

Article

How Toxic indeed is Oxymetazoline? Collection and Comparison of Toxicological Data of Pharmacologically Active Imidazoline Derivatives

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Abstract. Imidazoline derivatives, such as xylometazoline, naphazoline, tetryzoline, tramazoline or oxymetazoline play an important pharmacological role as nasal drops in the symptomatic treatment of rhinitis. When comparing the toxicological data of these substances, it is noticeable that Oxymetazoline has an LD₅₀ value which is two orders of magnitude lower than all other imidazoline derivatives. Thus, ten vials of commercially available oxymetazoline nasal drops already contain a lethal amount. An explanation for this unusually high toxicity has not yet been found.

Keywords. LD₅₀, lethal Dose, Xylometazoline, Oxymetazoline, Imidazoline Derivatives

1. Introduction

Many imidazoline derivatives are basic substances for pharmaceutical products. In 1941, the pharmacological effect of imidazoline derivatives was discussed for the first time on mucous membranes [1]. In 1955, Sahyun Labs secured several synthetic routes for imidazoline derivatives, including the tetryzoline [2]. Xylometazoline was first produced by A. Hüni in 1959 [3]. This was followed by the synthesis of oxymetazoline by W. Fruhstorfer and H. Müller-Calgan in 1961 [4]. Since the decongestant effect of oxymetazoline for the nose lasted longer than with other imidazoline derivatives, an oxymetazoline product was part of the on-board pharmacy of Apollo 11 on its way to the moon in 1969 [5].

Nowadays, the imidazoline derivatives xylometazoline, tramazoline, naphazoline, tetryzoline and oxymetazoline are important drugs for nasal decongestion and as ingredients for eye drops. As α -sympathomimetics, these substances (Figure 1.) are α_1 -adrenoceptor agonists. They are also used in ophthalmology to treat allergic forms of conjunctivites. It binds to the same receptors as adrenaline. In order to reduce nasal congestion during a cold, these substances have started their worldwide triumphal march in over-the-counter nasal drops. An antiviral effect has also been found in oxymetazoline. Viruses find fewer entrance gates to the nasal mucous membrane [6]. Oxymetazoline thus reduces the duration of nasal congestion by 30 % [7]. Since the imidazoline derivatives also have a systemic effect, they should not be used in the case of hypertension or heart diseases. Common symptoms are also burning or dryness of the nasal mucosa. Also remarkable with these materials is the privity. A five-day use already results in a so-called nasal drop addiction. Withdrawal from the medication leads to congestion of the mucous membrane and thus an increase in psychological strain, so that permanent damage of the mucous membrane and bark formation are the consequences of chronic use [8].

