Haemoperfusion of Amitriptyline and Nortriptyline – an in Vitro Study

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Abstract

Background. The sorption efficacy of an active charcoal, Amberlite XAD-2 and Amberlite XAD-4, in heamoperfusion with amitriptyline and nortriptyline was investigated in vitro.
Methods. Fifteen amitriptyline and nortriptyline haemoperfusions in vitro were carried out in a closed system using the above-mentioned sorbents. 3,000 ml of 0.9% NaCl was used as the perfusion solution. The amitriptyline and nortriptyline concentrations in perfusion solution were 13.1±0.5 mg/L and 12.1±0.6 mg/L, respectively. Individual haemoperfusion lasted 5 hours.
Results. Amitriptyline and nortriptyline values in perfusion solution at 300 min were 2.09±0.21mg/L and 1.95±0.14 mg/L, respectively during charcoal haemoperfusion. Amitriptyline and nortriptyline values decreased after haemoperfusion using Amberlite XAD-2 and XAD–4 to zero as early as 180 minutes. Amitriptyline and nortriptyline extraction and clearance rates reached the highest values (extraction: 1.0; clearance: 200 ml/min) at 120 min during haemoperfusion through Amberlite XAD-2 or XAD-4. In addition we performed two haemoperfusions through Amberlite XAD-4 in a 44-year-old woman ingesting an unknown amount of amitriptyline in a suicidal attempt. The patient recovered successfully.
Conclusions. Based on the results of our study in vitro, we recommend to use Amberlite XAD-4 or XAD-2 haemoperfusion for the treatment of acute poisoning with tricyclic antidepressants in patients, within 6 hours after acute poisoning regardless of clinical status.

Key words: Amitriptyline, Nortritriptyline, Haemoperfusion in vitro, Active charcoal, Amberlite XAD-2 and XAD-4

Introduction

Amitriptyline (M.W.: 277.4) is a tricyclic antidepressant with strong anticholinergic and sedative properties. Amitriptyline slowly resorbs from gastrointestinal tract and its plasma concentration is very low during 4-8 hours, only 0.2-0.5 % from used oral dose. The highest plasma value of amitriptyline occurs within 6 hours and persists in plasma until 8 hours, and is prolonged in overdose. The protein binding of amitriptyline and some of its metabolites in plasma and tissues are 75-95 %. Amitriptyline is lipophilic and its volume of distribution is very large and varies widely from 6-36 L/kg. The drug is rapidly distributed in tissues and its concentration in tissues is 3-180 times higher (e.g. in lungs) in comparison to plasma. Amitriptyline is metabolized and excreted by kidneys, partly in free or conjugated form with glucuronic acid (13). Amitriptyline is often prescribed together with another tricyclic antidepressant, by Imipramine, and therefore many suicidal attempts are caused by those two drugs (5). Active metabolite of amitriptyline is nortriptyline (M.W.: 263.4). Nortriptyline is a tricyclic antidepressant with mild anticholinergic and moderate sedative properties. That is almost completely absorbed from gastrointestinal tract and the highest plasma concentration of nortriptyline occurs within 4-8 hours. Toxic up to letal dose of amitriptyline is 0.5-4.5 g (10,14). Severe acute amitriptyline poisoning is manifested by unconsciousness, generalized cramps, various arrhythmias (7,8,16), severe involvement of vascular circulation (2), hypotension, hyperthermia, respiratory and cardiac failure. In addition, after acute amitriptyline poisoning rhabdomyolysis with myoglobulinuria and acute kidney failure may develop (14).
From above mentioned reasons the therapeutic influence of patient suffering from acute amitriptyline or nortriptyline poisoning is very difficult. Other therapeutic option which might be used are: gastrointestinal lavage with the use of active charcoal up to 50 g, and the use of i.v. sodium bicarbonate infusion in order to decrease the cardiotoxicity of the drug. Additionally, phenytoin was used in order to improve the conductivity of QRS interval on ECG. Furthermore, Physostigmin was recommended by several authors as an antidot (8,14) and diazepam was recommended in the presence of cramps. Peritoneal dialysis and haemodialysis were ineffective. According to Monhart (10) the tricyclic antidepressants were adsorbed on active charcoal and resins during haemoperfusion in vitro. According to some clinical papers, charcoal haemoperfusion (4,8,7,9,15) and resins haemoperfusions (5,6,10,11,13) were successfully used in the treatment of acute amitriptyline and of other tricyclic antidepressants poisonings in the last years. Ševela et al. (15) described a patient after a suicidal attempt, who ingested 1,250 mg Amitriptyline and 1,250 mg Nortriptyline. This patient was treated by gastrointestinal lavage, forced diuresis, haemodialysis and charcoal haemoperfusion and he survived. Trafford et al. (16) described a patient after amitriptyline poisoning, who suffered from ventricular tachycardia before Amberlite XAD-4 haemoperfusion and after 1.5 hour of haemoperfusion sinus rhythm on ECG was present and the patient survived.

