NEW PERSPECTIVE ARTICLE

Pharmacological Synergism: A Multimodal Analgesia Approach to Treat Dental Pain

Sinergismo Farmacológico: Un enfoque de analgesia multimodal para el manejo de dolor dental

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ABSTRACT

Dental pain is usually managed by clinical interventions and pharmacological coadjuvants such as NSAIDs. However, its perception and modulation is mediated by different nociceptive mechanisms and these strategies can be insufficient. The multimodal analgesia refers to the use of 2 or more analgesic drugs that attenuate or blockade different mechanisms of pain, obtaining a greater clinical effect. Within this concept, pharmacological synergism plays a leading role, combining different molecules in lower doses to diminish also side effects. Since there are no standard prescriptions to be use in all the patients, multimodal approaches allow the clinician to make responsible effective combinations, individualizing analgesia as the pathway to success.

KEYWORDS

Multimodal analgesia; Pharmacological synergism; Dental pain.

RESUMEN

El dolor dental generalmente se trata con intervenciones clínicas y coadyuvantes farmacológicos como los AINEs. Sin embargo, su percepción y modulación está mediada por diferentes mecanismos nociceptivos y estas estrategias pueden ser insuficientes. La analgesia multimodal se refiere al uso de 2 o más fármacos analgésicos que atenúan o bloquean diferentes mecanismos de dolor, obteniendo un mayor efecto clínico. Dentro de este concepto, el sinergismo farmacológico juega un papel importante, combinando diferentes moléculas en dosis más bajas para disminuir también los efectos secundarios. Dado que no hay prescripciones estándar para ser usadas en todos los pacientes, los enfoques multimodales permiten al clínico realizar combinaciones responsables y eficaces, individualizando la analgesia como el camino hacia el éxito.

PALABRAS CLAVE

Analgesia multimodal; Sinergismo farmacológico; Dolor dental.

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"A new patient had just left your office where a root canal treatment was done on a maxillary second left premolar diagnosed with symptomatic irreversible pulpitis. The patient reports severe pain for the last 5 days, and during the appointment the pain was still present (indicating failure of the anesthetic blockade). You decide to prescribe your "trusted" NSAID for 3 days and indicated a second appointment. Unfortunately, your patient calls three hours later, complaining that the pain increases, and the painkiller is not working. He wants to know if he can take a second dose, change the prescription or what else he can do!".

For some readers, this is a typical scenario. Many patients that suffers of severe algesic odontogenic inflammatory pathologies may continue feeling pain during the acute period (between 0 and 72 hours after clinical interventions), especially when anesthetics didn´t work as it was expected, or when the intervention was not comfortable. Although multiple doses of NSAIDs are still the gold standard to manage dental pain (1); in some cases, the complexity, the duration and the severity of pain may require more aggressive pharmacological interventions to achieve analgesia.

WHAT IS MULTIMODAL ANALGESIA?

Basically, multimodal analgesia refers to the simultaneous use of 2 or more drugs that act by different mechanisms (2), trying to increase the individual effect that will be obtain by each molecule. Of course, this approach will need a complete understanding not only of the individual benefits, but the side-effects and strict contraindications as well (such as individual allergic reactions); to plan an effective combinatory strategy. Multimodal analgesia can be applied combining also different administration routs when is indicated. The expected increment in analgesic terms from multimodal approaches, will improve the acceptance of the treatment by the patients, and will also diminish the need of long-lasting analgesic regimens (3).

SYNERGISM, ANTAGONISM OR ADDITIVE EFFECTS?