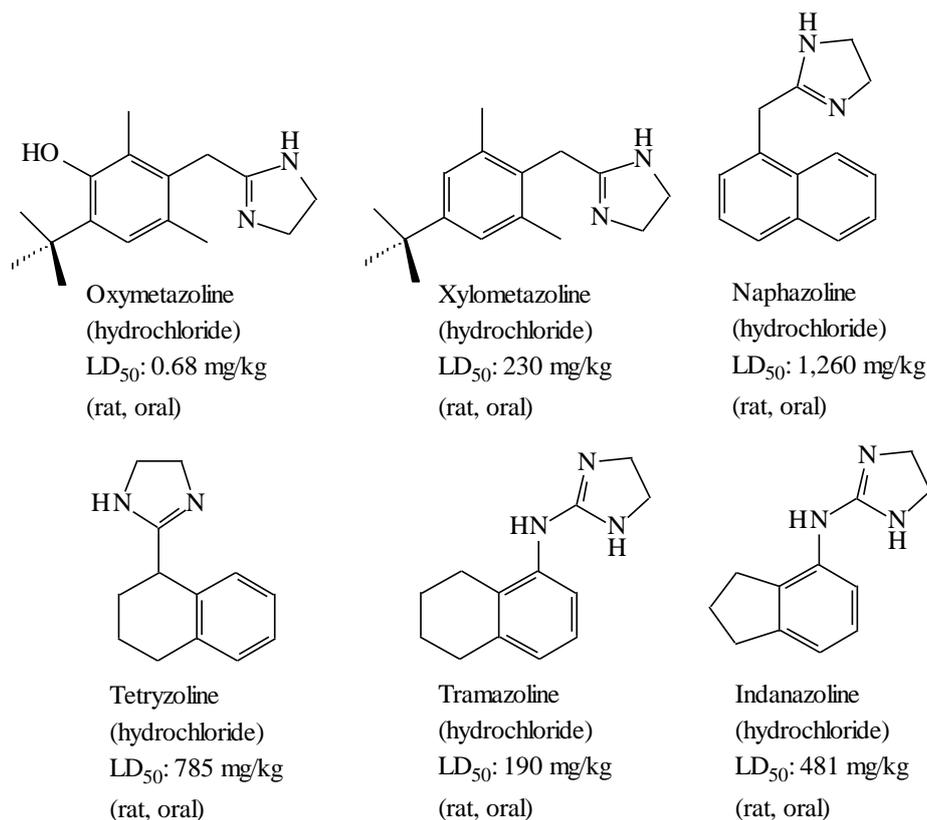


Figure 1. Structure and LD₅₀ values of a few imidazoline derivatives

2. Toxicity

Cases of poisoning by imidazoline derivatives have repeatedly been observed with children [9], [10]. The tenfold 1 ml therapeutic dose of a 0.05 % oxymetazoline solution (about 0.5 mg substance) already caused bradycardia and respiratory depression [11]. Together with alcoholic beverages tetryzoline is often misused as a so-called rape drug [12]. In 2018, there was actually a case in South Carolina, USA, where for three days a wife put large amounts of over-the-counter eye drops with tetryzoline into the drinks of her unfaithful husband. The 64-year old man died and his wife was charged [13]. All known LD₅₀ values of the pharmacologically important imidazoline derivatives are shown in Table 1. The LD₅₀ values of the hydrochlorides of xylometazoline, naphazoline, tetryzoline, indanazoline and tramazoline are between 190 and 1,260 mg/kg for oral administration to rats [14], [15], [16]. Surprisingly, according to Hotovy et al. [17] the LD₅₀ value of oxymetazoline hydrochloride (0.88 mg/kg) is two order of magnitudes lower. It is unusual that at about 1 mg/kg all toxicological data assessed with rats are very similar, no matter whether the administration was subcutaneous, intravenous or oral. For all other imidazoline derivatives the values for subcutaneous and especially intravenous administration are significantly lower than for oral administration. With mice, however, the LD₅₀ values differ significantly, as expected. At 34 mg/kg the LD₅₀ value for oxymetazoline hydrochloride for subcutaneous administration is in the range of the comparable value of xylometazoline.

19 years after Hotovy et al. Worstmann et al. analysed the toxicological characteristics of the new indanazoline and, for comparison purposes, determined on this occasion once more the LD₅₀ values of the hydrochlorides of tramazoline and oxymetazoline. At the same time, in comparison to Hotovy, an even lower LD₅₀ value of 0.68 mg/kg was found in female rats [16]. Worstmann writes that oxymetazoline in female rats is over 700 times more toxic than indanazoline. The LD₅₀ value for the intravenous administration of oxymetazoline hydrochloride to mice is, however, with 11.7 mg/kg in

the range of xylometazoline hydrochloride (12.5 mg/kg) [14], naphazoline hydrochloride (13.2 mg/kg) [21] or tramazoline hydrochloride (11.6 mg/kg). Even with indanazoline hydrochloride, the value found of 22.3 mg/kg is only twice as high. With 22.9 mg/kg, the LD₅₀ value for the oral administration of oxymetazoline hydrochloride to the female mouse is 33 times higher than that of the female rat. Already in 1961 Hotovy et al.'s LD₅₀ values were about 11 times higher for oral administration to mice than to rats.

Table 1. Lethal doses LD₅₀ in mg/kg of imidazoline derivatives

Substance [Ref.]	rat	rat	rat	mouse	mouse	mouse
	oral	s.c.	i.v.	oral	s.c	i.v.
Oxymetazoline HCl						
Hotovy [17]	0.88	1.63	1.07	10	34	5
Oxymetazoline HCl						
Worstmann [16]	0.68			22.9		11.7
Xylometazoline HCl [14]	230	90				12.5
Xylometazoline [18], [19]				180	63	
Naphazoline HCl [15], [20]	1,260	385		265	170	13.2
Naphazoline [21]		200	6		170	16.5
Tetryzoline HCl [23]	785	500	35	345	245	39
Tetryzoline [18], [22]				335	252	48.1
Tramazoline HCl [16]	190			130		11.6
Tramazoline [18]				195	77	
Indanazoline HCl [16]	481		16.3	179		22.3

