

This unique structure translates into distinct pharmacokinetic and pharmacodynamic properties. CLO is the only BP that forms a bidentate, rather than tridentate, bond with hydroxyapatite-a bond that can be further strengthened by the side chain structure [2]. Its weaker binding affinity to hydroxyapatite allows for faster clearance from bone after short treatment holidays, thus avoiding drug accumulation. Simultaneously, this feature permits deeper penetration into the bone matrix through Volkmann and Haversian canals, reaching deepest osteocytes and inhibiting their apoptosis. Osteocyte viability is essential for maintaining bone strength, signaling microdamage repair and preserving hydration [3].

Unlike N-BPs, CLO exerts its anti-resorptive effects through a different mechanism. N-BPs induce osteoclast apoptosis by inhibiting farnesyl pyrophosphate synthase in the mevalonate pathway and by converting isopentenyl pyrophosphate into a toxic ATP analogue [4] (Figure 2).

In contrast, CLO is metabolized within osteoclasts into a cytotoxic ATP analogue, adenosine dichloromethylene diphosphate ($AppCCl_2p$), which disrupts mitochondrial metabolism and induces apoptosis [5]. The concentration required to inhibit mitochondrial activity by 50% (IC_{50}) is approximately 50 μM, a level that is generally only achieved in the sub-osteoclastic resorption space.

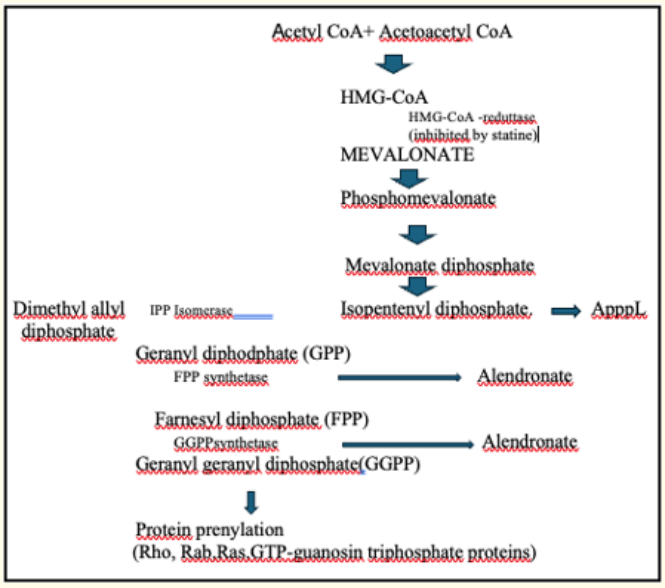

Figure 2: *Mevalonate pathway-Amino-BPs mechanism of action.*

Although CLO's anti-resorptive effect is less potent than that of N-BPs-requiring higher therapeutic doses-this is counterbalanced by a significantly lower incidence of adverse effects. CLO does not trigger acute phase reactions (which occur in 30-35% of systemic N-BP treatments) [6], does not cause injection-site inflammation or necrosis, and has not been associated with renal toxicity, osteonecrosis of the jaw, or esophagitis after oral administration [7].

Some adverse effects of N-BPs stem directly from their mechanism of action: inhibition of the Mevalonate pathway, essential to all eukaryotic cells, can lead to apoptosis even in non-target soft tissues, such as gingival keratinocytes. These effects may contribute to impaired wound healing in the oral mucosa and prolonged bacterial exposure. The entry of BPs into soft tissue cells is mediated by specific solute carrier (SLC) family transporters, particularly SLC20, SLC34, and SLC17 including some isoforms. When N-BPs persist in soft tissue environments, they may enter cells via these transporters and exert toxic effects through Mevalonate pathway inhibition. In contrast, CLO, due to its two chlorine atoms, inhibits these same chloride-dependent transporters, thus preventing soft tissue toxicity and potentially offering cytoprotective effects [8].