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With regards to the controversial results on the therapy of severe amitriptyline poisoning, it was recommended (9,14) to begin the haemoperfusion very early, regardless to the clinical status, i.e. up to 6 hours after poisoning (10). Recently, plasmapheresis was recommended after acute amitriptyline poisoning (12).

Aim of our study was to evaluate the sorption efficacy of various sorbents (active charcoal, Amberlite XAD-2 and Amberlite XAD-4) in haemoperfusion capsules during haemoperfusion of amitriptyline and nortriptyline in vitro.

Patients and methods

Fifteen haemoperfusions with amitriptyline and nortriptyline in vitro were performed. As the perfusion solution was used 3,000 ml of 0.9 % NaCl. The concentrations of amitriptyline and nortriptyline were 13.1±0.5 mg/L and 12.1±0.6 mg/L, respectively. We used three kinds of haemoperfusion capsules:

1) Hemasorb 800 C capsule containing active charcoal, and made from coconut shells of type Chemviron SC XII; the total volume of the capsule was 850 ml, the sorbent weight was 470 g, the sorbent surface was 1,000 m^2/g and the blood or perfusion solution volume, respectively, was 300 ml.

2) Hemasorb 800 A-2 capsule containing synthetic styren-divinyl-benzen resin (Amberlite XAD-2); the total volume of the capsule was 800 ml, the sorbent weight was 650 g, the sorbent surface was 217 m^2/g and the blood or perfusion solution volume, respectively, was 220 ml.

3) Hemasorb 800 A-4 capsule containing synthetic styren-divinyl-benzen resin (Amberlite XAD-4); the total volume of the capsule was 800 ml, the sorbent weight was 650 g, the sorbent surface was 730 m^2/g and the blood or perfusion solution volume, respectively, was 220 ml.

Sorbent particles were coated with a thin layer of biocompatible poly/2-hydroxyethylmetha-crylate. The haemoperfusion capsules were made in the Czech Republic.

From the 15 haemoperfusions with amitriptylin and nortriptyline in vitro, 5 were performed using active charcoal, 5 using Amberlite XAD-2 and 5 using Amberlite XAD–4. The recirculation of 3,000 ml 0.9% NaCl solution with amitriptyline and nortriptyline through haemoperfusion capsules was carried out in a closed system over 5 hours. The perfusion solution flow rate was 200 ml/min. The collection of the solution samples was performed before the inlet of perfusion solution in the haemoperfusion capsule and after the outlet at 0, 15, 30, 60, 120, 180, 240, and 300 min.

In addition, we performed two Amberlite XAD-4 haemoperfusions in vivo (4-hour and 5-hour) in a 44-year-old woman who was orally poisoned by an unknown amount of amitriptyline in a suicidal attempt. The blood flow rate as well as the perfusion solution was 200 ml/min.

The amitriptyline and nortriptyline concentrations in perfusion solutions (0.9 % NaCl) were determined by the homogenous enzymeimmunoassay using Emit SYVA assay. The tricyclic antidepressant concentration in plasma was determined by enzymeimmunoassay Emit SYVA assay.

The values of extraction and clearance of amitriptyline and nortriptyline were calculated from their concentrations and from the flow rate of perfusion solution. The ideal value of extraction was 1.0 and clearance was equal to the flow of perfusion solution. These values were reached when after a single flow of perfusion solution through haemoperfusion capsule the substance was completely removed.

Statistical analysis of obtained results was performed by Student`s t-test in Institute of Medical Informatics of the Medical Faculty of University of P. J. Safarik.

