Assessing the Capacity of Various Substances to Act as Neutralizing Treatment in Organophosphoric Acute Intoxications

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Neutralization represents an important goal in toxicology, reducing exposure to poison being crucial in any management plan of any intoxication. Controversial data actually exists in the literature regarding activated charcoal capacity to bind organophosphates. To determine and compare organophosphate binding capabilities for different hydrophobic substances, considered to have neutralising properties. 14 hydrophobic substances (Dextrane, medicinal charcoal, activated charcoal, Eucarbon, Lysozyme, activated fluorisyl, β cyclodextrine, N vinyl polybenzimidazol, plasma –dextran, Silica gel, Celytte, aluminium monoxide, Sephadex G, C18) were tested regarding their ability to bind Triclorfon an organophosphate widely used by general population.

After four hours of direct interaction between neutralizer and Triclorfon the suspension was filtered and the unbind organophosphate quantitatively evaluated through gas chromatography. Activated charcoal was proved to bind Triclorfon but in a low efficiency manner. The necessary quantity is almost diminished to half if medicinal charcoal is used. The most powerful binding effect was retrieved for C18. Many of the analysed substances (Dextrane, Eucarbon, Lysozyme, activated fluorisyl, β cyclodextrine, N vinyl polybenzimidazol, plasma –dextran, Silica gel, Celytte, aluminium monoxide, Sephadex G) were proved to have no binding effect to Triclorfon. Activated and medicinal charcoal has proved such a capability, but the maximum efficiency was obtained for C18, a siliceous powder used in gas chromatography as absorbent material. In the acute intoxication with organophosphate substances activated charcoal could be substituted by medicinal charcoal due to its superior efficiency and availability.

Keywords: activated charcoal, organophosphate, activated fluorisyl, β cyclodextrine

Controversial data persist in the literature regarding activated charcoal capacity to bind organophosphates [1]. Some accept its use as a potent therapy but other researchers have failed in proving any binding capacity that might exert regarding organophosphates. Due to its large utilization in Poisons Centres for binding other kind of toxics, so its availability and routine in administration, lack of known related adverse reactions, ease of administration using an already placed tube at gastric level (necessary for the performance of the gastric lavage) its use is largely encounter in medical practice [2].

Over the time, many substances have been proposed as neutralizers: sodium bicarbonate, alginate etc. stressing that a major chapter from the management of organophosphates poisoning – neutralization – is still incompletely exploited through the existent substances [3].

Neutralization represents an important goal in toxicology, reducing exposure to poison being crucial in any management plan of any intoxication [4]. Situations of poison that remain in an active form in the body make its absorption to persist and the therapeutic manoeuvres to fail.

Due to the fact that, in our study, we intend to analyse the capacity of certain substances to bind organophosphates and not, at this stage, the way in which this binding occur, we will refer to this effect with the general term of neutralization although we are aware that exist neutralization – chemical interaction that lead to poison inactivation and decorporation – physical and chemical interaction with the toxic leading to his elimination.

The substances believed to possess neutralising capacities were included in the study after revising specialized literature, consultative brainstorming discussions with specialists from the Petru Poni Institute of Macromolecular Chemistry of Iasi, Department of Chemistry from the University Al. I. Cuza of Iasi, Institute of Public Health of Iasi and from the University of Medicine and Pharmacy “Grigore T. Popa” of Iasi the Department of Pharmacology and Toxicology [5]. Restricted by the availability of the selected substances, a list of them was conceived. The substances were after that grouped in regard to their water solubility. For those insoluble in water an in vitro experiment was designed in order to assess them capacity of binding organophosphates.

Experimental part

Materials and methods

Triclorfon – produced by SC Chimcomplex SA Borzesti, 90% purity, wettable powder, doze used: 200 mg/kgbw.

Hydrophobic substances to act as neutralisers in acute organophosphate intoxication:
- dextrane – as microparticle – polysaccharide with a branched structure suitable for absorption processes;
- medicinal charcoal – largely used until few years ago, by his similar name with the activated charcoal and the low availability of the last one;
- activated charcoal – largely accepted for neutralization of poisons, has no proves of associated benefits for organophosphates intoxication. The reason of his inclusion in the research was not only for the aim to study its neutralizing capabilities but also to act as term of comparison regarding the neutralizing effect of the other studied substances;