The clinical effect that can be obtained from multimodal combinations may very not only between the molecules, but the doses combined. The ideal effect will be to combine lower doses of two different analgesics but obtaining an increased effect than the one expected for each drug. Of course, this will lead to a second benefit: Security. The incidence and severity of most of the drugs` side effects are dose-related; so, diminishing individual doses will have a clinical improvement (Figure 1) (4). Overall this combination strategy is known as pharmacological synergism. In other cases, to diminish doses is not possible without sacrificing the clinical effect, so effective doses must be use but combine. When regular doses are used but combined to achieve a clinical benefit, then the concept is known as an additive effect (5). Finally, some combinations may not be increased but attenuated, like if one of the molecules compete against the second drug. When the combination decreases the individual effect of the first drug is known as pharmacological antagonism. In dentistry, it is common to combine some of the molecules with analgesic/anti-inflammatory properties available: NSAID´s, paracetamol, opioids, steroids, local anesthetics and dual analgesics (such as tramadol and tapentadol). Besides these families, other alternatives can be considered (including adjuvants with analgesic properties such as anti-depressants, membrane stabilizers, anticonvulsives, etc.) but these are kept for complex non-inflammatory disorders, especially non-odontogenic orofacial pain. The amounts and schemes of how to combine is complex, and all the alternative must seek for improved clinical benefits, ideally synergistic effects.

HOW IS ANALGESIC SYNERGISM DEMONSTRATED?

To obtain a suitable combination depends of three steps: a- A theoretical proposal; b- An animal

model; and c- the design and implementation of human clinical trials. The first step will demand a complete literature review to stablish the scientific background that will support the new combination. This stage is contextualized in the clinical needing of the population, such as minor side-effects or the need of stronger analgesic strategies for a certain pathology. Any proposal must be evidence-based supported, without considering arbitrary options. Once the drugs to be combined are selected, then the design and experimental animal model must be developed. Several nociception models in animals are available and depending of the kind and duration of the noxious stimuli they will be chosen (i.e. different models can be applied to test inflammatory, neuropathic or mechanical nociception). One of the most standardize experiment to evaluate post-operatory inflammatory nociception is the formalin model, where the application of formalin dilution will evoke a biphasic nociceptive response in the animal, initiating by an immediate response and then followed by inflammatory reaction; both represented by paws´ flinches (6). The number of flinches are compared with different groups were the formalin is applied in the presence of analgesic molecules (7). This measurement allows to quantify the effective dose of each drug, in order to develop an isobolographic analysis (figure 2). This analysis requires of meticulous calculation, to see if lower doses of combined drugs will obtain a similar effect than the one observed in single-drugs groups. Briefly, an additive line is created between the two effective doses and the groups are evaluated. The final responses will be plotted in the isobologram, were 3 different options can be identified. If the response lies far below from the additive line, then synergism will be established. If an increase effect is obtained by almost identical individual doses, then the effect will be catalogue as “additive”; and finally, if the combination of both drugs didn´t increase, but instead decrease the clinical effect then the combination is considered antagonistic (figure 2).

Data from isobolographic analysis is used to propose the third step: the clinical validation. Different models can be use in human trials in dentistry, especially those were preoperative pain is absent, but a severe reaction is expected from a surgical intervention, like the third molar surgery model. This model allows to select homogeneous non-compromised populations, in order to diminish biased responses. To evaluate analgesic synergism, the data from animal models (such as proportions between drugs, antinociceptive response etc.) is calculated and extrapolated to experimental doses in humans. The trials will reveal if the combinations behave ideally in human beings, improving analgesia and decreasing side effects.

In summary, the multimodal analgesia involves drug combination with different action mechanism to enhance the analgesic effect and reduce the potential adverse effect; keeping a deep understanding of the pain physiopathology. There are no standard prescriptions to be use in all our patients, instead, multimodal approaches allows the clinical to make responsible combinations that will fit to each patient, individualizing analgesia as the pathway to success.

