satisfactory postoperative analgesia during, at last, for another 18 minutes. I prefer to call it "real" analgesia caused by sufentanil and not residual analgesia. It is not residual. It is deliberate, since it was not caused by residual circulating amounts of the drug, but by a considerable circulating dose of the drug.

4) Finally, I think it is important to mention that the approach of potency relationships between two drugs is currently related not only to the Cp of each drug with a measurable effect, but Cp *versus* drug *versus* a third variable, which is the effect to be measured. This is explained by the fact that effect should be considered when determining the potency. For example: the C_{50} of alfentanil for the return of spontaneous ventilation is 40% of the C_{50} of that drug that causes changes in EEG [1,2]. Thus, one can see that the potency relationship between two drugs can be altered according to the clinical effect measured: skin incision, change of the EEG, blockade of the responses to intubation, return of spontaneous ventilation, etc. It is complex, but that is what has been described. Rigid potency relationships for all clinical outcomes have not been described. This has explained, for example, why patients awake after TIVA with propofol and remifentanil before hemodynamic changes become apparent. The rate of remifentanil removal from the vascular smooth muscle is lower than the rate of removal from the opioid receptor [3]. I would like to congratulate the authors for the study. It was well designed and, for this reason, their results are in accordance with the results reported in the literature.

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Reply

Dear Editor,

In reply to the letter of Dr. Fernando Squeff Nora on our study, I would like to thank him for his comments and critics, as well as to answer some topics to advance the discussion of such intricate and enthusiastic subject.

1. The potency relationship between two drugs is in fact described through the plasma concentration (Cp) capable of generating a measurable clinical effect; among them we can mention the loss of consciousness, reduction of the minimal alveolar concentration of inhalational anesthetics, and prevention of movement with skin incision. The same mass of opioids administered in the same way may lead to different plasma concentrations, especially when the study population has such a wide individual variety: young-old, fat-thin, etc. However, in our study, demographic characteristics (age, gender, weight, and height) in both groups were similar, eliminating or minimizing this discrepancy factor. The simulation of plasma concentrations (Cp) obtained for sufentanil (Bovill's model) and remifentanil (Minto's model) using the mean consumptions described in the study is very enlightening. We are in agreement regarding the maximal sufentanil Cp achieved (0.6 $ng.mL^{-1}$). However, we considered that the maximal remifentanil Cp achieved to be 12.6 $ng.mL^{-1}$, instead of the concentration suggested by Dr. Nora, 7.8 $ng.mL^{-1}$. In our study, the infusion of remifentanil was based on the real weight of the patient. Therefore, to calculate the mean remifentanil Cp, we used the total amount of remifentanil used divided by the real weight of the patient and by the duration in minutes of the infusion, yielding a mean of 0.29 $\mu g.kg^{-1}.min^{-1}$. However, we are aware that the pharmacokinetic model used in Minto's algorithm for remifentanil uses the lean body weight and, therefore, the maximal Cp achieved was 12.6 $ng.mL^{-1}$ and not 7.8 $ng.mL^{-1}$, as predicted by our colleague. Consequently, the potency relationship between both opioids would have been 1:21, much closer of the 1:18 proportion indicated in the study as the potency relationship based on the differences of the masses administered. Thus, we continue to say that the infusion schedule of opioids used were not equipotent, justifying the higher values of MAP in the sufentanil group.
2. The concept of synergism between two drugs involves addition mechanisms (1 + 1 = 2) and potentiation (1 + 1 > 2), and in this case the latter causes a higher effect than the simple addition of their separate effects. In our understanding, the critic of our colleague considered only the possibility of an addictive effect between opioids and hypnotics on EEG depression, ignoring the possibility of a potentiation. Among CNS depressants, we have several drugs that when used isolatedly do not have a specific effect in clinical doses, but that "potentiate" this same effect exerted by other drugs used concomitantly. In fact, high Cp levels of remifentanil (10 to 15 $ng.dL^{-1}$) and sufentanil (0.5 to 0.75 $ng.dL^{-1}$) to cause changes in the EEG. However, we believe in the potentiating synergistic effect when opioids are associated with propofol. Even isolatedly, the maximal Cp obtained with sufentanil was 0.6 $ng.mL^{-1}$, well within the margin capable of causing EEG changes in 50% of the patients. Since we used proportionally more remifentanil than sufentanil and obtained the same consumption of propofol in both groups to maintain BIS between 40 and 50, we suggested that the sufentanil-propofol synergism is greater than the remifentanil-propofol.
3. Regarding recovery, we are in agreement that the correct description would be "de facto" analgesia caused by sufentanil, since the concept of residual analgesia is related with concentrations below 0.05 $ng.dL^{-1}$. However, this does not change the fact that, in our study, patients in the

sufentanil group had decreased postoperative pain and, therefore, the length of stay in the recovery room was smaller than in the remifentanil group.