Results

A significant concentration of amitriptyline and nortriptyline using haemoperfusion capsule Hemasorb 800 C with active charcoal at 300 min of haemoperfusion in vitro was still found. The values of extraction and clearance of amitriptyline and nortriptyline were very low even at the beginning of haemoperfusion, and the lowest values at 300 min were found. At this time the adsorption capacity of the haemoperfusion capsule was almost exhausted (Table 1). The concentration of amitriptyline and nortriptyline during Amberlite XAD-2 and XAD-4 haemoperfusions in vitro rapidly decreased. Zero concentrations in the perfusion solution before the inlet into the haemoperfusion capsule and after the outlet from haemoperfusion capsule at 180 min were found. The extraction and clearance of amitriptyline and nortriptyline during haemoperfusion through Amberlite XAD-2 and XAD-4 reached maximal values already at 120 min (Table 2, 3).

Serum tricyclic antidepressants concentration in our patient, who suffered from acute amitriptyline poisoning, significantly decreased during 4-hour and 5-hour Amberlite XAD-4 haemoperfusions. At the end of the 2nd haemoperfusion serum concentration of tricyclic antidepressants was above the upper margin of therapeutic range and the patient survived (Table 4).

Table 1. Concentration, extraction and clearance of amitriptyline/nortriptyline in 0.9 % NaCl solution during 5-hour charcoal haemoperfusion in vitro

Time of Hp (min)	Amitriptyline /Nortriptyline in 0.9 % NaCl solution (mg/L)		Extraction of amitriptyline/ nortriptyline	Clearance of amitriptyline/ nortriptyline (ml/min)
	inlet	outlet		
0	13.16/11.88± 0.54/0.70	-	-	-
15	8.62/8.14 ± 0.33/0.43	7.08/6.85 ± 0.28/0.49**	0.178/0.172 ± 0.03/0.02	35.8/34.4 ± 5.1/4.6
30	7.37/7.29 ± 0.37/0.34	6.26/6.01 ± 0.43/0.38**	0.171/0.148 ± 0.03/0.02	34.2/28.5 ± 6.2/2.1
60	5.70/5.33 ± 0.36/0.34	4.83/4.50 ± 0.28/0.42*	0.151/0.130 ± 0.02/0.01	30.3/25.9 ± 3.6/1.2
120	4.43/4.21 ± 0.30/0.51	3.84/3.65 ± 0.28/0.28*	0.133/0.115 ± 0.01/0.01	26.7/22.9 ± 1.4/2.1
180	3.34/3.16 ± 0.32/0.23	2.93/2.86 ± 0.25/0.21	0.120/0.108 ± 0.01/0.01	24.1/21.6 ± 2.6/2.2
240	2.57/2.43 ± 0.25/0.35	2.39/2.28 ± 0.23/0.23	0.065/0.056 ± 0.04/0.05	13.1/11.3 ± 8.1/9.3
300	2.09/1.95 ± 0.21/0.14	1.96/1.91 ± 0.13/0.10	0.050/0.025 ± 0.01/0.02	10.0/4.9 ± 7.8/4.9

* $p < 0.05$, ** $p < 0.01$ versus inlet values, Hp- haemoperfusion

Table 2. Concentration, extraction and clearance of amitriptyline/nortriptyline in 0.9 % NaCl solution during 5-hour Amberlite XAD-2 haemoperfusion in vitro

Time of Hp (min)	Amitriptyline /Nortriptyline in 0.9 % NaCl solution (mg/L)		Extraction of amitriptyline/ nortriptyline	Clearance of amitriptyline/ nortriptyline (ml/min)
	inlet	outlet		
0	13.10/12.4 ± 0.5/0.36	-	-	-
15	4.87/4.85 ± 0.42/0.31	0.028/0.042 ± 0.004/0.01**	0.994/0.990 ± 0.01/0.01	198.8/198.3 ± 0.1/0.2
30	2.46/2.44 ± 0.41/0.48	0.080/0.081 ± 0.066/0.07**	0.968/0.967 ± 0.02/0.02	193.7/193.3 ± 4.0/4.9
60	0.63/0.56 ± 0.16/0.16	0.010/0.015 ± 0.005/0.01**	0.983/0.978 ± 0.02/0.01	196.6/195.6 ± 3.3/2.7
120	0.03/0.03 ± 0.02/0.02	0.0 / 0.0	1.0 / 1.0	200.0 / 200.0
180	0.0 / 0.0	0.0 / 0.0	-	-

