und -auswertung mit Chromeleon 4.2 (Dionex); Säule: 5 µm Partikelgröße, 125 mm × 4 mm i. D., Edelstahl-Kartusche LiChroCART; Superspher 100 RP-18 endcapped, Merck 16855; Elutionsmittel: Acetonitril/Kaliumdihydrogenphosphat, 0,02 mol/l + 0.5 ml Phosphorsäure (pH 4) (20/80 v/v); Flußrate: 1,8 ml/min (Druck 180 bar); Säulenofen Gynkotek STH 585; Temperatur: 40 °C; Laufzeit einer Analyse: 6 min.

3. Verwendete Substanzen und Lösungsmittel

Lamotrigin Fa. Wellcome. Acetonitril LiChrosolv für die Chromatographie, Merck. Methanol LiChrosolv für die Chromatographie, Merck. Reinstwasser, 0,05 µS/cm, 0,2 µm Filter, SG Klein-Reinstwassersystem RS 40 E. Kaliumdihydrogenphosphat zur Analyse, MERCK.

4. Auswertung der Chromatogramme

Die Daten auf den Chromatogrammen wurden auf Plausibilität und auf die richtige Peakzuordnung überprüft. Die Auswertung erfolgte über die Peakhöhen von Lamotrigin mit den Programmen Chromeleon 4.2 (dionex) und Excel 7.0 (Microsoft). Die Regressionsgeraden werden mit einer Wichtung 1/× berechnet.
Die Retentionszeit für Lamotrigin beträgt 2,4 min.

Literatur

1 Lensmeyer, G. L.; Gidal, B. E.; Wiebe, D. A.: Ther. Drug Monit. **19**, 292 (1997)
2 Matar, K. M.; Nicholls, P. J.; Bawazir, S. A.; al Hassan, M. I.; Tekle, A.: J. Pharm. Biomed. Anal. **17**, 525 (1998)
3 Ren, S.; Scheuer, M. L.; Zheng, W.: Ther. Drug Monit. 20, 209 (1998)
4 Sinz, M. W.; Remmel, R. P.: J. Chromatogr. **571**, 217 (1991)

Eingegangen am 12. Februar 1999
Angenommen am 1. April 1999

Dr. Reinhard Oertel
Institut für Klinische Pharmakologie
Fiedlerstr. 27
D-01307 Dresden
reioer@rcs.urz.tu-dresden.de

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, J. A. Comenius University, Bratislava, Slovak Republic

Thermodynamic study of the local anaesthetic heptacaine

Study of local anaesthetics, part: 149*

F. Andriamainty and J. Čižmárik

Heptacaine, the hydrochloride of the piperidinoethylester of 2-heptyloxyphenylcarbamic acid [1, 2], is a local anaesthetic. Herein, a basic thermodynamic study of this drug is presented.
The Fig. shows the dependence of the electromotoric force E (mV) upon the heptacaine concentration c ($mol \cdot l^{-1}$) ($E = E_0 + (kRT/F)\log(C^A)$) in saline solution (E: electromotoric force, R: gas constant, T: absolute temperature, C^A: total heptacaine concentration in a sample). We can divide the dependence of E upon log c to three parts: a linear loss of E (mV) from the concentration corresponding $\log c = 3.27 \times 10^{-5}$ $mol \cdot l^{-1}$, then a more significant loss of E follows to $C = 7 \times 10^{-3}$ $mol \cdot l^{-1}$ corresponding c.m.c.
The equation c.m.c. = f(T) represents the dependence of the critical micellar heptacaine concentration (c.m.c.) upon temperature at pH ≈ 4.5–5, for example at T = 298.15 K (c.m.c. ≈ 0.0070 $mol \cdot l^{-1}$), T = 301.15 K (c.m.c. ≈ 0.0074 $mol \cdot l^{-1}$), T = 309.15 K (c.m.c. ≈ 0.0077 $mol \cdot l^{-1}$), T = 314.15 K (c.m.c. ≈ 0.0082 $mol \cdot l^{-1}$), T = 318.15 K (c.m.c. ≈ 0.0087 $mol \cdot l^{-1}$). Based on this dependence, the thermodynamic magnitudes were calculated ($-\Delta G^\circ$, $-\Delta H^\circ$, $-\Delta S^\circ$) according the model "action masse" [3]. Gibbs energy change can be estimated according the equation;

$$\Delta G^\circ = (2 - \beta)\, RT \ln (c.m.c.)$$

where β = anti-ions level and calculated according to [4] (β = 0.59), R = gas constant and T = absolute tempera-

