

## Paper

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# Clinical pharmacology and rationale of analgesic combinations

J. Demeules, V. Rollason, V. Piguët, P. Dayer

*Clinical Pharmacology & Multidisciplinary Pain Centre, University Hospital, Geneva, Switzerland*

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### Summary

**Background and objective:** Oral fixed drug combination analgesics have potential advantages over monotherapy, but these can only be attained through careful design.

**Results:** The main reasons for developing combination analgesics are to gain efficacy and to reduce toxicity. Analgesic combinations interact pharmacokinetically, or pharmacodynamically, or both, in positive or negative terms. The  $t_{\max}$  value for both enantiomers of tramadol occur two hours following administration, and that for the active, (+)-M1 metabolite occurs after three hours. Thus, pairing tramadol with acetaminophen, a rapid-onset analgesic, represents a pharmacokinetically rational combination. Analgesic combinations should satisfy two important pharmacodynamic criteria: the components of the combination should display additive or synergistic analgesia; and this interaction should allow lower doses of each substance to be used in combination, resulting in an improved safety profile. Clinical studies of the pharmacodynamic between oral tramadol and acetaminophen in third molar extraction and cold pressor models have provided evidence that this combination provides better efficacy than either individual component of the combination.

**Conclusions:** In summary, combination analgesics can play a valuable role in pain management. However, dubious combinations (directed against the same targets or with unwanted interactions) and 'old fashioned' fixed-dose multiple analgesic agent combinations should be avoided. Fixed-dose combination analgesics are of value only when they have been developed according to rational pharmacokinetic and pharmacodynamic criteria, and when claims for their benefits have been supported by evidence-based data and well-designed clinical studies.

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Oral fixed drug combination analgesics potentially have a number of advantages over monotherapy, but these benefits can only be attained through careful design that is not the case in some available preparations. This article discusses the rationale for analgesic combination approaches, in terms of efficacy and safety, and summarises the pharmacokinetic and pharmacodynamic criteria necessary to logically develop useful analgesic combinations.

### The rationale for combination analgesics

The main reasons for developing combination analgesics are to gain efficacy and to reduce toxicity [1]. Combining analgesics that act at different locations along the pain pathway may do this. An example of this is to combine a non-steroidal anti-inflammatory drug (NSAID; acting mainly at the periphery) and an opioid (centrally acting). Centrally acting analgesics may also be combined if they have different modes of action. For example, opioids may be combined with monoaminergic agonists that inhibit nociceptive transmission (e.g., clonidine). Agents such as tramadol, which exerts both central opioid and monoaminergic effects [2], may be combined with peripherally acting

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Correspondence to: Dr J A Desmeules, Geneva University Hospital, Division of Clinical Pharmacology and Toxicology, 24, Rue Micheli-du-Crest, 1211 Geneva 14, Switzerland. E-mail: jules.desmeules@hcuge.ch; Tel: +41 (0)22 372 99 42; Fax: +41 (0)22 372 99 40

NSAIDs. This combination aiming at three types of action provides the opportunity to reduce the NSAID dosage to achieve an optimal efficacy/toxicity ratio [3]. This approach may be especially useful in the elderly population.

Other potential benefits of combining analgesics include increasing the duration of analgesia, and widening the spectrum of efficacy. For example, local anaesthesia may be prolonged by co-administering epinephrine, and opioids may be combined with NMDA receptor antagonists (e.g., ketamine or dextromethorphan) to increase efficacy, decrease tolerance development or prevent postoperative central sensitisation and hyperalgesia [4]. Combining analgesics may improve patient compliance [1]. Lastly, parenteral abuse potential may also be reduced, for example, by combining opioids with an antagonist (e.g., tilidate with naloxone [5]).

### Undesirable drug interactions in combination analgesics

Analgesic combinations can be considered to interact either pharmacokinetically and/or pharmacodynamically. A rationally developed analgesic combination should therefore fulfil certain pharmacokinetic and pharmacodynamic criteria. In terms of pharmacokinetic criteria, unwanted interactions that affect the absorption, distribution, metabolism, or elimination of one or more of the drugs should be avoided. In terms of pharmacodynamic criteria, unwanted interactions may either increase the risks or severity of side-effects, or reduce efficacy.

Ideally, analgesic combinations should be screened for unwelcome pharmacokinetic and pharmacodynamic interactions in preclinical studies. As an example to illustrate the predictability and the rationale development we shall examine weak or 'atypical' opioids such as codeine and tramadol, frequently used as free or fixed combinations.

