Fentanyl Analogs: Structure-Activity-Relationship Study

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Abstract: Fentanyl is the prototype of the 4-anilidopiperidine class of synthetic opioid analgesics. This study was aimed to review the structure-activity-relationship (SAR) of fentanyl analogs substituted in the position 3, or 4 of the piperidine ring. Pharmacological results show that the groups in position 3 of the piperidine ring, which are larger than methyl, severely reduce the analgesic potency compared to fentanyl. It is likely that the steric factor alone (i.e., voluminosity of the group and cis/trans isomerism), rather than the polarity and/or chemical reactivity, plays a crucial role in the analgesic potency of this series. Although the duration of action, in general, does not depend on the stereochemistry, longer action of the most potent 3-alkyl fentanyl analogs such as cis-3-methyl- and cis-3-ethyl fentanyl, is more likely influenced by pharmacodynamic, rather than pharmacokinetic variables. Also, it is possible that the introduction of a functional group such as 3-carbomethoxy reduces the duration of action by altering pharmacokinetic properties. SAR findings obtained by evaluating the neurotoxic effects of fentanyl analogs substituted in the position 3 of the piperidine ring parallel the SAR findings on analgesia in regard to potency and duration of action. This might suggest that similar receptors are involved in producing both antinoceptive and neurotoxic effects of these drugs. It appears that both the potency and the duration of action in the series of fentanyl analogs substituted in position 4 of the piperidine ring is influenced only by the steric requirement and not by the chemical nature of the substituent.

Keywords: Fentanyl, analogs, structure-activity-relationship (SAR), analgesic activity, neurotoxicity

INTRODUCTION

Opioid analgesics are widely used in clinical practice, as well as research tools in ligand-receptor interactions and pain mechanism investigation. Although there are several selective μ, κ or δ agonists, the μ agonists are by far the most important clinically [1]. Among the major classes of μ agonists, e.g., 4,5-epoxymorphinans, morphinans, benzomorphan, arylmorphans, pethidines, etc., 4-anilidopiperidines have a prominent place due to their high potency, low cardiovascular toxicity, fast onset and often short duration of action Fig. (1) [1-2]. Some of them have been widely and successfully used to supplement general anesthesia, as well as to treat postoperative and chronic pain [1]. Fentanyl Fig. (1) is the prototype of the 4-anilidopiperidine class of synthetic opioid analogs. It is about 50-100 times more potent than morphine and is characterized by a rapid onset of analgesia and a relatively short duration of action [1, 3]. Sufentanil Fig. (1) is approximately 5 to 10 times more potent than fentanyl. It has a rapid onset and recovery is considered to be more rapid than with fentanyl [1, 4-5]. Carfentanil Fig. (1) is about 20-30 times more potent than fentanyl [2]. It is used in veterinary medicine for immobilization of wild animals [6]. Lofentanil Fig. (1) is approximately five times more potent than fentanyl, with a remarkably long duration of action, though not with clinical significance [7-8]. Alfentanil Fig. (1) is an analog of fentanyl with around 1/4 the potency of fentanyl and around 1/3 of the duration of action, but with an onset of effects that is 4 times faster than fentanyl [9-10]. However, alfentanil has been used frequently in clinical practice [1]. Remifentanil Fig. (1) is approximately as potent as fentanyl [11]. It has a more rapid onset of analgesia than fentanyl or sufentanil and an ultrashort duration of action [1]. Like other μ agonists, all these drugs suffer from serious adverse effects including respiratory depression, muscle rigidity, nausea, sedation and with prolonged use, tolerance and addiction [1].

The objective of SAR studies is to discover compounds with adequate potency, greater selectivity and with enhanced pharmacokinetic properties in comparison to existing drugs. The development of novel opioids as research tools is almost equally important. They serve as probes for 3D structures of binding domains of opioid receptors, which are presently only poorly understood [12]. The establishment of detailed SAR, in combination with conformation analysis of the ligands, is an important approach to studying receptors [13-20]. Isotopically labeled fentanyl derivatives have been employed in opioid receptor studies, both in vitro and in vivo [21-23]. For example, positron emission tomography, (PET), with 11C labeled carfentanyl, has been used in healthy volunteers to observe the opioid receptor distribution in the body organs and other receptor properties [24-25]. Furthermore, novel opioid ligands are indispensable in studies of pain transmission mechanisms [26-27].