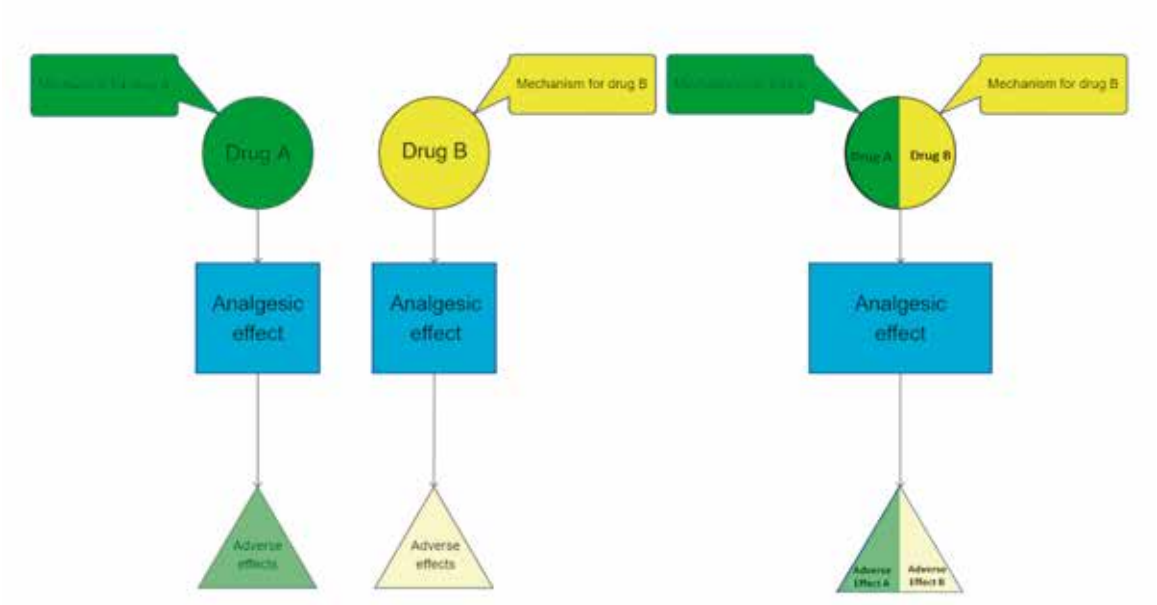

Figure 1. Hypothetical explanation of pharmacological synergism as multimodal analgesic strategy. Drug A and drug B are two analgesics with different mechanisms of action, and also individual side effects. Theoretically when combined in lower doses, the simultaneous action of their mechanisms will create an increased analgesic effect.

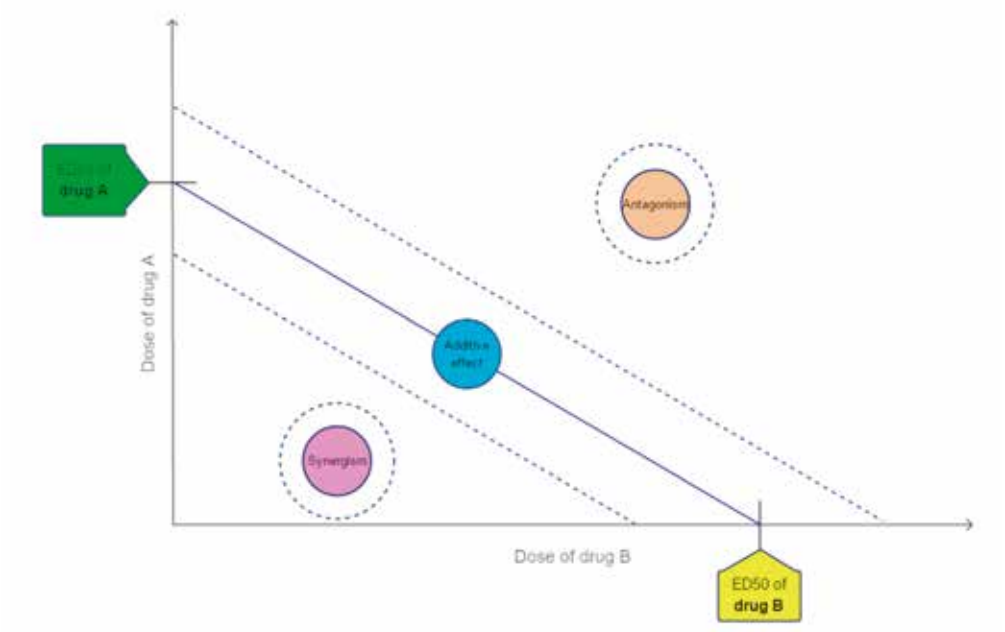

Figure 2: Representative diagram of an isobolographic analysis.

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