### Pharmacokinetic interactions in analgesic combinations

#### Codeine

*In vitro* data can be used to understand the pathways of drug metabolism, and the induction or inhibition of metabolic enzymes, and therefore to predict potential clinical interactions. The various mechanisms of pharmacokinetic drug interaction, those affecting the cytochrome P450 metabolic pathways are by far the most important. An example of a drug that is affected by this kind of interaction is codeine, a drug frequently used in analgesic combination.

The opioid activity of codeine is closely related to the production of morphine following metabolism

by cytochrome CYP450D6 [6]. Almost 10% of Caucasians are deficient for this enzyme and several drugs have been shown to reduce or abolish its activity. The influence of CYP450D6 phenotype on *in vivo* codeine bioactivation was investigated in a double-blind, randomised, placebo-controlled, crossover study in healthy volunteers [7]. In extensive metabolizer (EM) subjects, the codeine was activated into morphine; however, virtually no morphine production was detectable in the poor metabolizer or the extensive metabolizer subjects pre-treated with quinidine, a potent CYP2D6 inhibitor. Concomitant pain threshold tests showed that poor morphine production was associated with insignificant analgesia. For poor metabolizer subjects, therefore, codeine is an inefficient analgesic [7].

The potential metabolic interactions between codeine and other commonly prescribed analgesics or adjuvants have been investigated in *in vitro* studies using human (extensive metabolizer) liver microsomes [8]. It was found that morphine production from codeine was not affected by co-incubation with various NSAIDs (acetylsalicylic acid, diclofenac, indomethacin, piroxicam, or piroprofen), benzodiazepines (chlor-diazepoxide, clonazepam, diazepam, flunitrazepam, or midazolam), or anticonvulsants (carbamazepine, or phenytoin). However, significant inhibition of morphine production occurs when the microsomes were co-incubated in the presence of either neuroleptic drugs (chlorpromazine, haloperidol, levomepromazine, or thioridazine), or tricyclic antidepressants (amitriptyline, clomipramine, desipramine, imipramine, or nortriptyline) [8]. The likelihood of clinical interactions between codeine and these latter compounds precludes developing combinations of these drugs despite the well established additive effect of antidepressants and opioids.

Other pharmacokinetic criteria may be tested in clinical trials. Phase I studies should demonstrate bioequivalence (comparable areas under a serum concentration-time plot) between each drug in combination and when administered singly. These studies would additionally show whether the pharmacokinetics, including the elimination half-lives ( $t_{1/2}$ ), of the respective drugs are compatible. Whenever possible, data on the dose-concentration relation (from phase II trials), and the influence of co-variables such as age, gender, genetic factors, and renal and hepatic function on the pharmacokinetics of each component (from phase III trials) should be made available.

#### Tramadol

The bioequivalence between tramadol and acetaminophen (paracetamol) administered in combination

and alone was demonstrated in an open label, randomised, crossover, single-dose study in 24 healthy volunteers. Each subject received a single oral dose of three tablets, each containing 37.5 mg tramadol HCl plus 325 mg acetaminophen. The study measured serum concentrations of both the enantiomers of tramadol, which each have an analgesic effect and are both present in the marketed preparation. Serum concentrations of the M1 metabolite of (+)-tramadol (active at  $\mu$ -opioid receptors) were also recorded. The single dose pharmacokinetics of each tramadol enantiomer, the (+)-M1 tramadol metabolite, and acetaminophen were equivalent when the analgesics were given in combination or alone (Table 1).

The above study also demonstrated the complementary pharmacokinetic profiles of tramadol and acetaminophen. The  $t_{\max}$  values for both enantiomers of tramadol occur two hours following administration, and that for the (+)-M1 metabolite occurs after three hours. Thus, pairing tramadol, an analgesic with an effect that peaks at 2–3 h, [9] with a rapid-onset analgesic such as acetaminophen represents a pharmacokinetically rational combination.

### Pharmacodynamic interactions in analgesic combinations

In principle, analgesic combinations should satisfy two important pharmacodynamic criteria. Firstly, the components of the combination should display additive or synergistic analgesia. In other words, each

substance should contribute to the analgesic effect, and the analgesia achieved with the combination should be superior to that reached with any individual agent. Secondly, this additive or synergistic interaction should allow lower doses of each substance to be used in combination, resulting in an improvement in the safety profile. For a given level of efficacy, the combination should display greater tolerability or a lower risk of side-effects than each component drug.