This study is aimed at discussing the relationship between the structure and antinoceptive and neurotoxic activity (potency and the duration of action) in the series of fentanyl analogs substituted in the position 3, or 4 of the piperidine ring.
ANTINOCICEPTIVE ACTIVITY OF FENTANYL ANALOGS

Substituted in the Position 3 or in the Position 4 of the Piperidine Ring

A very large number of fentanyl analogs have been synthesized since 1963 [3]. The corresponding pharmacological data have been published and the structure-activity relationship established [15, 19, 28-47].

The SAR studies on fentanyl analogs revealed, among other factors, a great influence of the stereochemistry upon the analgesic activity. For example, it was disclosed that a methyl group introduced in position 3 of the piperidine ring may dramatically enhance the activity, depending on the relative and the absolute stereochemistry [28, 48]. Thus, (++)-cis-3-Me fentanyl (=19 x fentanyl) is about 100 times more potent than the (--)enantionmer (Table 1). The corresponding racemic trans isomer is approximately as active as fentanyl (Table 1) [48]. Also, it was revealed that replacing 3-methyl with an allyl or a propyl group significantly reduces overall potency (Table 1) [2, 49]. These facts encouraged the preparation of several novel 3-alkyl fentanyl derivatives and the evaluation of the correlation between the structure (including stereochemistry) of the 3-alkyl group and the analgesic activity [45, 50]. Ten of the synthesized 3-alkyl fentanyl analogs, all in the racemic form, were tested for antinociceptive activity and compared with the potency of fentanyl Fig. (2) (Table 1). Those included two known compounds, cis-3-Me fentanyl and trans-3-Me fentanyl, as well as eight novel derivatives: cis-3-Et fentanyl, trans-3-Et fentanyl, cis-3-i-Pr fentanyl, cis-3-Bu fentanyl, trans-3-Bu fentanyl, cis-3-Bn fentanyl, trans-3-Bn fentanyl and cis-3-Phen fentanyl Fig. (2). The relative potencies and durations of action are presented in Table 1. The duration of analgesic activity was determined by using equianalgesic doses of the compound tested (e.g. ED$_{99}$, the least dose that produce the maximum analgesic effect).

Based upon the results of the pharmacologic testing results of novel 3-alkyl fentanyl analogs and in agreement with previously published data, which is summarized in Table 1, some tentative conclusions on the structure - activity relationship of 3-alkyl analogs of fentanyl were drawn:

- The presence of an alkyl group substituent in position 3 of the piperidine ring generally decreases or completely inhibits the analgesic activity compared to fentanyl. The exceptions are the (++)-cis-3-Me analog (=19 x fentanyl) [48] and (++)-cis-3-Et fentanyl (=1.5 x fentanyl) (Table 1) [45]. In the latter instance, presumably, one of the enantiomers was much more active than the other. Also, with the exception of racemic cis-3-Me, and to a certain degree cis-3-Et fentanyl, the presence of 3-alkyl group, did not influence the duration of analgesic activity compared to fentanyl (Table 1) [50].

- With increasing voluminosity of the alkyl group, the potency decreases rapidly. Thus, (++)-cis-3-Pr fentanyl, (++)-cis-3-Bu fentanyl, and (++)-cis-3-Bn fentanyl, are 2, 16 and 126 times less potent than fentanyl, respectively. Derivatives which are even more bulky, (++)-cis-3-i-Pr fentanyl, and (++)-cis-3-Phen fentanyl, are inactive in doses up to 5 mg/kg (Table 1) [45]. Contrary to this, the duration of action of 3-alkyl fentanyl analogs, generally does not depend on the voluminosity of alkyl group (Table 1) [50].

