TILIDINE: A SPECIAL SUBSTANCE

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Abstract

With a production capacity of 40 tons a year, tilidine represents one of the most important prescribed analgetics. This review deals with its synthesis, its biological effect and the social consequences of a pharmaceutical substance, that is on the one side a very successful analgetic and on the other side a more and more popular "drug".

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1 In general

Tilidine belongs to the class of the completely synthetically produced opioid-analgetics. It constitutes the main active ingredient of the medicinal product Valoron® N., developed and launched by the German pharmaceutical concern Goedecke AG in the early 1970s. Nowadays the Goedecke AG belongs to the distributive channel of Pfizer. In addition to the original medicinal product there are some generic drugs available, e.g. Tiliador® (Hexal) Valomerck® (Merck) Gruntin® (Gruenenthal) Tilidine was erroneously considered to be the first fully oral resorbable and basically non-addictive opioid-analgetic without any benumbing effect concerning the respiration and the intestinal tract. These results based on animal and human experiments. [1] [2] [3]

2 Chemical aspects

2.1 Basical data

IUPAC-Name: (1S/R,2R/S)-Ethyl-2-(N,N-dimethylamino)-1-phenylcyclohex-3-ene-1-carboxylate[6]
Molecular weight: 273.37002 g mol[6]
Molecular formula: C_{17}H_{23}NO_{2} [6]
Melting point: 159°C (Tilidine-HCl) [4]
Lethal dose (rat): LD_{50} oral: 412 mg/kg [13]
LD_{50} intravenous: 74 mg/kg [13]
CAS-number: 20380-58-9 (Tilidine)
27107-79-5 (Tilidine-HCl)
2.2 Chemical structure

Tilidine belongs to the chemical class of the cyclohexene derivatives. The main central structure, the cyclohexene, is substituted by a phenyl- and an ethyl carboxylat-substituent in position 1 and by a N,N-dimethylamino-substituent in position 2. Caused by the 2 stereogenic centers there are 4 stereoisomers, whereas only the 2 enantiomers with (1S, 2R) - and (1R, 2S) – configurations are used medically and can be joined under the name “tilidine”. In contrast to the specified enantiomeric pair, the diastereomeric forms with (1R, 2R) – and (1S, 2S) – configurations have no or only weak analgesic properties. [1]

In 1969 respectively 1971 the Goedecke AG research institute conducted the total determination of the molecular structure in a chemical way as well as by using mass -, infrared -, spectrometric -, NMR- and UV- spectrometric research.[1] [2] Depending on the experimental conditions tilidine is able to crystallize anhydrous or with 0.5 mol H₂O. Furthermore a crystallization to Tilidine-hydrochloride with HCl is possible.

Remarkably tilidine (5) is used as a racemate for medical application. Because of this reason it is necessary to have a closer look at both structures of the enantiomeric pair.

**Figure 1:** (1S,2R)-Ethyl 2-(N,N-dimethylamino)-1-phenylcyclohex-3-ene-carboxylate

**Figure 2:** (1R, 2S)- Ethyl 2-(N,N-dimethylamino)-1-phenylcyclohex-3-ene-carboxylate
2.3 Synthesis

Tilidine shows a structural similarity to the formerly synthesised agents pethidine and prodine also belonging to the heterogeneous class of opioid-analgetics. In this way the main purpose of synthesising tilidine was to create new analgesic drugs whose potency was predictable by its chemical structure.\textsuperscript{[1]}

The synthesis of tilidine was firstly described by G. Satzinger in 1969. The main step of synthesis consists of a Diels-Alder-Reaction ([2+4] cycloaddition). The educts of this reaction are ethyl atropate (ethyl methylenephenylacetate) (4) as the dienophile and the electron-rich trans-1-dimethylamino-1,3-butadiene (3) as the diene. The cycloaddition of ethyl atropate with 1,3-butadiene was not realisable because of the weak activating influence of the ethyl carboxyl-substituent on the double bond of the dienophile. Therefore an introduction of a strong activating group, as a N,N-dimethylamino (2) function, in the diene was absolutely necessary. The synthesis of trans-1-dimethylamino-1,3-butadiene (3) can be achieved by an addition-substitution-reaction of crotonaldehyde (1) with N,N-dimethylamine. (2) \textsuperscript{[1]} \textsuperscript{[2]} \textsuperscript{[3]}