To understand one of CLO's most promising features, we must consider a fundamental biological principle: all cells, especially those of the immune and nervous systems, require ATP to respond to stress or damage. ATP is the central energy currency, converting food-derived energy into bioavailable energy used for biosynthesis, signaling and repair [9]. Beyond energy provision, ATP acts as a signaling molecule triggering cellular response to metabolic demands and stress condition being also involved in cell proliferation, differentiation and apoptosis [10-13]. ATP, outside the cells, together with some degradation products, (ADP, Adenosine and others) activates purinergic receptors (P2X, P2Y, and P1) on cell membranes, thereby eliciting autocrine and paracrine responses.

ATP is released into the extracellular space either directly through hemichannels (e.g. pannexins) or via vesicles. In the latter case, ATP is transported into vesicles through an electrochemical gradient maintained by a vesicular ATPase (v-ATPase), which pumps H^+ ions into the vesicle. The ATP transporter responsible for vesicular loading belongs to the phosphate transporter family, specifically SLC17A9 also known as the vesicular nucleotide transporter (VNUT) [14,15]. VNUT plays a critical role in ATP storage and purinergic transmission.

A comprehensive *in vitro* study by Kato Y., *et al*. (2017) [16] demonstrated that CLO is the only BPs capable of inhibiting VNUT at extremely low concentrations (IC_{50} =15.8 nM). This inhibition occurs via allosteric competition at Cl^--dependent binding sites, indicating a selective interaction between clodronate and the VNUT channel.

It has also been shown that, at low concentrations, CLO inhibits also ATP release from neurons, microglia and immune cells. *In vivo* analyses revealed that CLO is more effective than other therapeutic agents in alleviating neuropathic and inflammatory pain and accompanying inflammation without affecting basal nociception [16,17].

Clodronate and antalgic effect

Given its properties, CLO has also been investigated in the context of pain not associated with bone resorption. It is now well established that all osteoclast (OC) activity inhibitors also exert an analgesic effect, which is attributed to the reduced presence of hydrogen ions in the resorption pit and the decreased stimulation of pH-sensitive receptors (such as ASIC and TRPV1). Notably, CLO has demonstrated efficacy even in pain models where increased osteoclastic activity is not involved [18,19].

It is also important to consider that both activated OCs and damaged chondrocytes express Nerve Growth Factor (NGF) and Netrin-1, which promote nerve fiber sprouting, thereby increasing sensitivity. This process is further facilitated by the presence of chemokines (e.g. CCL2) and mast cells [20]. NGF also induces the expression of CGRP and substance P in Aδ and C nociceptive fibers, which are crucial mediators of pain and neuroinflammation. Therefore, pain is a complex event involving both increased osteoclastic activity and the release of numerous pro-inflammatory factors by immune cells. CLO appears capable of modulating or inhibiting these immune-mediated pathways through mechanisms not shared by nitrogen-containing BPs (N-BPs).

In the study by Kato Y [16], CLO was evaluated in models of inflammatory and neuropathic pain not associated with bone abnormalities. A 10 mg/kg dose of CLO significantly reduced inflammatory pain by approximately 40% in carrageenan-induced pain models and the von Frey test, as well as in complete Freund's adjuvant (CFA)-induced models. Its analgesic effect was found to be superior to that of diclofenac and acetaminophen, and comparable to that of tramadol. Furthermore, in the CFA model, CLO reduced paw edema similarly to hydrocortisone and prednisolone and significantly inhibited the release of TNF-α and IL-6.

In a comparative study with pregabalin and gabapentin, CLO exhibited analgesic activity similar to pregabalin, with a longer duration of action and complete reversibility [17].

Several authors have reported that vesicular nucleotide transporter (VNUT) and ATP release near purinergic membrane receptors are also involved in the *in vivo* immune response. The release of ATP and its degradation products ADP and adenosine modulate the expression of various pro-inflammatory mediators by monocytes, macrophages, neutrophils, and T lymphocytes [21-23].

The analgesic properties of CLO have been clinically demonstrated in several diseases characterized by altered bone metabolism and increased OC activity. Its efficacy in oncology is well established, with early studies showing a clear analgesic effect in the management of bone metastases [24-26], as well as in patients with CRPS-1 [27,28]. More recently, a study by Frediani B., *et al*. [29] on patients with symptomatic knee osteoarthritis definitively confirmed the long-lasting analgesic effect of intramuscular CLO administration.