- The relative cis/trans stereochemistry is important since the cis isomers are 1.5-6 times more active than the trans isomers (Table 1) [45]. However, with the exception of 3-Me fentanyl, and to a certain degree 3-Et fentanyl, the duration of action of equipotent analgesic doses of 3-alkyl fentanyl analogs is not significantly affected by relative stereochemistry (Table 1) [45].
Table 1. Analgesic (Antinociceptive) Activity of Fentanyl Analogs

<table>
<thead>
<tr>
<th>No</th>
<th>Compound (Fentanyl Analog)</th>
<th>$ED_{50}$ (µg/kg) (confidence limits)</th>
<th>Route of administration</th>
<th>Species and test</th>
<th>Potency ratio</th>
<th>References</th>
<th>Duration of action</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fentanyl</td>
<td>11 (9.5 - 14)</td>
<td>iv</td>
<td>Rat TWT</td>
<td>1</td>
<td>[57]</td>
<td>F</td>
<td>[42, 50]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11 (6-18)</td>
<td>ip</td>
<td>Rat TWT</td>
<td>1</td>
<td>[42, 45]</td>
<td>F (50 min)$^b$</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>(±)-cis-3-Me Fentanyl</td>
<td>1.8 (1.3-2.4)</td>
<td>iv</td>
<td>Rat TWT</td>
<td>6.1</td>
<td>[48]</td>
<td>&gt;F (90 min)$^b$</td>
<td>[50]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.3 (1.2-1.4)</td>
<td>ip</td>
<td>Rat TWT</td>
<td>8</td>
<td>[45]</td>
<td>≥ F (60 min)$^b$</td>
<td>[50]</td>
</tr>
<tr>
<td>3</td>
<td>(±)-trans-3-Me Fentanyl</td>
<td>9.4 (7-12.7)</td>
<td>iv</td>
<td>Rat TWT</td>
<td>1.17</td>
<td>[48]</td>
<td>= F (40 min)$^b$</td>
<td>[50]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.25 (4-6)</td>
<td>ip</td>
<td>Rat TWT</td>
<td>1.98</td>
<td>[45]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(−)-cis-3-Me Fentanyl</td>
<td>68 (51-91)</td>
<td>iv</td>
<td>Rat TWT</td>
<td>0.16</td>
<td>[48]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>(+)-cis-3-Me Fentanyl</td>
<td>0.58 (0.49-0.68)</td>
<td>iv</td>
<td>Rat TWT</td>
<td>18.97</td>
<td>[48]</td>
<td>&gt;F</td>
<td>[48]</td>
</tr>
<tr>
<td>6</td>
<td>(±)-cis-3-Et Fentanyl</td>
<td>6.8 (2.6-18)</td>
<td>ip</td>
<td>Rat TWT</td>
<td>1.49</td>
<td>[45]</td>
<td>≥ F (60 min)$^b$</td>
<td>[50]</td>
</tr>
<tr>
<td>7</td>
<td>(±)-trans-3-Et Fentanyl</td>
<td>11.6 (11-12)</td>
<td>ip</td>
<td>Rat TWT</td>
<td>0.9</td>
<td>[45]</td>
<td>= F (40 min)$^b$</td>
<td>[50]</td>
</tr>
<tr>
<td>8</td>
<td>(±)-cis-3-allyl Fentanyl</td>
<td>80$^c$</td>
<td>iv</td>
<td>Rat TWT</td>
<td>0.138</td>
<td>[2, 49]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>(±)-cis-3-Pr Fentanyl</td>
<td>20$^+$</td>
<td>iv</td>
<td>Rat TWT</td>
<td>0.55</td>
<td>[2, 49]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>(±)-trans-3-Pr Fentanyl</td>
<td>40$^+$</td>
<td>iv</td>
<td>Rat TWT</td>
<td>0.275</td>
<td>[49]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>(±)-cis-3-i-Pr Fentanyl</td>
<td>no activity in doses up to 5000 µg/kg</td>
<td></td>
<td>Rat TWT</td>
<td></td>
<td>[45]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>(±)-cis-3-Bu Fentanyl</td>
<td>162 (82-320)</td>
<td>ip</td>
<td>Rat TWT</td>
<td>0.064</td>
<td>[45]</td>
<td>≥ F (50 min)$^b$</td>
<td>[50]</td>
</tr>
<tr>
<td>13</td>
<td>(±)-trans-3-Bu Fentanyl</td>
<td>348 (181-669)</td>
<td>ip</td>
<td>Rat TWT</td>
<td>0.03</td>
<td>[45]</td>
<td>= F (50 min)$^b$</td>
<td>[50]</td>
</tr>
<tr>
<td>14</td>
<td>(±)-cis-3-Bn Fentanyl</td>
<td>1310 (700-2460)</td>
<td>ip</td>
<td>Rat TWT</td>
<td>0.0079</td>
<td>[45]</td>
<td>= F (50 min)$^b$</td>
<td>[50]</td>
</tr>
<tr>
<td>15</td>
<td>(±)-trans-3-Bn Fentanyl</td>
<td>1910 (390-9400)</td>
<td>ip</td>
<td>Rat TWT</td>
<td>0.0054</td>
<td>[45]</td>
<td>= F (50 min)$^b$</td>
<td>[50]</td>
</tr>
<tr>
<td>16</td>
<td>(±)-cis-3-Phen Fentanyl</td>
<td>no activity in doses up to 5000 µg/kg</td>
<td></td>
<td>Rat TWT</td>
<td></td>
<td>[57]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>(±)-cis-3-carbomethoxy Fentanyl</td>
<td>23 (9-60)</td>
<td>ip</td>
<td>Rat TWT</td>
<td>0.48</td>
<td>[40, 42]</td>
<td>&lt;F (30 min)$^b$</td>
<td>[40, 42]</td>
</tr>
<tr>
<td>18</td>
<td>(±)-trans-3-carbomethoxy Fentanyl</td>
<td>100 (50-190)</td>
<td>ip</td>
<td>Rat TWT</td>
<td>0.11</td>
<td>[40, 42]</td>
<td>&lt;F (20 min)$^b$</td>
<td>[40, 42]</td>
</tr>
<tr>
<td>19</td>
<td>Carfentanil (4-carbomethoxy Fentanyl)</td>
<td>0.41 (0.29 - 0.58)</td>
<td>iv</td>
<td>Rat TWT</td>
<td>26.8</td>
<td>[57]</td>
<td>&gt;F</td>
<td>[6]</td>
</tr>
<tr>
<td>20</td>
<td>4-methyl Fentanyl</td>
<td>2.8 (2.3-3.3)</td>
<td>ip</td>
<td>Rat TWT</td>
<td>3.8</td>
<td>[41]</td>
<td>&gt;F</td>
<td>[41]</td>
</tr>
<tr>
<td>21</td>
<td>Morphine</td>
<td>3150 (2820 - 3520)</td>
<td>iv</td>
<td>Rat TWT</td>
<td>0.0035</td>
<td>[57]</td>
<td></td>
<td>[57]</td>
</tr>
</tbody>
</table>