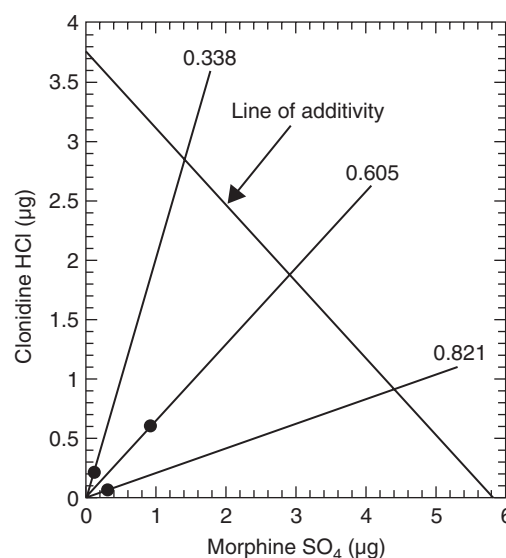
Preclinical studies can be used to evaluate the role of each analgesic in a potential combination [10]. This is done by using validated experimental models to construct classical dose–response relations, which can then be used to obtain the dose that produces a 50% response ( $ED_{50}$ ). However, comparison of  $ED_{50}$  values cannot readily distinguish whether two drugs are acting additively or synergistically with each other. Isobolograms (see below) provide a useful tool to explore potential synergism [11,12].

Isobolograms are used to define the optimal ratio for the desired pharmacodynamic analgesic interactions. The  $ED_{50}$  values for each of the components of the combination under study are obtained in dose–response studies. These values are then marked on a graph where the axes represent the doses of each compound. An example is shown in Figure 1. A line drawn connecting these two  $ED_{50}$  values represents the theoretical additivity of both drugs when they are used in different proportions. Points on the isobologram that fall below the ‘line of additivity’ correspond to concentrations that are predicted to act synergistically. For points above the line, the

**Table 1.** The bioequivalence of tramadol and paracetamol administered in combination and alone.

Drug administered	Drug studied		
	$C_{\max}$ (ng mL <sup>-1</sup> ) <sup>1</sup>	$t_{\max}$ (h) <sup>2</sup>	AUC (ng h mL <sup>-1</sup> ) <sup>3</sup>
Tramadol/acetaminophen 37.5 mg/325 mg			
(+)-Tramadol <sup>4</sup>	148	1.9	1385
(-)-Tramadol <sup>5</sup>	132	1.9	1145
(+)-M1 <sup>6</sup>	32	2.9	407
Tramadol alone 37.5 mg			
(+)-Tramadol <sup>4</sup>	148	2.1	1504
(-)-Tramadol <sup>5</sup>	132	2.1	1217
(+)-M1 <sup>6</sup>	31	2.9	393
Tramadol/acetaminophen 37.5 mg/325 mg			
Acetaminophen	12.3	1.1	50.8
Acetaminophen 325 mg			
Acetaminophen	13.2	1.0	51.7

<sup>1</sup>: Maximum serum concentration; <sup>2</sup>: time to maximum serum concentration; <sup>3</sup>: area under the curve of the serum concentration–time plot; <sup>4</sup>: (+)-enantiomer of tramadol; <sup>5</sup>: (-)-enantiomer of tramadol; <sup>6</sup>: M1 metabolite of the (+)-enantiomer of tramadol (active at  $\mu$ -opioid receptors).

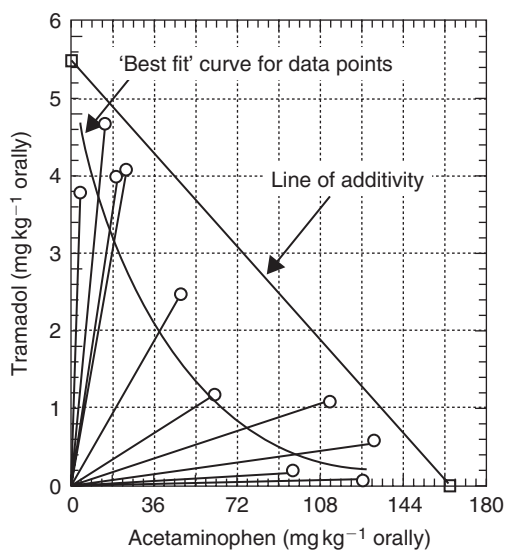


**Figure 1.** Isobologram of clonidine and morphine combinations. Drugs were delivered intrathecally to the mouse. Response was measured using the tail flick test. Based on data from [13]. ●:  $ED_{50}$  values of 3 morphine–clonidine combinations.

reverse is true. In other words, for synergy to occur, the required dosages of each drug are lower than may be expected from their individual potencies [12]. This is demonstrated in the figure by the ED<sub>50</sub> values for three different morphine–clonidine combinations in this model [13]. If necessary, the isobolographic analysis of interaction can be extended by adding a third axis representing the magnitude of the analgesic effect. The surface obtained offers greater insight into the magnitude of interaction as a function of the doses used [13].

