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Operational evaluation of wet/dry autoinjectors containing atropine in solution and powdered HI 6

Horst Thiermann, Ute Spöhrer, Peter Eyer *

Walther-Straub-Institut für Pharmakologie und Toxikologie der Universität München, Nussbaumstrasse 26, D-80336 München, Germany

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Abstract

Autoinjectors containing atropine and the oxime HI 6 are considered valuable in the pre-clinical treatment of nerve agent poisoning. To circumvent the problem of limited stability, dry/wet autoinjectors were developed in which the unstable HI 6 is dissolved by an atropine-containing diluent in an adjacent chamber upon activation of the device. While investigating the operational performance of two different autoinjector types we became aware that the autoinjectors from Astra Tech only partially delivered their contents during the 5 s injection against increasing back pressure. This malfunction was assumed to be due to defective teflon-coated O-rings which may result in greater friction in the injection system. The present investigation shows that the Astra Tech HI 6 autoinjectors of the regular production line function properly. In contrast to the previous batch, the autoinjectors are able to surmount a back pressure between 1.5 and 2 atm, probably sufficient to deliver the specified content when injected into muscles.

Keywords: Atropine; Autoinjector; Oxime HI 6

The rapid onset of cholinergic crisis after intoxication with highly toxic organophosphorus compounds calls for pre-clinical administration of effective antidotes as early as possible. For this purpose, i.m. applicability of the antidotes by autoinjectors is desirable to permit early treatment also in the absence of a physician. Besides atropine, oximes with a broad antidotal spectrum are acknowledged as valuable adjuncts that should be included in antidotal mixtures. Of these, the oxime HI 6 is presently considered as most promising (1-(((4-(aminocarbonyl)pyridinio)methoxy)methyl)-2-((hydroxyimino)methyl)pyridinium dichloride monohydrate). To circumvent the problem of limited stability, dry/wet autoinjectors have been developed in which the unstable HI 6 is dissolved by a atropine-containing diluent in an adjacent chamber upon activation of the device.

While investigating two autoinjector systems from different manufacturers (Astra Tech AB, Mølndal, Sweden and STI International Ltd, Rochester, Kent, U.K.) in vitro we became aware that the Astra Tech autoinjectors only partially delivered their contents during the 5 s injection against increasing back pressure (Thiermann et

* Corresponding author: Tel. (89) 51 45 22 81; Fax (89) 51 45 22 24.

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Table 1
Delivery of HI 6 after activation of the autoinjectors without back pressure

Autoinjector	Density ($kg\ l^{-1}$)	Volume (ml)	Amount (ejected) (mg)	Amount (rest) (mg)	Amount (Σ) (mg)
AT 1	1.059	2.94	457.51	45.77	501.56
AT 2	1.061	2.90	464.56	44.05	506.94
AT 3	1.058	2.95	456.23	45.70	500.31
AT 4	1.057	2.97	418.82	82.38	498.49
AT 5	1.054	2.95	443.72	54.69	496.50
Mean	1.058	2.94	448.17	54.52	500.76
±SE	0.001	0.01	8.07	7.21	1.77

al., 1994). In contrast, Astra Tech autoinjectors filled with atropine alone functioned properly. According to the manufacturer, an irregular production batch was delivered for our experimental purposes. This batch was rejected in the final quality control inspection of the regular production line because of defective teflon-coated O-rings that may have resulted in higher friction in the injection system. For this reason the device was probably not able to surmount the back pressure that develops in the musculature during injection of 2–3 ml (Spöhrer et al., 1994). Therefore, we investigated a new batch of HI 6 autoinjectors from Astra Tech which according to the manufacturer was found to meet the specifications.

Autoinjectors: according to the manufacturer, autoinjectors were filled with 475–525 mg HI 6 dichloride monohydrate and 2.26 mg atropine sulfate in citrate buffer (3.0 ml, pH 3.9). With a complete ejection, the injectors were specified to have a fairly consistent residual volume of approx. 10%. According to the instructions, the autoinjector should be shaken for 5 s after activation of the assembly. To ensure complete dissolution, we decided to shake the autoinjectors by hand with 60 strokes in 1 min.