$ED_{50}$ values refer to the free bases of the tested compounds and are expressed in µg per kg of body weight; iv=intravenous; ip=intraperitoneal. $^c$Confidence limits not reported. $^b$Duration of action (in minutes) obtained after iv administration $ED_{50}$, (the least dose that produce the maximum analgesic effect); Duration of action $>$ (greater) $\simeq$ (similar) $<$ shorter compared to fentanyl (F). - No available data ; TWT=Tail Withdrawal Test.

Note: The observed $ED_{50}$ (µg/kg) values for a given compound often vary substantially (2-10 times), depending upon various factors such as the type of test, criterion used to define analgesia, route of drug administration, experimental conditions, species and strain of experimental animals and others. However, if all measurements are done under the same conditions, reliable results for the relative analgesic activity (i.e., potency ratio) are usually obtained. In this regard, we use potency ratio to compare the results taken from different laboratories.
The absolute stereochemistry appears to be critical, judging from the fact that (+)-cis-3-Me fentanyl is about 100 times more active than the (-) enantiomer. Due to insufficient data on duration of action of (+) and (-) enantiomers of 3-alkyl analogs, the influence of absolute stereochemistry on duration of action cannot be determined (Table 1).

At equianalgesic doses, more potent 3-alkyl analogs ((±)-cis-3-Me fentanyl and (±)-cis-3-Et fentanyl) exhibit longer duration of action in comparison to fentanyl and less potent 3-alkyl analogs. This finding might suggest that duration of action is more likely influenced by pharmacodynamic, than pharmacokinetic variables, as it has been already shown in the cases of (±)cis 3-methyl fentanyl [51-53], buprenorphine [54-55], etc.