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- eucarbon – a type of vegetal charcoal that is considered to be superior to medicinal charcoal in its medical indications (constipation etc.);
- lysozyme - lysozyme fixed on an organic support;
- activated fluorisyl – also a mineral compound, similar to charcoal (requiring also activation), used in gas chromatographic methodology of organophosphate isolation (organophosphates being retained by fluorisyl). Possible inactivation in aqueous environment that could generate bias for the research. In case of positive results could be incorporated in the filters used in gas masks or in other devices supposed to work in dry conditions);
- β ciclodextrine – natural polymers with binding capabilities with molecular conformations that mimic the aspect of a bucket in which various components can be included;
- N vinyl polybenzymidasol – benzymidadol possess studies indicating organophosphate binding capabilities but also carcinogenic effects. Integration in a non resorbable polymer could constitute a solution for human usage, after subsequent researches, if the complex proves efficient in neutralising organophosphates. [6, 7];
- plasma –dextran – in order to use the existent useful compound from plasma (hydrolases, serum cholinesterase, proteins etc.) capable to neutralise organophosphates, plasma was bind on micro particles of dextran. The resulted complex was thought to resist digestion inside digestive tract without secondary absorption of the released toxic;
- silica gel – a siliceous derivate;
- celytte – aluminium trioxide;
- aluminium monoxide;
- Sephadex G – a dextran with high level of reticulation; C18 – siliceous powder used in gas chromatography as absorbent material that capture organophosphate at filter cartridge level.

0.5 g of each analysed substance was individually placed in a tube of 30 mL volume with glass stopper in which the level of 10 mL was previously marked. In each tube, by pipetting, distilled water was added until the level of 10 mL was achieved. By doing so, each tube contained a volume of 10 mL total in which 0.5 g of substance was mixed with water.

14 test tubes have resulted that were numbered according to the number of the studied neutraliser contained in.

In the morning of the experiment the total necessary quantity of Triclorfon was weighted at the analytical balance for a 0.2 g per sample. 0.2 g multiplied with 15 (14 substances plus one control) gave the final quantity of 3.3 f commercial Triclorfon.

Triclorfon 90% → 90 g Triclorfon pure ....100 g commercial Triclorfon
0.2 g ......................x

x=100/90x0.2 =0.22; 0.22x 15 =3.3g commercial Triclorfon

For Triclorfon the solution was used in a total volume of 10 mL per each sample leading to a total volume of 10 x 15 samples = 150 mL final volume. 3.3 g commercial Triclorfon were weighted and placed in a 150 mL flask fitted with a glass stopper and a small volume of distilled water was added. By shaking the flask which was fitted with the glass stopper, at room temperature, the Triclorfon powder was completely dissolved. After that the flask was filled with distilled water until the sign, to a final volume of 150 mL.

By pipetting 10 mL of this solution were transferred in each 14 of the previously prepared tube. The remaining 10 mL were placed in a new tube to which 10 mL of distilled water was added to form the control, which was numbered 15. All the 15 tubes were kept in same conditions of temperature and humidity as the rest of the samples: 4 h in a thermostatically controlled water bath at 37°C and shaken by placing the pan on a shaking plate system.

The resulted suspensions were after that filtered using a glass funnel with a valve, inside of which a filter paper was placed. The valve was necessary to recover the resulted liquid after filtration in the same glass tube in which the suspension was prepared. In order to recuperate all the Triclorfon that was not retained by the analyzed neutralizer, the filter paper was washed after that with a supplementary volume of distilled water, collected also in the correspondent glass tube, until a total final volume of 20 mL per tube.

By doing so, at the end, we have obtained a 20 mL volume of solution in all the 15 tubes (14 samples and one control) and we have avoided situations in which the final concentration of Triclorfon to be even higher than the control. This situation could appear if the analysed substance binds only water, by this increasing the concentration of Triclorfon.

Gas chromatography [8] was used to assess the content of Triclorfon in the analysed solutions.

Results and discussions

Table 1 Binding capacity for Triclorfon, of the substances included in the study, quantified through gas chromatography.