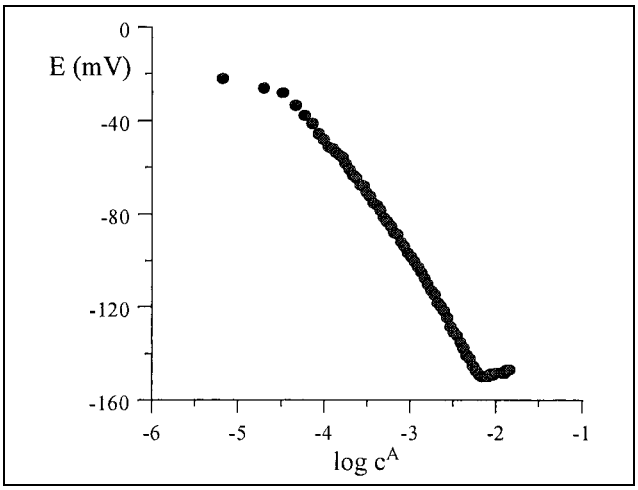

Fig.: Dependence of the electromotoric force E [mV] upon the heptacaine concentration ($mol \cdot l^{-1}$) in 0.1 $mol \cdot l^{-1}$ NaCl solution at 25 °C

Table: Free energy ΔG°, enthalpy ΔH°, entropy ΔS° of heptacaine micellization in 0.1 $mol \cdot l^{-1}$ NaCl at various temperatures

T (K)	ΔG° ($kJ \cdot mol^{-1}$)	ΔH° ($kJ \cdot mol^{-1}$)	$T\Delta S^\circ$ ($kJ \cdot mol^{-1}$)
298.15	-17.3 ± 2.3	-11.2 ± 1.1	6.2 ± 3.5
301.15	-17.4 ± 2.4	-11.4 ± 1.2	5.9 ± 3.5
309.15	-17.5 ± 2.5	-12.1 ± 1.2	5.5 ± 3.7
314.15	-17.6 ± 2.5	-12.4 ± 1.3	5.2 ± 3.8

ture. The enthalpy of micellization is defined by the equation

$$\Delta H^\circ = -(2 - \beta)\, RT^2\, [\partial \ln (\text{c.m.c.})/\partial T]$$

and the entropy contribution of micellization can be calculated as follows:

$$\Delta S^\circ = (\Delta H^\circ - \Delta G^\circ)/T\,.$$

ΔG°, ΔH°, ΔS° values are presented in the Table.
Based on the presented results it can be generalized that

- ΔG° values are negative and slightly decline with temperature
- Depreciations of standard molar enthalpy ΔH° are more significant at more negative values. It means that micellization process becomes more exothermic at increasing temperature.
- $T\,\Delta S^\circ$ values are positive and decline at increasing temperature.

Experimental

Heptacaine was prepared by a literature method [1, 2]. NaCl (Lachema, s.p., Brno) was used to prepare the stock solution with a concentration of 0.1 mol · l^{-1}. NaCl solution was used to prepare the local anaesthetics solution with pH ≈ 4.5–5 at 25–45 °C.
KNO_3 and KCl were analytically pure (Lachema, s.p., Brno) as filling-out solutions for electrodes. KNO_3 solution was used with the concentration 0.1 mol · l^{-1} and formed the external solution of the electrode. Further, we prepared 100 ml saturated KCl solution formed the internal solution of the electrode.
A membrane with the tetracaine-SDS (dodecylsulphatsodium) complex was prepared [5, 6]. A little wheel of 5 mm diameter was cut out from the formed membrane of about 0.1 mm thickness in a Petri dish and glued via a hole to the bottom of a plastic PVC tube using tetrahydrofurane.
The electrodes was constructed as follows: Ag/AgCl/saturated KCl/0.1 mol · l^{-1} KNO_3/standard heptacaine solution/PVC membrane/solution with a sample/0.1 mol · l^{-1} KNO_3/saturated KCl/AgCl, Ag. The electromotoric force was measured with OP 208/1 pH meter (Radelkis, Hungary).
The concentration change of heptacaine homologues was measured using the automatic burette (Radelkis, Hungary) and controlled by a computer.
The work was supported by grant 1/50008/98 of Ministry of Education and Science of Slovak Republic.