Although BPs are primarily used for skeletal pathologies, CLO unlike N-BPs also exhibits anti-metaloprotease activity and has demonstrated a chondroprotective and anabolic effect on the extracellular cartilage matrix [30].

Clodronate and immunological effects

To better understand its anti-inflammatory mechanisms, it is essential to explore how BPs enter cells other than OCs, particularly macrophages and neutrophils, where they alter cellular metabolism. Despite uncertainties regarding the exact mechanisms of cellular

entry, some Authors suggest BPs are internalized via fluid-phase endocytosis, packaged into endosomes, then lysosomes, and subsequently released into the cytoplasm via a SLC37A3 phosphate channel forming a complex with the All-Trans Retinic Acid Induced Differentiation Factor (ATRAID) [31,32] in an acidic environment induced by a V-ATPase as a driving force. According to other Authors, BPs may enter cells through specific phosphate transporters, such as SLC20 and SLC34 [33,34]. However regardless of the entry mechanism, it is within the intracellular environment that different BPs exert distinct biological effects. The mechanism of action of nitrogen-containing bisphosphonates (N-BPs) theoretically involves the inhibition of cellular activity by interfering with the mevalonate pathway and leading to the formation of ApppI, which subsequently induces apoptosis, following a pathway similar to that observed in osteoclasts [35]. Although precise data on the intracellular concentrations of ApppI required to trigger apoptosis are lacking, [36] calculated that the half-maximal inhibitory concentration (IC_{50}) of $AppCCl_2p$ for inducing apoptosis in osteoclasts is approximately 50 μM a concentration likely achievable only within the confined microenvironment of the osteoclastic resorption lacuna.

However, in the case of monocytes or neutrophils whether circulating or tissue-resident such concentrations are unlikely to be reached, as systemic levels of BPs are typically very low and rapidly cleared from circulation and soft tissues. Only in cases where immune cells are in close proximity to areas of active bone resorption may they come into contact with higher concentrations of BPs, potentially leading to inactivation, provided intracellular uptake is sufficient to affect the mevalonate cycle [37]. Consequently, under physiological conditions, immune cells are unlikely to reach intracellular BP concentrations high enough to produce inhibitory amounts of ApppI. Thus, the effects of N-BPs on immune cells are highly dependent on the amount of drug internalized by these cells.

Regarding CLO, no definitive data are available concerning the intracellular concentrations it may reach in immune cells or the levels of AppCCl2p that may form. However, unlike N-BPs, CLO primarily exerts its activity even at very low concentrations by inhibiting the vesicular nucleotide transporter SLC17A9 (VNUT). This inhibition prevents ATP, generated endogenously by immune cells, from entering storage vesicles, resulting in reduced extracellular ATP release, lack of interaction with purinergic receptors, and inhibition of macrophage and neutrophil activation into a pro-inflammatory phenotype. A similar effect may also occur in lymphocytes [31]. This mechanism explains why CLO is capable of inhibiting inflammatory responses mediated by immune cell activation, even at low concentrations, while preserving their viability and reactivity.

It is important to note that the purinergic receptor system plays a broader role beyond modulating osteoarticular disorders or neuronal signal transmission. It also contributes significantly to the pathophysiology of various systemic diseases. Due to its ability to modulate ATP kinetics, CLO has been investigated in multiple disease contexts.

Clodronate and mechanism of action beyond bone resorption

In a recent study by Hasuzawa N., *et al.* (2021) [38], the selective VNUT-inhibiting action of CLO was evaluated in models of acute and chronic liver inflammation. In a mouse model of non-alcoholic steatohepatitis (NASH), CLO administration led to reduced hepatic inflammation, fibrosis, and triglyceride accumulation. CLO also protected mice from steatohepatitis induced by a high-fat, high-cholesterol diet. In another model, CLO prevented d-galactosamine and lipopolysaccharide-induced acute liver injury by downregulating inflammatory cytokines. These results demonstrate that VNUT inhibition and subsequent ATP release modulation by CLO effectively attenuate hepatic inflammation, fibrosis, and steatosis [39].