Dr. Ricardo Francisco Simoni

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Estudo Comparativo entre Bupivacaína Racêmica (S50-R50) a 0,125% e Bupivacaína em Excesso Enantiomérico de 50% (S75-R25) a 0,125% e 0,25% em Anestesia Peridural para Analgesia de Parto

(Rev Bras Anestesiol, 2008;58:5-14)

A soberania da Clínica: um dado de realidade

Senhora Editora,

O estudo conduzido por Duarte e col. [1] veio referendar o embasamento teórico pelo qual o composto bupivacaína em excesso enantiomérico ou mistura enantiomérica da bupivacaína foi concebido.

Quando criamos essa mistura, direcionamos a fase pré-clínica para investigar se o manuseio dos isômeros seria factível quanto à capacidade de bloquear o nervo. Para tanto, o nervo ciático de rato foi utilizado. Confirmada a atividade anestésica local, a "certidão de nascimento" da bupivacaína em excesso enantiomérico ou mistura enantiomérica da bupivacaína apareceu no *Regional Anesthesia and Pain Medicine*, em 1999 [2] e foi "apadrinhada" pelo trabalho de Trachez e col. no *Acta Anaesthesiologica Scandinavica*, em 2005 [3]. Ambos os estudos básicos foram realizados com a mistura na concentração de 0,5%, a qual foi capaz de bloquear fibras motoras e induzir analgesia. Restava ainda demonstrar se haveria minimização da cardiotoxicidade, pois teoricamente o isômero direito seria o responsável pela maior afinidade para os canais de sódio, sobretudo das células cardíacas e, por isso, reduzido, proporcionalmente, com relação ao antípoda, o isômero canhoto. E Trachez e nós encontramos redução da toxicidade desse composto em preparações diferentes no rato sob variáveis hemodinâmicas e eletrofisiológicas [3,4].

Em virtude da grande aceitação desse novo anestésico local na clínica e sendo a clínica soberana, os ensaios em pacientes humanos vieram suprir a pesquisa básica bastante escassa nesse particular.

O estudo de Duarte e col. [1] utilizando concentrações menores do agente confirmou a atividade anestésica local e particularmente a estereosseletividade dos isômeros da bupivacaína. É um trabalho original, pois concentrações a 0,125% e 0,25% não tinham sido ainda utilizadas. Nessas diluições, o composto mostrou resultados teoricamente esperados, o que assegura confiabilidade na utilização desse novo anestésico local na analgesia de parto.

A redução em 75% do isômero direito, que particulariza esse composto, é um dado de realidade, pois houve redução na intensidade do bloqueio motor, de tal ordem a não ocasionar aumento na incidência de partos instrumentais e sequer prejuízo na deambulação das pacientes em trabalho de parto.

Tendo em mente a soberania da Clínica, congratulo-me com os Autores pela complementação dada aos estudos básicos preliminares. Esses estudos tiveram como premissa a inferência de que a bupivacaína em excesso enantiomérico ou mistura enantiomérica da bupivacaína seria tão eficaz quanto a bupivacaína racêmica, todavia, sem a cardiotoxicidade correspondente [5].

Aproveitando a citação ao trabalho de Nakamura e col. [6], cujos resultados mostram bloqueio motor mais intenso com a levobupivacaína (composto homoquiral) com relação à bupivacaína racêmica (o que é teoricamente um contra-senso), sugiro aos Autores que seja acrescentado à pesquisa um grupo a mais, com o agente homoquiral. Mesmo que a levobupivacaína não esteja disponível no Brasil comercialmente, esse confronto poderia confirmar ou infirmar tais resultados. Assim, essa investigação, tão bem conduzida por Duarte e col. [1], daria uma expressiva contribuição ao fenômeno Estereoisomeria "e seus mistérios..."

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Réplica

Os autores da publicação agradecem a atenção dedicada ao seu trabalho por tão importante figura humana e pesquisadora, como a Dra. Maria dos Prazeres Simonetti. Conhe-