Oxymetazoline would therefore be more toxic than mercury (II) chloride which has an LD₅₀ value of 1 mg/kg for oral administration to rats [23]. Extrapolated to human beings, the lethal dose of xylometazoline hydrochloride would be about 16.1 g. A 10 ml vial of xylometazoline nasal spray contains 10 mg of the compound. Thus, 1,610 vials would contain the lethal amount which is about the same as the content of a large bucket. On the other hand, 10 vials of oxymetazoline nasal spray (5 mg active substance per vial) with 50 mg oxymetazoline hydrochloride would already contain the lethal dose, the same as the content of a champagne glass.

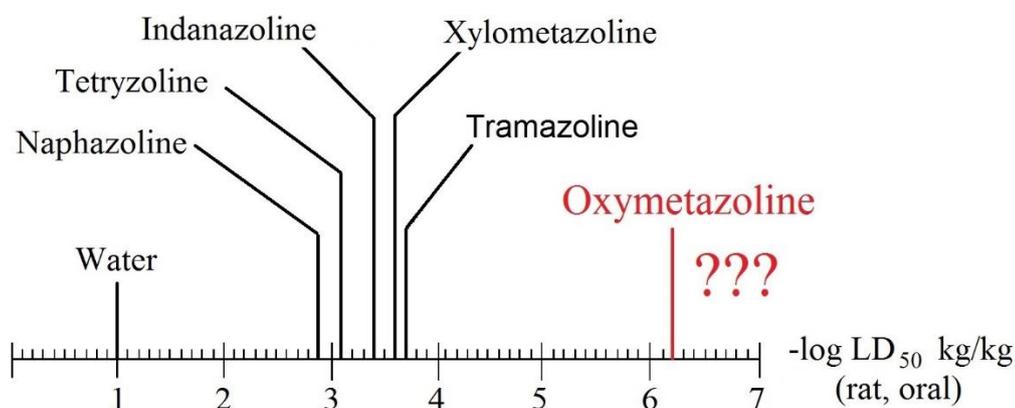


Figure 2. Poison scale [24] of some α_1 -adrenoceptor agonists (HCl) and water [25]

The big difference in toxicity between oxymetazoline and other imidazoline derivatives is shown in Figure 2. by means of the poison scale [24] that shows the negative logarithmic values of LD₅₀. Imidazole and the alpha-blockers tolazoline and phentolamine are three other imidazoline derivatives which are chemically similar to oxymetazoline. Nevertheless, the LD₅₀ values of 220 mg/kg [26], 400 mg/kg [27] and 1,000 mg/kg [28] (Figure 3.) are in the range of xylometazoline or naphazoline. The high LD₅₀ value of phentolamine is quite remarkable, since this molecule also contains a hydroxy function on a benzene ring, as in the probably over 1,000 times more toxic oxymetazoline.