Back in 2012, Burnstock., *et al.* [40] showed that both exocrine and endocrine pancreatic cells store ATP and express purinergic receptors (P1 and P2 types). As early as 1975, it was demonstrated that ATP is co-released with insulin via exocytosis from secretory granules in pancreatic cells and that ATP can stimulate the secretion of both glucagon and insulin upon perfusion of rat pancreas. These processes, too, may be modulated by CLO.

In 2018, Maruyama K., *et al*. [41] demonstrated that infections with *Candida albicans* cause pain and allodynia as a result of ATP release from keratinocytes and subsequent activation of P2X3 receptors. The β-glucan component of the *Candida* cell wall activates Dectin-1 receptors on both keratinocytes and immune cells, promoting ATP release via a VNUT-dependent mechanism. This ATP, in turn, activates P2X3 receptors on the free nerve endings of peripheral sensory fibers, initiating pain transmission. The study further indicated that VNUT inhibition by clodronate may be effective in treating discomfort and pain induced by fungal β-glucan.

More recently, Mizuhara M., *et al*. (2020) [42] demonstrated that periodontal ligament fibroblasts, in response to mechanical stress, release ATP via VNUT, contributing to pain associated with tooth movement. In a rat model, experimentally induced tooth movement triggered nocifensive behavior that was suppressed by intravenous administration of CLO at a dose of 0.1 mg/kg. These findings indicate that ATP release mediated by VNUT in periodontal ligament cells is a key factor in pain transmission during orthodontic tooth movement.

A similar conclusion was reported by Mihara H., *et al*. (2020) [43], who observed that certain intestinal epithelial cells also release ATP via a VNUT-dependent mechanism. The presence of TRPV-4 receptors on these epithelial cells makes them responsive to mechanical, thermal, and specific fatty acid stimuli. TRPV-4 activation induces ATP exocytosis and results in visceral hypersensitivity. This relationship is further supported by the co-expression of TRPV-4 and ATP in intestinal epithelial tissues. These Authors also recognize CLO as a promising therapeutic agent due to its ability to inhibit VNUT-mediated ATP release, thereby limiting purinergic receptor activation, inflammatory factor expression, and nociceptive pain.

In recent decades, numerous experimental and clinical studies have highlighted the potential of CLO not only to alleviate tumor-related pain via osteoclast inhibition, but also to suppress tumor progression, metastatic spread, and improve patient survival.

Among the key contributors to tumor development are innate immune system cells, particularly tumor-associated macrophages (TAMs), which are known to promote tumor proliferation and invasiveness [44] High TAM infiltration in tumor tissues is associated with poor prognosis, which has led to the hypothesis that TAM depletion may improve disease outcomes [45]. CLO has been identified as an effective agent for reducing macrophage populations and inhibiting their activity [46]. CLO may be internalized by macrophages, especially when present in tumor areas at sufficient concentrations to interfere with ATP transport into vesicles by blocking VNUT.

Encapsulation of CLO in liposomes (Italian Patent, 1984) or similar formulations enhances its uptake by TAMs and improves its therapeutic efficacy compared to the sodium salt form, offering faster and more potent effects [47,48].

Conclusion

In recent years, widespread expression of purinergic receptors throughout the body and the pivotal role of VNUT in ATP transport have been well documented, reaffirming the therapeutic relevance of clodronate as the only known selective VNUT inhibitor. This property makes CLO a clinically effective analgesic for both inflammatory and neuropathic pain, with proven anti-inflammatory effects mediated by immune system modulation. Moreover, it reduces the risk of bone fractures with an efficacy comparable to N-BPs.

Its high tolerability in both oral and parenteral (intramuscular and intravenous) use, along with its low risk of inducing bisphosphonate-related osteonecrosis of the jaw (BRONJ), makes CLO a promising candidate for broader clinical applications beyond musculoskeletal disorders. Further investigation into its therapeutic potential across other fields is warranted.

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