According to G. Satzinger the dielectric-coefficient of the solvent has no influence on the ratio of the appearing stereoisomers, whereas the spatial requirements of the substituents of the diene and the dienophile is the determining factor.\textsuperscript{[1]} The reaction period takes about 15h at 20°C.\textsuperscript{[1]} Under these conditions a total rate of yield of 87% of cyclohexene derivatives can be reached. Admittedly, with a ratio of 3:1, the main product of this cycloaddition reaction is the enantiomeric pair with its (1S, 2S)- and (1R, 2R)- forms, whereas the favoured (1S, 2R) - and (1R, 2S) – configured enantiomeric pair just appears as a secondary product.\textsuperscript{[1]} The main reason for this ratio of products seems to be the stronger sterical hindrances between the phenyl-substituent of the dienophile and the dimethylamino-function of the diene in contrast to the lower appearing sterical hindrances between the ethyl carboxylat-substituent of the dienophile and the dimethylamino-function of the diene in the transition state.
2.3.1 Steps of synthesis

1. Manufacture of trans-1-dimethylaminobuta-1,3-diene (3):

\[
\text{H} + \text{N} \rightarrow \text{N}
\]

Figure 3: (1) \hspace{1cm} Figure 4: (2) \hspace{1cm} Figure 5: (3)

2. Diels-Alder-reaktion between dimethylaminobuta-1,3-diene (3) and ethyl atropate (4):

\[
\text{N} + \text{O} \rightarrow \text{N}
\]

Figure 6: (3) \hspace{1cm} Figure 7: (4) \hspace{1cm} Figure 8: (5)

2.4 Reprocessing and chemical cleaning

The separation of the generated diastereomeric forms is achieved by precipitation with chiral zinc complexes. \(^\text{[4]}\)

In 1979 the Goedecke AG filed a patent for the separation of the racemates. The need of such a separation consists in the different analgesic potency of the medically used enantiomeric pair. In this way the D(+)-tilidine and its crystalline forms show twice as much an analgesic potency compared to the racemic mixture, whereas the LD\(_{50}\) is nearly comparable.

The separation of the racemates is carried out with D(+)-tartrate. In an adequate solvent a formation of a hardly soluble salt with L(-)-tilidine can be observed. After the distillation of the solvent and the desiccation there rests a residue with an enantiomeric excess of D(+)-tilidine of 60-90\%. In a following procedure a crystallization of D(+)-tilidine in a pure constitution in alcoholic or aliphatic solvent at low temperatures (\(<0\text{°C}\)) takes place, whereas the racemate remains in salvation.\(^\text{[5]}\)
3 Biological effect of tilidine

3.1 Tilidine and its metabolites

Tilidine proved to be a potent analgetic that is easily absorbed and has a wide area of application.\textsuperscript{[1]} As a matter of fact it is not tilidine itself but its metabolites nortilidine and bisnortilidine which evoke the analgetic effect.\textsuperscript{[8][7]} Up to the present, the effect of tilidine, nortilidine and bisnortilidine were studied, although there is no sufficient data for bisnortilidine.

\begin{figure}[h]
\centering
\includegraphics[width=0.3\textwidth]{tilidine.png}
\caption{Tilidine}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=0.3\textwidth]{nortilidine.png}
\caption{Nortilidine}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=0.3\textwidth]{bisnortilidine.png}
\caption{Bisnortilidine}
\end{figure}

The difference between tilidine and nortilidine is the demethylation of the tertiary amine-function, whereas a double demethylation leads to bisnortilidine. Further research into the biological action made it certain, that tilidine and its metabolites take effect in the so called $\mu$-receptors. These receptors are located presynaptically where they take control on the pain perception via an enzymatical cascade with cAMP as the main second messenger. Thierry et al. were able to prove that tilidine and its metabolites only occupy the $\mu$-receptors. Furthermore, nortilidine has a hundredfold stronger action compared to tilidine and also a significant stronger action compared to bisnortilidine.\textsuperscript{[9]} So nortilidine is similar to the well-known $\mu$-receptor agonists morphine and DAMGO. According to these results, it is justified to classify tilidine as a prodrug, because tilidine itself shows only a limited analgetic impact. One question left to answer was the enzymatical degradation of tilidine.