* Part 148: Acta Poloniae Pharm.-Drug Res. **55**, 453 (1988)

References

1 Čižmárik, J.; Borovanský, A.; Švec, P.: Acta Fac. Pharm. Univ. Comen. **29** 297 (1976)
2 Čižmárik, J.; Borovanský, A.; Švec, P.: Pharmazie **33**, 297 (1978)
3 Lee, D. J.: Colloid Polym. Sci. **273**, 539 (1995)
4 G. Sugihara, Y. Arakawa, K. Takana, S. Lee, Y. Moroi, J. Colloid Interfac Sci. **170**, 399 (1995)
5 Malovíková, A.; Hayakawa, K.; Kwak, J. C. T.: J. Phys. Chem. **88**, 1930 (1984)
6 Malovíková, A.; Hayakawa, K.; Kwak, J. C. T.; in: Rosen, M. J. (ed.): Structure Performance Relationships in Surfactant, ACS Symp. Ser. No. 253, 25 (1994)

Received December 28, 1998
Accepted March 13, 1999

Mgr. Fils Andriamainty, PhD.
Odbojárov 10
83232 Bratislava
Slovakia

Department of Pathophysiology[1], Faculty of Medicine, and Department of Pharmacology and Toxicology[2], Faculty of Pharmacy, Komensky University, Bratislava, Slovak Republic

Effect of captopril on the contraction of the aorta after chronic volume overload in rabbits

F. Simko[1], P. Martinka[2], J. Brassanova[2], J. Klimas[2] and J. Kyselovic[2]

There is ample evidence that the functional state of peripheral or coronary arteries is impaired in cardiac haemodynamic overload [1, 2]. Most studies on the vascular function deal with models of pressure overloaded circulation, while corresponding data in volume overload are extremely rare. We therefore studied the responsiveness of the aorta to vasoconstrictor stimuli after long term volume overload provoked by insufficiency of aortic valves in rabbits. Further, we investigated the abiltity of the angiotension converting enzyme (ACE) inhibitor captopril to reverse the potential alterations of aortic contractility.
Four groups of rabbits were studied: control(c) (n = 11) − sham operation + four months without any drug + 5 week placebo treatment, control + captopril (cC) (n = 11) − sham operation + 4 months without any drug + 5 week captopril treatment (twice daily intramuscularly 10 mg/kg), aortic insufficiency (AI) (n = 8) − operation + 4 months without any drug + 5 week placebo treatment, aortic insufficiency + captopril (AIC) (n = 8) − operation + 4 months without any drug + 5 week captopril treatment as above. The rabbits were male, Chinchilla species, with an average body weight of about 3000 g. Aortic insufficiency was induced according to Fizel and Fizelova [3] and the period of developed hypertrophy was investigated [4]. Contractility of aorta was tested with two different vasoactive drugs: prostaglandin (PGF) F2α (10^{-5} mol · l^{-1}) and potassium chloride (KCl) (50 mmol · l^{-1}). Eight rabbits were used for contractility investigation in each group. After killing the animals, a six centimeter long segment of the thoracic aorta was dissected free, and placed in an ice-cold Krebs solution, cleaned of connective tissue and cut into segments about 4 mm long. The individual segments were attached between an isometric force transducer (Sanborn FT 10) and a holder under a tension of 20 mN in a 20 ml organ bath containing Krebs solution. After a resting period of 90 min the contraction of the aorta was observed 30 min after administration of the vasoactive substance [5, 6].
Aortic pressures were measured by a catheter with an electric transducer (Statham DB P23, GB) introduced into the aorta through the left carotid artery and recorded on an oscillographic recorder Mark VII, type WR 3101 (Graphtec Corp., USA). The measurements were performed under thiopental anaesthesia [7].
Hypertrophy was determined by weighing the left ventricle and the ratios of its weight to the body weight are calculated for each animal. The results are expressed as means ± S.E.M. Differences between the groups were assessed by one way ANOVA test with $p < 0.05$ taken as significant.
Hypertrophy (weight increase by 62%) of the LV in the AI group was not reversed by five week captopril treatment. In the AI group the reactivity of the aorta was decreased to KCl (by 44%), and to PGF2α (by 51%). Five week captopril treatment improved the reactivity of the aorta to KCl but not to PGF2α.