** $p < 0.01$ versus inlet values

Table 3. Concentration, extraction and clearance of amitriptyline/nortriptyline in 0.9 % NaCl solution during 5-hour Amberlite XAD-4 haemoperfusion in vitro

Time of Hp (min)	Amitriptyline /Nortriptyline in 0.9 % NaCl solution (mg/L)		Extraction of amitriptyline/ nortriptyline	Clearance of amitriptyline/ nortriptyline (ml/min)
	inlet	outlet		
0	13.04/12.05 ± 0.30/0.69	-	-	-
15	4.35/4.52 ± 0.22/0.31	0.009/0.004 ± 0.005/0.001**	0.995/0.997 ± 0.01/0.01	199.1/199.5 ± 1.1/0.6
30	1.70/1.79 ± 0.09/0.10	0.017/0.012 ± 0.008/0.003**	0.985/0.993 ± 0.01/0.01	197.4/193.3 ± 1.6/4.9
60	0.26/0.23 ± 0.03/0.10	0.004/0.004 ± 0.001/0.001*	0.982/0.980 ± 0.01/0.02	196.5/195.6 ± 6.1/2.7
120	0.03/0.02 ± 0.01/0.01	0.0 / 0.0	1.0 / 1.0	200.0 / 200.0
180	0.0 / 0.0	0.0 / 0.0	-	-

* $p < 0.05$. ** $p < 0.01$ versus inlet values

Table 4. Amberlite XAD-4 haemoperfusion in 44-year-old woman after acute amitriptyline poisoning

Amberlite XAD-4 haemoperfusion	Time of haemoperfusion (min)	Serum tricyclic antidepressants (Amitriptyline, Nortriptyline) (mg/L)
1.	0	3.61
	60	3.10
	240	1.28
2.	0	1.80
	180	1.00
	300	0.5

Discussion

Haemoperfusion through active charcoal and resins was successfully used in the patients after amitriptyline and nortriptyline poisoning despite of the high affinity fpr protein binding and/or a high distribution volume. Even the results of haemoperfusion therapy are partly controversial, since in the last years charcoal haemoperfusion was successfully used also in the children after amitriptyline poisoning (4,7). According to our results which were obtained from haemo-perfusion in vitro, the use of haemoperfusion through Amberlite XAD-4 and XAD-2 is more effective than the use of charcoal haemoperfusion. At the end of 5-hour haemoperfusion through active charcoal the concentrations of amitriptyline and nortriptyline in perfusion solution were still increased in comparison to haemoperfusion through Amberlite XAD-4 or XAD-2.

Based on the literature data (10), which were confirmed in this study, we treated successfully a 44-year-old woman after severe amitriptyline poisoning by two Amberlite XAD-4 haemoperfusions.

According to our results we recommended in the poisoned patients by oral amitriptyline, nortriptyline and other antidepressant drugs the following therapy: gastrointestinal lavage, oral use of active charcoal, i.v. use of bicarbonate, parenteral use of Diazepam in the presence of cramps and Amberlite XAD-4 or XAD-2 haemoperfusion up to 6 hours after poisoning regardless of the clinical status. During that time plasma concentrations of antidepressant drugs are the highest and still not bound on plasma proteins and distributed to various tissues. Early combined treatment prevents the toxic influence of amitriptyline and nortriptyline on cardiovascular system (arrhythmia, hypotension) and the onset of other signs (10, 16).

Conclusion

Based on our experimental results in haemoperfusion with amitriptyline and nortriptyline in vitro, we can recommend the use of haemoperfusion capsules with Amberlite XAD-4 or Amberlite XAD-2 in patients after acute poisoning by tricyclic antidepressants. This extracorporeal elimination treatment has to begin until 6 hours after acute poisoning regardless to the clinical status. Efficacy of early use of Amberlite XAD-4 haemoperfusion was confirmed in our 44-year-old woman ingesting amitriptyline after a suicidal attempt.

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