Sample preparation: in order to analyse the dispensed amount, each autoinjector was fired in a flask (4.65 ml) sealed with parafilm to avoid splashing. The ejected content was weighed, the volume measured, and the density calculated ($\delta = m/V$ (g/ml)). After dilution in 20 mM phosphoric acid (1:5000) HI 6 was determined photometrically and by HPLC as described previously (Thiermann et al., 1994). Following ejection, the autoinjectors were disassembled and rinsed with water that was collected in a volumetric flask (250 ml) to determine the remaining oxime.

Determination of the back pressure: the back pressure was determined under equilibrium conditions by firing the injector's content into a rub-

Table 2
Delivery of HI 6 after activation of the autoinjectors against a back pressure up to 1.5 atm

Autoinjector	Density ($kg\ l^{-1}$)	Volume (ml)	Amount (ejected) (mg)	Amount (rest) (mg)	Amount (Σ) (mg)
AT 1	1.052	2.78	444.48	71.48	515.96
AT 2	1.054	2.83	424.92	67.80	492.72
AT 3	1.052	2.69	410.88	97.60	508.48
AT 4	1.054	2.78	434.55	72.02	506.57
AT 5	1.049	2.87	436.59	67.87	504.46
AT 6	1.054	2.72	417.99	90.58	508.57
Mean	1.053	2.78	428.24	77.89	506.13
±SE	0.001	0.03	5.13	5.25	3.11

Table 3
Delivery of HI 6 after activation of the autoinjectors against a back pressure up to 1.9 atm

Autoinjector	Density ($kg\ l^{-1}$)	Volume (ml)	Amount (ejected) (mg)	Amount (rest) (mg)	Amount (Σ) (mg)
AT 1	1.047	3.13	395.97	97.27	493.25
AT 2	1.048	3.01	397.82	116.58	514.40
Mean	1.048	3.07	396.90	106.93	503.83
±SE	0.001	0.06	0.92	9.66	10.58

ber septum-sealed flask (4.65 ml air volume). The pressure was calculated based on the equation:

$$\Delta p = p_o(V_o/(V_o - V_i) - 1)\ (kg/cm^2)$$

where Δp is the increase in pressure, p_o denotes atmospheric pressure, V_o is the volume of the empty flask, i.e., 4.65 ml, and V_i represents the injected aqueous volume.

All experiments were performed at room temperature.

Delivery of the autoinjector contents without back pressure: the results shown in Table 1 indicate that the total amount of HI 6 exactly fits that specified. The same holds true for the ejected amount, i.e., 90%. The coefficient of variation, due to one outlier (AT 4), however, was rather high (4%). Since the ejected volume of this outlier was normal, incomplete dissolution of the solid HI 6 may have occurred.

Delivery of the autoinjector contents against various back pressures: as shown in Table 2, the autoinjectors delivered nearly completely the HI 6 solution (2.78 ± 0.03 ml) against a pressure of about 1.5 kg/cm^2. Without back pressure the delivered volume was 2.94 ± 0.01 ml. The concentration of the delivered HI 6 solution was identical with and without back pressure. The delivered amount, however, was somewhat smaller, i.e., 85%, although this difference was not significant.

To determine the maximal back pressure that could be overcome by the autoinjectors we prefilled the flasks with 0.50 ml water. As shown in Table 3, the autoinjectors made up the fluid volume to 3.07 ml whereby a back pressure of 1.94 atm was built up. The ejected amount was reduced to 79% of the amount filled in.

These data show that the Astra Tech HI 6 autoinjectors function properly. In contrast to a previous batch with defective O-rings, the autoinjectors of the regular production line are able to overcome a back pressure between 1.5 and 2 atm, probably sufficient to deliver the specified content when injected into muscles.

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