The research group of Weiss et al. finally found out, that tilidine is metabolised by the enzymatical superfamily of cytochrome P450 (CYP).\textsuperscript{[10]} This superfamily possesses a heme-cofactor with enzymatically activity and plays a major role in multiple metabolising reactions of other opioid substances. The substrates of the enzymatical group of CPY often include metabolic intermediates. CYPs are considered as the major enzymes involved in drug metabolism, nearly accounting for 75% of the total metabolism. The analgetic effect of tilidine was firstly demonstrated by assays with naloxone. Naloxone is a pure opioid antagonist and inhibits competitively
all opioid receptors. The main clue was that naloxone also indicated an inhibition of tilidine and nortilidine.

3.2 Tilidine and the Michaelis-Menten-Kinetics

Beside the inhibition with naloxone, it was also evaluated, that the metabolism of tilidine follows a Michaelis-Menten kinetic with a $K_M$ value of $36 \pm 13 \mu$M and a $V_{max}$ value of $85\pm 18 \frac{nmol}{mg h}$. The Michaelis-Menten kinetic is the basis theory of enzymatic kinetics and describes a term that represents the reaction rate subject to the two quantities $\mu$M and the maximum reaction rate $V_{max}$. Whenever a metabolic reaction follows a Michaelis-Menten kinetic with characteristic values, the chance is high to postulate that enzymes are involved in this step.

Different enzymatic inhibitors were used to determine the involved enzymes, like voriconazole, ritonavir, miconazole and ketoconazole. These inhibitors are well-known inhibitors of two sub enzymes of the enzymatical superfamily CYP: CYP3A4 and CYP2C19. The result was that these inhibitors inhibit also the N-demethylation of tilidine, indicated by a significant increase of nortilidine, because tilidine and nortilidine can not be metabolized any more. So both sub enzymes, CYP3A4 and CYP2C19, are catalyzing the metabolic reactions, that lead from tilidine via nortilidine to bisnortilidine and yet unknown polar substances. Latest research results have confirmed these findings, showing that voriconazole (a novel triazole antifungal agent) is in competition with tilidine and inhibits its metabolism almost totally.

"Voriconazole inhibits both metabolic steps in the sequential metabolism of tilidine, resulting in an increased exposure of the active nortilidine. Furthermore, the number of ADEs doubled after administration of these two drugs in typically used clinical doses. Therefore we recommend avoiding the combination of tilidine/naloxone and voriconazole in clinical practice"

Barbara Gruen et al.

According to the hundredfold stronger action of its metabolite nortilidine, it seems fair enough to call tilidine a prodrug, that is quickly metabolized through enzymatic action in a so called
“first-pass metabolism” in the liver to nortilidine and bisnortilidine\textsuperscript{[12]}. From the original dose two-thirds are metabolized to nortilidine and again one-third to bisnortilidine. With this at least one-third of the original dose is available in the active form nortilidine. Nortilidine itself is quickly transported and distributed throughout the blood and passes easily the blood-brain barrier after what it can interacts with the opioid µ-receptor.

3.3 Application and pharmaceutical form

Being a potent analgetic with good absorption properties, a fast launching effect and striking potency, tilidine became a widespread pharmaceutical, exerted to fight heavy aches. At the same time Goedecke misleadingly promoted Valoron\textsuperscript{®} as the first oral absorbable and especially non-addictive analgetic without a paralyzing effect on respiration and intestine. Because of this tilidine soon was used to decrease withdrawal symptoms of opium abuse, which made it an alternative drug for consumers. Tilidine can be applied parenterally, intravenously and as a intramuscular remedy but most common are pills and liquid variants which are mainly used for oral application and represent the most popular dosage form. Naloxone, an opioid antagonist is added to medicinal tilidine in order to inhibit its effect completely if the pharmaceutical is used in a high dosage for abuse.\textsuperscript{[1][13]}

In case of a normal exhibition of tilidine, naloxone gets completely catabolised similar to tilidine in a “first-pass metabolism” at the liver and stopped from unfolding its antagonistic effect. Just if tilidine is taken as an overdose, in case of abuse for example, naloxone starts working as a competitive inhibitor at the opioid receptors because its accumulation caused by the saturation of a important enzyme in the liver which is responsible for degradation of the opioid antagonist.\textsuperscript{[4][13]}