From the aspect of SAR studies, it was interesting to introduce some functional groups in the position 3 of the piperidine ring. In an earlier paper, the regioisomer of carfentanyl Fig. (1) (Table 1), 3-carbomethoxy fentanyl, or "iso-carfentanil" Fig. (2) was prepared and tested for analgesic activity [40, 42]. It was found that the introduction of a carbomethoxy group in position 3 of the piperidine ring of fentanyl decreased antinociceptive activity by a factor of 2 and 10 in (±)cis and (±)trans 3-carbomethoxy fentanyl, respectively (Table 1). It is evident that 3-carbomethoxy fentanyl is far less active than 3-methyl and 3-ethyl fentanyl [45, 48]. Otherwise, it seems that (±)cis 3-carbomethoxy fentanyl is equipotent to the (±)cis 3-propyl fentanyl and exceeds the potency of (±)cis 3-allyl fentanyl, (±)cis 3-buty1 fentanyl, and (±)cis 3-benzyl fentanyl [45]. In addition, since no functionality is present in the 3-propyl fentanyl, the observed similarity in antinociceptive potency would result exclusively from the similar voluminosity of the 3-carbomethoxy and 3-propyl group. Also, the potency of (±)cis and (±)trans 3-carbomethoxy fentanyl is in agreement with SAR of 3-alkyl fentanyl analogs, since the cis isomer is about 4 times more active than the trans isomer (Table 1). Consequently, it seems that a steric factor (voluminosity of the group and the cis/trans isomerism) has a predominant role in the antinociceptive potency of 3-substituted fentanyl analogs, while the nature of the substituent is probably irrelevant. Furthermore, based on the available information on the pharmacological properties of 4-carbomethoxy fentanyl, it is evident that (±)cis 3-carbomethoxy fentanyl is considerably (about 60 times) less potent in comparison with its regioisomer, carfentanil. Here again, the influence of the steric factor has been confirmed, since there is no difference in functional groups between 3-carbomethoxy and carfentanil (4-carbomethoxy fentanyl). Therefore, the antinociceptive potency of fentanyl analogs substituted in the position 3 of the piperidine ring is independent of the nature of the substituent group, i.e., it is influenced by the steric factor only.

At the doses that produce comparable changes in the antinociceptive response measures (e.g. ED$_{99}$), (±)cis and
(±)trans 3-carbomethoxy fentanyl produced effects which were substantially shorter compared to the effects produced by fentanyl and its 3-alkyl analogs, including 3-Pr fentanyl (Table 1) [50]. Also, there is no difference between cis and trans isomers regarding duration of effect. These findings are in agreement with the results of SAR studies obtained with 3-alkyl fentanyl analogs.

Therefore, it might be concluded that the duration of action of fentanyl analogs substituted in the position 3 of the piperidine ring is not significantly influenced by stereochemistry (i.e. voluminosity of the group and cis/trans isomerism). At present, we can only speculate that differences in the physicochemical characteristics and/or metabolism are responsible for the shorter duration of action of 3-carbomethoxy fentanyl. It has already been observed that the more hydrophilic or ionized substituents lead to analgesics with less lipid solubility (lower partition coefficients), little or no accumulation in fat tissues, and rapid excretion [56]. Therefore, in contrast to potency, the influence of chemical nature of the carbomethoxy group upon the duration of antinociceptive activity is more probable. For example, the shorter duration of action of 3-carbomethoxy fentanyl could be due to susceptibility of the carbomethoxy group to rapid hydrolysis by non-specific esterases, as is the case with the ultra-short-acting fentanyl analog remifentanil [11]. Specifically, carbomethoxy group undergoes rapid hydrolysis by plasma and tissue esterases in the tail of N-alkyl substituent of remifentanil, which provides the ultrashort action of this compound. On the other side, it is well known that series of super potent fentanyl analogs with carbomethoxy group in the position 4 of the piperidine ring (e.g. carfentanil, lofentanil, sufentanil), exhibit diverse durations of action [4, 6, 8]. Since, 4-methyl fentanyl (Table 1) also possesses long action compared to fentanyl [41] these finding indicate that the functionality of the group has no impact on the duration of the action of 4-substituted fentanyl analogs. It might be possible that carbomethoxy group in the position 3 is less susceptible to hydrolysis than in the tail of N-alkyl substituent of remifentanil. In the position 4 of the piperidine ring it might be somehow completely steric protected, and therefore its ester nature is irrelevant for the duration of action of the compound. It appears that the chemical nature of the substituent in the position 4 of the piperidine ring of fentanyl, also has little influence on potency, since groups as diverse as carbomethoxy, methoxymethyl, hydroxymethyl, methylketone, methyl and aryl, all cause significant rise (2-30 times) in potency compared to fentanyl [29, 41, 57]. Finally, it appears that the analgesic activity in this series of anilidopiperidines is influenced only by the steric requirement and not by the chemical nature of the substituent in the position 4 of the piperidine ring.