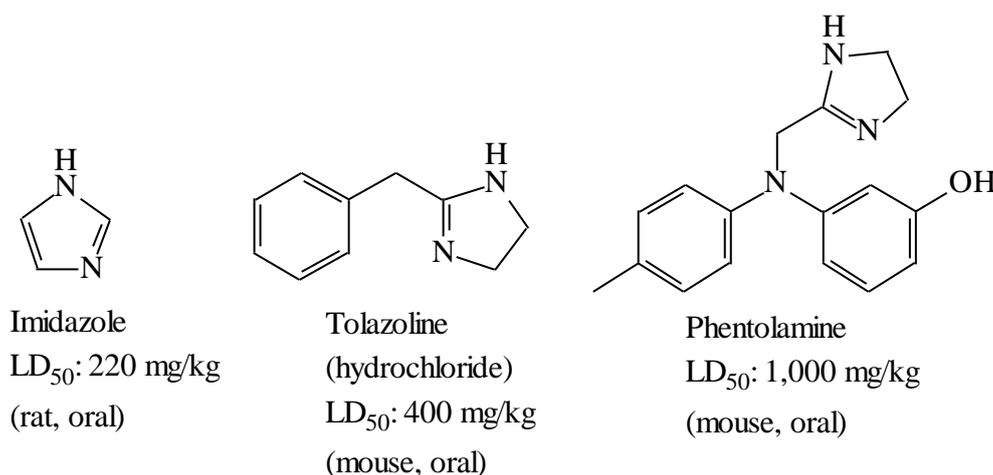


Figure 3. Structure and LD₅₀ values of imidazole, tolazoline and phentolamine

The strikingly low LD₅₀ value of 0.68 mg/kg for the oral administration of oxymetazoline to the rat is reported in several data sheets [29], [30]. Goldenthal collected various toxicological data and indicated the value of 0.8 mg/kg for oxymetazoline [31]. Also the slightly higher Hotovy value of 0.88 mg/kg was found [32]. The higher values for mice remain unconsidered.

3. Conclusion

The comparison with the available toxicological data of other imidazoline derivatives, however, contests the generally accepted LD₅₀ value of 0.68 mg/kg for oxymetazoline hydrochloride. The chemical functions and structure of oxymetazoline do not obviously explain the strikingly high toxicity with rats. Therefore, new toxicological studies should review the data of Hotovy et al. and Worstmann et al. of 1980, correct them, if necessary, or find an explanation for the high toxicity.

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Conflicts of Interest: The author declares there is no conflict of interest.

References

1. Meier, R; Müller, R. Pharmakologische Untersuchungen über eine neuartige Substanz mit anämisierender Wirkung auf den Schleimhäuten. *Schweiz. Med. Wschr.* **1941**, *17*, 554-556.
2. Sahyun, M. US-Patent 2,890,984, Pharmaceutical composition containing 2-(1,2,3,4-tetrahydro-1-naphthyl)imidazoline. **1955**.
3. Hüni, A. Ger. Patent 1,049,387, Verfahren zur Herstellung einer neuen stickstoffhaltigen Verbindung. **1959**.
4. Fruhstorfer, A; Mueller-Calgan, H. Ger. Patent 1,117,588, Verfahren zur Herstellung eines neuen Imidazolinderivates. **1961**.
5. Saiger, C. Krank im All – Weltraumapotheke für alle Fälle. *Pharmazeutische Zeitung* **2009**, *28*, 2588-2595.