Tilidine can be administered both orally and intravenously.\textsuperscript{[14]}
<table>
<thead>
<tr>
<th>Substance</th>
<th>Oral biological availability [%]</th>
<th>Plasma half-value period [h]</th>
<th>Protein binding [%]</th>
<th>Dose/interval of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tilidine with naloxone</td>
<td>Hepatic biotransformation to pharmacologic active nortilidine (100 %)</td>
<td>4</td>
<td>25</td>
<td>p.o retard form: 100(200mg) 12-(8-) hourly non retarded: 50(-100)mg up to 2- to 3-hourly as needed (no exclusive therapy chronical pain!) maximum/day 600mg</td>
</tr>
</tbody>
</table>

4 Abuse of tilidine

"Unrestrained Violence. Designer-drug makes youngsters go berserk" - that's the heading of an article about the pharmaceutical tilidine, Spiegel Online came up with. But what makes the actual pain reliever a drug, which becomes more and more popular these days? Tilidine is mainly used for the treatment of tumor-diseases or heavy burns, and is considered as a very strong pain-killer, it's power is 0.16-0.19 in comparison to morphine (which means it has one fifth of the analgetic efficacy). In addition to the anesthesia tilidine has an euphoric effect, inhibits trepidation and lowers the inhibition threshold of the consumer. According to this facts, another statement of Spiegel Online says:"A consumer of tilidine is cold-blooded, free of pain and ready to mug other teenagers, win a fight or commit robbery at a filling station." An interesting aspect of this drug is its attractiveness especially to young people with Arabic ancestry. In the Islam drugs are forbidden but medicine is not, because of that Muslims can legitimate the abuse of tilidine in front of uninformed parents or even in front of their own conscience. Also the purchase of this drug pushes its popularity. It is less risky and much easier in comparison to other drugs like cocaine or heroin regarding the legal facts.

In section 3 of German Narcotics Law (BtMG), tilidine is listed as marketable and available on prescription only, which means that violation is treated like dealing with illegal drugs is. There is also the Narcotics Book where the prescription of pure tilidine has to be documented and justified by the doctor. In contrast, the purchase of tilidine combined with naloxone is a little bit different. Due to the fact that naloxone inhibits the striking effect of tilidine, this composite is not controlled by the Narcotics Law. That means that only a prescription of a doctor is needed,
without an journalization in the Narcotics Book, to get tilidine from the apothecary and that violation is only treated as forgery. A prescription is available at the doctor for 5 euro and at the black market for 60 euro. An important fact is that naloxone only inhibits 60% of the tilidine and that the property is not illegal.\[19\]

Obtained and ingested, tilidine begins to unfurl its addictive power, another effect which is typical for a heavy drug. Addicted to this pharmaceutical, consumers can hardly escape the grip of it. That’s why the Tagesspiegel quotes Mrs. Constanze, member of the Ärztekammer Berlin: "A big problem is the addictive potency. Mental addiction comes very quick, consuming it even triggers physical addiction. Tilidine would free you from any fears, you’ll become more willing to take risks and you’ll feel euphoric and uninhibited." The power of this effect is appears in the reaction of Berlin’s prevention programs, which caution against the abuse of tilidine and instituted a homepage.

Facing all this aspects, especially tilidine’s violence boosting effect, its obvious that tilidine is not just a problem for doctors and prevention anymore, but that it has reached the streets and is threaten the police. Tilidine was involved in several conflicts in the past and especially when the police had to deal with violent tilidine-consumers this was present in the media which began to focus more and more on this issue. The Spiegel published an article where some police officers voice their worries concerning this drug. Tilidine consumers are free of pain and fears and, combined with a certain social background they can become extremely violent, which makes a normal seizure walking a tightrope. Chief inspector Andreas Wolter for example is describing a tilidine-consumer’s resistance like this: "Like a berserk - he is kicking, biting, spitting and he isn’t sensitive to pepperspray". According to this, tilidine is also known as "the Amokdrug" to the police. Coming under the influence of tilidine, normal painful policegrips won’t work, officers would even have to brake a consumer’s arm to have him under control. Famous examples of tilidine abuse are Mike.P, the knifer who attacked people at the opening of Berlin’s central station, or Robert Steinhäuser, the person running amok at Erfurt, Germany (April 26, 2002). At the end it becomes evident, that tilidine has made his way from a normal medicine to a very dangerous drug which is mainly used in big cities an which should not be underrated. Unfortunately it will go on producing bad news in the media and being a threat to urban society. [15][16][17][18]
References


[5] Deutsche Patentschrift 2261462


