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Prednisolone concentration in the cochlea of patients with perilymph fistula

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After iv administration of 200 mg prednisolone in patients with perilymph fistula, concentrations of the drug in the cochlea were determined. A specially adapted LC method was used for analysis. Mean concentrations of prednisolone in the perilymphe reached 95 ng/ml after 15–25 min, and 338 ng/ml after 30–45 min. The values reached 8 and 41% of the corresponding serum concentrations, respectively.

Corticosteroids are often used in inner-ear disorders like sudden deafness. In animal experiments, the pharmacokinetics of corticosteroids were studied (Parnes et al. 1999; Chandrasekhar et al. 2000; Bachmann et al. 2001) It is, however, unknown whether and after which time the drug reaches the target region. In humans, the prednisolone concentration has been determined in peripheral venous blood only. The concentration in the target region in the cochlea has not been investigated so far (Rarey and Curtis 1996; Sismanis 2005).

Patients with perilymph fistula were treated with 200 mg prednisolon iv (Prednisolut®, Jenapharm, Germany). During 20 operations it was possible to get some microliters of perilymphe from the cochlea. The cochlea was opened. A capillary blood sampling glass pipet (1–5 µl; FA Drummond Scientific Company, Broomall, USA) was used to withdraw perilymph from the round or oval window. Simultaneously peripheral venous blood was sampled. The study was reviewed by the local ethic committee.

Because of the very small perilymph sample volumes it was necessary to adapt sensitive HPLC methods with tandem mass spectrometry to determine the prednisolone concentration in cochlea and serum (Shibaski et al. 1997; Cirimele et al 2000).

Patients were divided in two groups: group A sampling 30–45 min after injection and group B sampling 15–25 min after injection.

The prednisolone serum concentration in group A (n = 15) ranged from 296 ng/ml to 2117 ng/ml (mean 955 ng/ml) and in group B (n = 5) from 670 ng/ml to 1925 ng/ml (mean 1187 ng/ml). No significant difference in the serum prednisolone concentration was found.

Table: Serum and perilymph drug concentrations after i.v. administration of 200 mg prednisolone

	Concentration		Ratio
Group A Patient	Serum ng/ml	Perilymph ng/ml	Lymph/serum
A1	719	508	71%
A2	654	345	53%
A3	2117	637	30%
A4	932	373	40%
A5	1520	160	11%
A6	656	240	37%
A7	1031	15	2%
A8	296	130	44%
A9	926	917	99%
A10	304	180	59%
A11	1209	633	52%
A12	603	286	47%
A13	1060	343	32%
A14	1626	59	4%
A15	668	240	36%
Mean	955	338	41%
SD	500	246	25%
CV	52%	73%	62%
Group B			
B1	717	72	10%
B2	1925	89	5%
B3	1914	229	12%
B4	710	74	10%
B5	670	13	2%
Mean	1187	95	8%
SD	669	80	4%
CV	56%	84%	55%

SD . . . standard deviation, CV . . . coefficient of variation

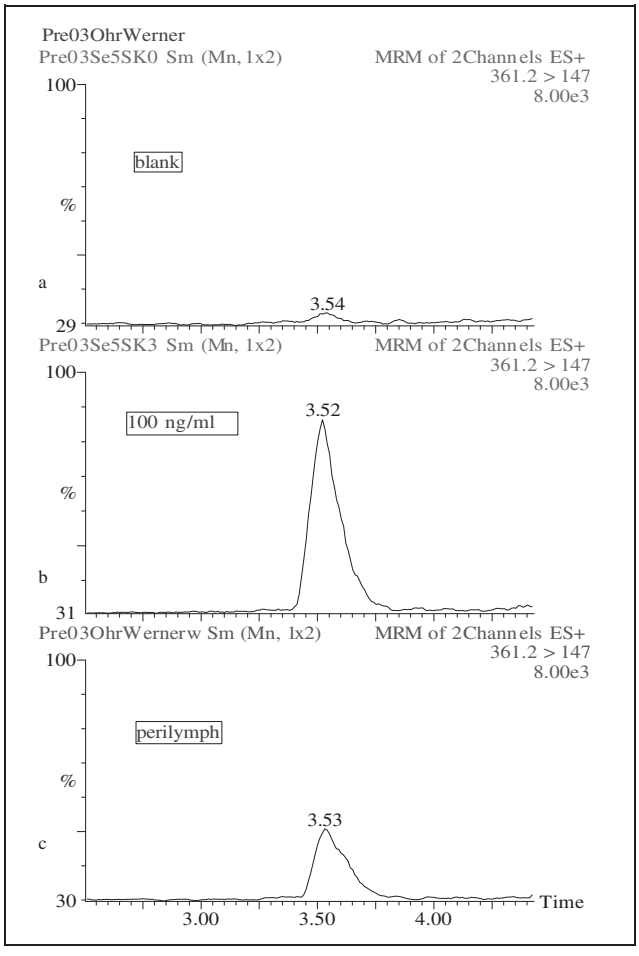

Fig.: a) mass traces blank serum, b) serum standard with 100 ng/ml and c) perilymph sample

The prednisolone concentration in the perilymphe in group A ranged from 59 ng/ml to 917 ng/ml (mean 338 ng/ml) and in group B from 13 ng/ml to 229 ng/ml (mean 95 ng/ml). The drug concentration in the perilymphe of group A was three times higher than in group B. The ratio of lymph and serum concentration was 41% in group A and 8% in group B (Table). The differences were significant (t-test).

The results correspond to clinical experience: The effect of prednisolone is often observed 30 min after injection. 200 mg prednisolone iv. are supposed to be a sufficient dosage for inner-ear disorders. In the animal experiments the highest level was found after approximately 1 h (Bachmann et al. 2001).

The drug was detectable in all perilymph samples. The developed LC/MS/MS method is suitable for the determination of prednisolone in the target region in the cochlea.

Experimental

A sufficient chromatographic retention of the analyte is necessary to achieve high-quality analytical data for biological samples containing low levels of analytes. To minimise signal suppression and other matrix effects and to obtain a separation of prednisolone and cortisone a Purospher Star C18 column (55 mm × 2 mm, endcapped, 3 µm, Merck, Darmstadt, Germany) and a gradient of the mobile phase containing acetonitrile, ammonium acetate in water (0.002 mol/l) and formic acid were used. The LC-MS-MS system used was a Quattro micro (Micromass, Manchester, GB) equipped with an electrospray interface (ESI). The multiple reaction monitoring (MRM) was performed by monitoring the transitions between m/z 361.2 (parent ion) and m/z 147 (daughter ion). An automated solid phase extraction of prednisolone in human serum samples was performed with Oasis MCX cartridges (Waters). Perilymph samples were diluted with 50 µl water and injected directly. The limit of quantification was 10 ng/ml (Fig.).

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