NEUROTOXICITY OF FENTANYL ANALOGS
Substituted in the Position 3 of the Piperidine Ring

In accordance with the experiments performed using fentanyl in rats [58-59] the side effects of fentanyl analogues substituted in the position 3 of the piperidine ring (Table 1) are morphine-like; i.e., characterized by stiffness of the tail, rigidity of the skeletal muscles, catalepsy, loss of righting reflex, increased and/or decreased body temperature, etc.

Doses that are 2—3 times higher than those required to produce complete block on the tail-withdrawal test were commonly associated with a loss of pinna reflex and tail stiffness, while much higher doses produced a significant increase in the incidence of other toxic effect that mostly appeared in the following order: loss of motor coordination, catalepsy, trunk rigidity, loss of the corneal reflexes and loss of righting reflex [59-61]. Also, in preliminary testing, it has been revealed that the relative potencies that produce neurotoxic effects of fentanyl analogues substituted in position 3 of the piperidine ring are similar to the relative potencies used to induce analgesia [59-63]. Also, there are no significant differences between the relative duration of antinociceptive and toxic effects among this series of fentanyl analogs. Therefore, SAR findings obtained by evaluating the neurotoxic effects of fentanyl analogs substituted in the position 3 of the piperidine ring parallels the SAR findings on analgesia in regard to potency and duration of action. This might suggest that similar receptors are involved in producing both antinociceptive and neurotoxic effects of these drugs. All of the observed effects were fully antagonized by the nonselective opioid antagonist naloxone, which corroborates the hypothesis that the tested compounds are opioid agonists, most likely acting predominantly on μ opioid receptors.

FUTURE DEVELOPMENT OF OPIOID ANALGESICS

Among the important properties of the opioids that can be altered by structural modification are their affinities for various types of opioid receptors, activities as agonists versus antagonists, lipid solubilities, and their susceptibility/resistance to metabolic breakdown.

Most of the currently available opioid analgesics exert their analgesic and adverse effects primarily through the opioid μ receptors. However, it is well known that “opioid rotation” can be beneficial for some patients after an opioid therapy loses efficacy or becomes associated with intolerable side effects [64-66]. The clinical success of “opioid rotation” likely involves pharmacokinetic and/or pharmacodynamic factors both of which may be subject to pharmacogenomic influence. For example, individual strong opioids may interact, at least in part, with different opioid receptor subpopulations or modulate μ opioid receptor signaling in subtly different ways [12-13, 15, 20]. Identification of novel μ opioid splice variants with different intron 1 sizes that heterodimerize with, and modulate the function of, native μ opioid receptors provide insight into potential diversity in opioid signaling [67]. Opioid analgesic combinations administered as tethered bivalent ligands or admixture, demonstrate good pain relief with improved side effect profiles [18, 68-70].

Enhanced understanding of diversity in opioid signaling has the potential to produce novel strong opioid analgesics with improved tolerability. Also, an array of new drug formulations and delivery systems (e.g. transdermal delivery systems, controlled-release enteral and epidural drug encapsulated technologies, oral concentrated elixirs, lozenges, buccal tablets, inhalable nasal agents, etc.) have been developed that may help further individualization of analgesic regimens for those patients who have both acute and chronic pain.
CONCLUSION

In conclusion, the antinociceptive potency of 3-substituted fentanyl analogs is independent of the nature of the substituent group, i.e., it is influenced by the steric factor only. Generally, the duration of action does not depend on the stereochemistry. However, it is possible that the introduction of a functional group, such as 3-carboxemthoxy, affects duration of action by altering pharmacokinetic properties. It appears that the analgesic activity in the series of fentanyl analogs substituted in the position 4 of the piperidine ring is influenced only by the steric requirements of a group, rather than its chemical nature.

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