Development of Three-Chambered Autoinjector with Acetylcholinesterase Reactivator HI-6 Dimethanesulfonate

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Abstract

Oxime HI-6 [1-(2-(hydroxyiminomethyl)pyridinium)-3-(4-carbamoylpyridinium)-2-oxapropane] belongs to the most promising acetylcholinestrase reactivators – antidotes used against nerve agent (e.g. sarin, cyclosarin, tabun, VX.) intoxications. According to the present knowledge, its reactivation potency is the highest compared to other available commercial oximes (pralidoxime, obidoxime, trimedoxime, MMB4). Thanks to its promising reactivation potency, the development of this compound and its further large-scale production were done at our department within last four years. We prepared twelve different HI-6 salts (sulfate, chloride, acetate, bromide, phosphate, mesylate, tartrate, iodide, malonate, salicylate, maleinate, tosylate), and we developed their quick TLC and HPLC analysis and solubility testing. Furthermore, chloride (Cl) and dimethanesulfonate (DMS) salts of the HI-6 were tested *in vitro* and *in vivo* to compare their reactivation differences. Currently, prototype of three-chambered autoinjector filled with HI-6 DMS is under development.

Keywords: autoinjector, HI-6, oxime, reactivator, nerve agents, antidotes

Introduction

Bisquaternary pyridinium aldoxime HI-6 (1-(4-hydroxyiminomethylpyridinium)-3-(4-carbamoyl -pyridinium)-2-oxapropane) is considered at present time as the most promising acetylcholinesterase (AChE) reactivator. Because of its extraordinary potency to reactivate sarin, cyclosarin, VX, Russian VX and soman (if administered in short period after intoxication) inhibited AChE, it is reactivator with the broadest utilization. The only disadvantage of its use is its lower efficacy in treatment of tabun and pesticides inhibited AChE. Compared with other market reactivators (pralidoxime, obidoxime, trimedoxime, obidoxime), its reactivation potency is higher and it has broader reactivation spectrum. Due to these facts, many countries throughout the world are interested in its development and introduction among their antidotal means (Lundy et al. 2006).

The first salt of this reactivator was dichloride since the first HI-6 compound was prepared via bis(chlormethylether), which was found to be carcinogenic. Due to the alkylating agent (bis(chlordimethylether)) toxicity, a replacement of this agent by appropriate analogues was tested. At present time, most preferred salt seems to be dimethanesulfonate. It exceeds dichloride not only for the synthetic process omitting the carcinogenic compound, but also thanks to its better stability and solubility in water.

As it is generally known, the different anions of pharmaceutical preparations are generally developed to achieve better pharmacological effect through their adsorption phase.

Results and Discussion

During last five years we were focused on the development of the appropriate salt of the oxime HI-6. We were focused on subsequent topics:

- Optimization of the HI-6 synthesis (12 different HI-6 salts) (Kuca et al. 2007a; Kuca et al. 2008)
- Comparison of the solubility of all prepared HI-6 salts (till now not published data)
- Development of the appropriate analytical method for resolution of the product and by-products (TLC and HPLC) (Jun et al. 2007; Jun et al. 2008)
- In vitro evaluation of the prepared HI-6 salts (Kuca et al. 2007a; Kuca et al. 2007b)
- In vivo comparison of HI-6 dichloride and dimethanesulfonate (Kassa et al. 2008)

According to the obtained data, HI-6 dimethanesulfonate was recommended in the Czech Army as replacement of currently available dichloride salt. At present time, this compound is produced by company Vakos XT, a.s. (Prague, Czech Republic) and ChemProtect, a.s. (Prague, Czech Republic). Moreover, there is currently three-chambered autoinjector in preparation (1st chamber - HI-6 DMS, 2nd chamber –anticholinergic drug and 3rd chamber – anticonvulsive drug). The final prototype will be finished at the end of year 2009.

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References

Jun D., Stodulka P., Kuca K., Koleckar V., Dolezal B., Simon P., Veverka M.: HPLC analysis of HI-6 dichloride and dimethanesulfonate – antidotes against nerve agents and organophosphorus pesticides. Analytical Letters. 2007, 40, 2783 – 2787.

Jun D., Stodulka P., Kuca K., Koleckar V., Dolezal B., Simon P.,Veverka M.: TLC analysis of intermediates arising during the preparation of oxime HI-6 dimethanesulfonate. Journal of Chromatographic Science. 2008, 46, 316-319.

Kassa J., Jun D., Kuca K., Bajgar J.: A comparison of reactivating and therapeutic efficacy of two salts of the oxime HI-6 against tabun, soman and cyclosarin in rats. Basic & Clinical Pharmacology & Toxicology. 2007, 101, 328-332.

Kuca K., Musilek K., Stodulka P., Marek J., Hanusova P., Jun D., Hrabinova M., Kassa J., Dolezal B.: Twelve different HI-6 salts and their potency to reactivate cyclosarin inhibited AChE in vitro. Letters in Drug Design and Discovery. 2007a, 4, 510-512.

Kuca K., Jun D., Bajgar J.: Currently used cholinesterase reactivators against nerve agent intoxication: comparison of their effectivity in vitro. Drug & Chemical Toxicology. 2007b, 30, 31-40.

Kuca K., Stodulka P., Hrabinova M., Hanusova P., Jun D., Dolezal B.: Convenient preparation of the oxime HI-6 (dichloride and DMS) – antidote against nerve agents. Defence Science Journal. 2008, 58, 399–404.

Lundy PM, Raveh L, Amitai G. Development of the bisquaternary oxime HI-6 toward clinical use in the treatment of organophosphate nerve agent poisoning. Toxicological Reviews. 2006, 25, 231-243.