6. Koelsch, S; Tschaiquin, M.; Sacher, F. Anti-Rhinovirus-specific Activity of the Alpha-sympathomimetic Oxymetazoline. *Arzneimittel-Forsch.* **2007**, *57*, 475-482. <https://doi.org/10.1055/s-0031-1296635>
7. Reinecke, S.; Tschaiquin, M. Untersuchung der Wirksamkeit von Oxymetazolin auf die Schnupfendauer. *MMW-Fortsch. Medizin.* **2005**, *147*, 113-118.
8. Graf, P. Rhinitis Medicamentosa – a Review of Causes and Treatment. *Treat. Respir. Med.* **2005**, *4*, 21-29. <https://doi.org/10.2165/00151829-200504010-00003>
9. Mahieu, L.M.; Rooman, R.P.; Goosens, E. Imidazoline intoxication in children. *Eur. J. Pediatr.* **1993**, *152*, 944-946. <https://doi.org/10.1007/BF01957538>
10. Neubert, A. Oxymetazolin und Xylometazolin - Gefahr für Säuglinge und Kleinkinder. *Pharmazeutische Zeitung* **2013**, *34*. www.pharmazeutische-zeitung.de/index.php?id=48320
11. Nordt, S.P.; Vivero, L.E.; Cantrell, F.L. Not Just a Drop in the Bucket - Inversion of Oxymetazoline Nasal Decongestant Container Increases Potential for Severe Pediatric Poisoning. *J. Pediatr.* **2016**, *168*, 240-241. <https://doi.org/10.1016/j.jpeds.2015.09.067>
12. Stillwell, M.E.; Saady, J.J. Use of tetrahydrozoline for chemical submission. *Forensic Sci. Int.* **2012**, *211*, 12-16. <https://doi.org/10.1016/j.forsciint.2012.04.004>
13. Betuel, E. How eyedrops were used as a poison in South Carolina murder case. *Inverse*, September 4th. **2018**. inverse.com/article/48622-eyedrops-used-poison-south-carolina-murder
14. Ueda, K.; Nishimura, M.; Maebashi, H.; Tanabe, M.; Konishi, T.; Yamamura, T.; Morimoto, K. Acute, subacute and chronic toxicity tests of Xylometazoline Hydrochloride. *Kiso to Rinsho. Clinical Report* **1971**, 55-85.
15. Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances: Syntheses, Patents, Applications of the most relevant APIs*. 5th ed.; Thieme Verlag, Stuttgart, pp. 1358, **2009**.
16. Worstmann, W.; Leuschner, F.; Neumann, W.; Kretzschmar, R. Toxicity studies on N-(2-imidazolinew-2yl)-N-(4-indanyl)amine monohydrochloride (indanzoline), a new rhinologic drug. *Arzneimittel-Forsch.* **1980**, *30*, 1760-1771.
17. Hotovy, R.; Enenkel H.J.; Gillissen, J.; Jahn, U.; Kieser, H.; Kraft, H.G.; Mueller-Calgan, H.; Sommer, S.; Wahlig, H. On the pharmacology of 2-(4-tert-butyl-2,6-dimethyl-3-hydroxybenzyl)-2-imidazolinumchloride. *Arzneimittel-Forsch.* **1961**, *11*, 1016-1022.
18. Engelhorn, R.; Klupp, H. Pharmakologische Wirkung von 2-(1,2,3,4-Tetrahydro-1-naphthylamino)-2-imidazolin-hydrochlorid. *Arzneimittel-Forsch.* **1962**, *12*, 971-975.
19. Picciola, G.; Carissimi, M.; Ravenna, F.; Gentili, P.; Carenini, G. Cyclohexylphenoxy amidoximes and imidazolines with antidepressive and alpha-adrenergic activity. *Arzneimittel-Forsch.* **1979**, *29*, 729-738.
20. Gylfe, J.; Hendricks, R.; Ochs, S.; Williams, H.L. Hypothermic agents: I: 4-amyl N-benzohydrilpyridinium bromide (B-45) and alpha naphthylmethyl imidazoline (privine). *Fed. Proc.* **1950**, *9*, 280-281.
21. Hutcheon, D.E.; P 'An, S.Y.; Gardocki, J.F.; Jaeger, D.A. The sympathomimetic and other pharmacological properties of DL 2-(1,2,3,4-tetrahydro-1-naphthyl)-imidazoline (tetrahydrozoline). *J. Pharmacol. Exp. Ther.* **1955**, *113*, 341-352.
22. Sunshine, I.: *CRC Handbook of analytical toxicology*. Chemical Rubber Company, Cleveland, Ohio, **1969**.
23. Worthing, C. *Pesticide Manual*. 9th Ed. Farnham, Surrey, British Crop Protection Council, p. 550. **1991**.
24. Strey, K. Die Gifte-Skala. *Chem. Unserer Zeit* **2019**, *53*, 386-399. <https://doi.org/10.1002/ciuz.201900828>
25. Eagle, E.; Poling, C.E. The oral toxicity and pathology of polyoxyethylene derivatives in rats and hamsters. *J. Food Sci.* **1956**, *21*, 348-361. <https://doi.org/10.1111/j.1365-2621.1956.tb16931.x>
The LD₅₀ of water is above 0.09 kg/kg. For this, the most non-toxic substance obtains the notable value of 1 on the poison scale.
26. Kostka, G.; Palut, D. Toxicity of aldehydes used as disinfectants. *Przegl. Epidemiol.* **1973**, *67*, 295-303.
27. Carron, C.; Jullien, A. Bucher, B. Synthesis and pharmacological properties of a series of 2-piperidino alkanol derivatives. *Arzneimittel-Forsch.* **1971**, *21*, 1992-1998.
28. Harvengt, C.; Jeanjean, M. Acute toxicity of phentolamine in rabbits. *Arch. Int. Pharmacodyn. Ther.* **1968**, *174*, 243-245.
29. sciencelab.com/msds.php?msdsld=9926366
30. abcam.com/ps/Products/120/ab120712/Msds/ab120712_CLP1_EN.pdf
31. Goldenthal, E.L. A compilation of LD₅₀ values in newborn and adult animals. *Toxicol. Appl. Pharm.* **1971**, *18*, 185-207. [https://doi.org/10.1016/0041-008X\(71\)90328-0](https://doi.org/10.1016/0041-008X(71)90328-0)
32. toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+3143.