<table>
<thead>
<tr>
<th>Studied substance</th>
<th>utilised quantity (grams)</th>
<th>GC signal amplitude (mm)</th>
<th>Elution of Triclorfon</th>
<th>Binding capacity</th>
<th>degree (%) of GC signal reduction</th>
<th>quantity of Triclorfon neutralised by 1 gram of substance (grams)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma + dextran</td>
<td>0.5</td>
<td>121</td>
<td>0.2</td>
<td>122</td>
<td>100-99.2=0.8</td>
<td>-</td>
</tr>
<tr>
<td>Dextran</td>
<td>0.5</td>
<td>121</td>
<td>0.2</td>
<td>122</td>
<td>100-99.2=0.8</td>
<td>-</td>
</tr>
<tr>
<td>Activated charcoal</td>
<td>0.5</td>
<td>118</td>
<td>0.2</td>
<td>178</td>
<td>100-66.3=33.7</td>
<td>0.135</td>
</tr>
<tr>
<td>Medicinal charcoal</td>
<td>0.5</td>
<td>118</td>
<td>0.2</td>
<td>178</td>
<td>100-95.9=4.1</td>
<td>-</td>
</tr>
<tr>
<td>Fluorisil</td>
<td>0.5</td>
<td>168</td>
<td>0.2</td>
<td>178</td>
<td>100-94.5=5.6</td>
<td>-</td>
</tr>
<tr>
<td>N vinyl polybenzymidasol</td>
<td>0.5</td>
<td>119</td>
<td>0.2</td>
<td>178</td>
<td>100-97.6=2.4</td>
<td>-</td>
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<tr>
<td>Lysozyme</td>
<td>0.5</td>
<td>122</td>
<td>0.2</td>
<td>122</td>
<td>100-100=0.0</td>
<td>-</td>
</tr>
<tr>
<td>Peclidextrine</td>
<td>0.5</td>
<td>121</td>
<td>0.2</td>
<td>122</td>
<td>100-99.2=0.8</td>
<td>-</td>
</tr>
<tr>
<td>Silica gel</td>
<td>0.5</td>
<td>168</td>
<td>0.2</td>
<td>178</td>
<td>100-94.5=5.6</td>
<td>-</td>
</tr>
<tr>
<td>Celite</td>
<td>0.5</td>
<td>168</td>
<td>0.2</td>
<td>178</td>
<td>100-94.5=5.6</td>
<td>-</td>
</tr>
<tr>
<td>Aluminium oxide</td>
<td>0.5</td>
<td>168</td>
<td>0.2</td>
<td>178</td>
<td>100-94.5=5.6</td>
<td>-</td>
</tr>
<tr>
<td>Sephadex G</td>
<td>0.5</td>
<td>174</td>
<td>0.2</td>
<td>178</td>
<td>100-97.8=2.2</td>
<td>-</td>
</tr>
<tr>
<td>C18</td>
<td>0.5</td>
<td>26</td>
<td>0.2</td>
<td>52</td>
<td>100-50=50</td>
<td>0.2</td>
</tr>
</tbody>
</table>

**Table 1**
BINDING CAPACITY FOR TRICLORFON, OF THE SUBSTANCES INCLUDED IN THE STUDY, QUANTIFIED THROUGH GAS CHROMATOGRAPHY
Gas chromatographic method that we used involves an error interval until 10% so those differences were not taken into account at the final analyse.

A clear effect of binding with Triclorfon was proved only for:
- activated charcoal;
- medicinal charcoal;
- C18.

Activated charcoal was proved to bind Triclorfon but in a low efficiency manner. 1g of activated charcoal appears to be bind only 0.065 g of Triclorfon. For only 5 g of Triclorfon the necessary quantity of activated charcoal already equals the routinely used 1g per kg body weight in a poisoned patient of 75 kg.

The necessary quantity is almost diminished to half if medicinal charcoal is used which appear to be a more available, least expensive solution for this type of intoxications.

The most powerful binding effect was retrieved for C18, only 22.5 g of this substance being necessary to completely bind 5 g of Triclorfon. In this respect until the dose of 1g/kgbw, a good interval for therapeutic efficiency is obtained.

Conclusions

Many of the analysed substances (Dextrane, Eucarbon, Lysozyme, activated fluorisyl, β cyclodextrine, N vinyl polybenzimidasol, plasma –dextran, Silica gel, Celytte, aluminium monoxide, Sephadex G) were proved to have no binding effect to Triclorfon.

Three studied substances have proved such a capability, maximum efficiency being obtained for C18, a siliceous powder used in gas chromatography as absorbent material to capture organophosphate at filter cartridge level, which bind 0.2 g of Triclorfon per each gram of C18.

For the activated charcoal a binding capability was observed, but reduced and its use in medical practice, based on its availability and lack of side effects, could be substituted by the administration of medicinal charcoal, in the acute intoxication with organophosphate substances.

References

1. LHEUREUX P., ASKENASI R - Place of activated charcoal and gastric emptying in acute toxic ingestions: A critical reappraisal, Yearbook of Intensive Care and Emergency Medicine, 1992, 1992, p.656;

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