The isobolographic approach has been used to study the analgesic interactions of oral fixed-ratio concentrations of tramadol and acetaminophen combinations in animal models [14]. As shown in Figure 2, synergism clearly occurred with all combinations used in the experiments. Following such preclinical screening, combination analgesics must be shown to demonstrate pharmacodynamic advantages in clinical studies.

Phase I clinical studies of the pharmacodynamic interactions in experimental models between oral tramadol and paracetamol have been carried out in man. Phase I trials generally involve studies with a factorial design and a randomised, parallel comparison of each analgesic component with the combination, a placebo and, if possible, an active control. These trials are usually performed in clinical pain models, such as third molar extraction, which produces moderate-to-intense postsurgical pain. Those models have provided evidence that the combination of tramadol and acetaminophen provides better

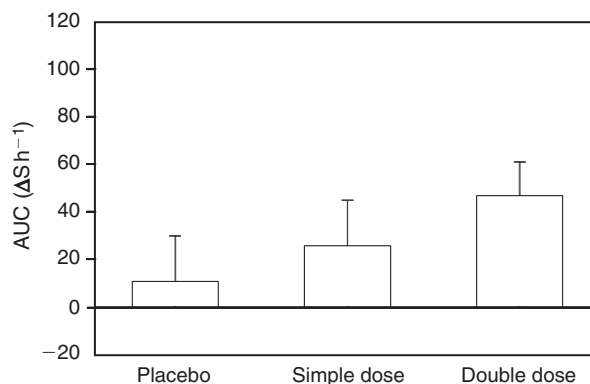


**Figure 2.** Isobologram of tramadol and paracetamol combinations by mouth in mice. Based on data from [14]. ○: Different tramadol–acetaminophen fixed ratio combinations.

efficacy than either placebo or the individual components of the combination.

Experimental models like the cold pressor test were more sensitive than the previously described pain models. The latency of hand withdrawal from an iced water bath (temperature 0°C) following ingestion of tramadol 37.5 mg plus acetaminophen 325 mg, tramadol 75 mg plus acetaminophen 650 mg, or a corresponding placebo was tested in a randomized controlled cross-over trial performed with healthy volunteers. Placing the hand in iced water causes C fibre stimulation and thereby induces moderate-to-severe pain. The area under the curve of the latency of hand withdrawal over four hours following ingestion of the study medication is shown in Figure 3. The study showed that the analgesic combination possesses significant efficacy even when single tablet of the individual drugs are used (i.e., the lowest tested dose) as compared to placebo.

When extrapolating the results of both preclinical and clinical studies to use in patients, several caveats should be borne in mind. Firstly, the phenotype of the individual may affect the response to an analgesic (as for codeine, mentioned earlier) [7]. Moreover, the drugs in fixed combinations may interact to different extents depending on the doses used, methods of administration, and racemic content. Secondly, the experimental method used may be misleading. Animal pain obviously diverges somewhat from human pain; in fact, all experimental models of pain can be shown to differ from clinical pain in important aspects and the models may also differ in sensitivity to different analgesics [15]. For example, success in treating experimental acute pain does not guarantee success in treating chronic pain. Thirdly, and perhaps most importantly, different types of pain react differently to different analgesics, depending upon the



**Figure 3.** Latency of hand withdrawal from an iced water bath. The cold pressor test that stimulate the C fibres, was sensitive enough to point out the difference between the placebo and the single and double dose in healthy volunteers ( $P < 0.05$ ; mean  $\pm$  sem,  $n = 10$ ).

pathologies involved. As instance, neuropathic pain could be in some circumstances less sensitive to conventional opioids than nociceptive pain [16].

## Conclusions

In summary, combination analgesics can play an extremely valuable role in pain management. However, dubious combinations directed against the same targets (e.g., mixed opioids) or with unwanted interactions (e.g., with antidepressants) should be avoided. Furthermore, 'old fashioned' fixed-dose multiple analgesic agent combinations are not well suited for clinical use since their rationale in terms of efficacy and safety is at best controversial. Fixed-dose combination analgesics are of value only when they have been developed according to rational pharmacokinetic and pharmacodynamic criteria, and when claims for their benefits have been supported by evidence-based data and well-designed clinical studies.

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