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Aescin and troxerutin as a successful combination for the treatment of inner ear perfusion disturbances

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Abstract

A fixed combination of aescin and troxerutin has been developed for treating inner ear perfusion problems of different aetiology. The efficacy of this combination is tested versus pentoxyfyllin in a randomized clinical study as group comparison with 34 patients for each group. The improvement of hearing after 40–44 days of treatment is determined as end point of treatment. Hearing was measured by threshold, whereby a difference of more than 10 dB is judged as a significant improvement. After the treatment with the combination of aescin and troxerutin hearing is significantly improved, in 23 of 34 patients the threshold is changed more than 10 dB, which is checked by sign-test with $p<0.05$. With pentoxyfyllin hearing is also improved, although to a lesser degree. Both drugs are well tolerated, major adverse drug effects are not observed with either treatment.

Keywords: Inner ear disturbances; Aescin; Troxerutin; Hypacusis

Introduction

Disturbances of the inner ear are more relevant from year to year. A missing or not optimal therapy can generate a stronger progress with possible dramatic consequences like sudden loss of hearing loss, tinnitus or non reversible insufficient hearing. For that therapy concepts should be developed to increase a diminished circulation of blood flow through the inner ear, whereby well known substances are elected, which are proved in the general therapy of disturbed circulation (Eisenmann and Arts, 2000; Tra Ban Huy, 1999; Zachriat and Kröner-Herwig, 2004).

The main indications of a fixed combination of 25 mg aescin and 450 mg troxerutin in one capsule are inner ear perfusion problems of different aetiology. Aescin (Fig. 1) is a combination of approximately 30 saponines with the main aglucon protoaescigenin, which is extracted from horse chestnut seeds [*Aesculus hippocastanum* L.]. Extracts of this plant and also aescin alone are used in the therapy of chronic venous disease (Felix, 1992; Markwardt, 1996). So a treatment with an of 70% aescin standardized extract lead to an increasing of venous tonus, vascular protection and anti-inflammatory activity (Guillaume and Padioleau, 1994). Preclinical studies with mice and rats showed that the anti-inflammatory effect of aescin proved to increase the capillary permeability (Matsuda et al., 1997). Also positive effects on the venous tonus for the human *V. saphena* was described and noticed after a treatment of aescin (Brunner et al., 2001).

Troxerutin (Fig. 2), a rutoside derivative, is known as a radical scavenger drug with antioxidant effects, so that a treatment with this flavonoid increases the healing of capillary endothelial defects (Siegers et al., 1992; Robak

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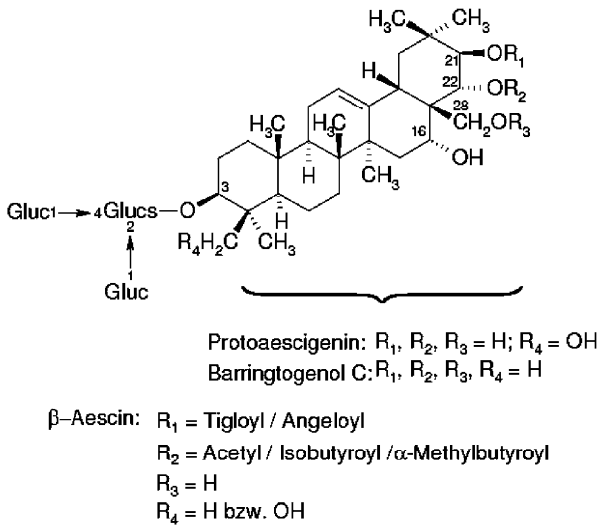

Fig. 1. Aescin is a combination of approximately 30 saponines, which occurs from horse chestnut, the seeds of *Aesculus hippocastanum* L.

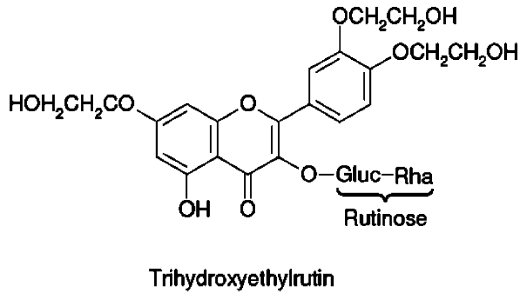

Fig. 2. Troxerutine (3′,4′,7-Tris(hydroxyethyl)rutin according to the WHO-nomenclature).

and Gryglewski, 1988; Younes and Siegers, 1981). In general, several studies have shown the beneficial properties of troxerutin for the indication of chronic venous insufficiency, especially in combination with coumarin (Felix, 1992; Boisseau et al., 1995; Kiesewetter et al., 1997; Schmeck-Lindenau et al., 2003; Vanscheidt et al., 2002). Troxerutin decreases in preclinical studies the permeability of vascular capillaries and the capillary filtration of electrolytes and H_2O in contrast to the reduced development of parenchymal oedemas (Markwardt, 1996; Wadworth and Faulds, 1992). Additionally positive effects for the rheology of the blood can be observed by a reduction of aggregations of erythrocytes and thrombocytes and by a better deformability of erythrocytes (Krupinski et al., 1996). Furthermore hepatic protective effects have been reported for troxerutin and there are remedies, which can be used for the (adjuvant) therapy of retinopathy especially in the case of diabetes (Felix, 1992; Adam et al., 2005; Siegers et al., 1998).

For the described indication the synergistic effects of both components are used. The results of a clinical study document the successful therapy with this combination.

Materials and methods

The test preparations were soft gelatine capsules, which contain 25 mg aescin and 450 mg troxerutin per capsule. The quality of troxerutin and aescin, which were purchased by Merck, Germany, fulfilled all requirements of the current monograph of the German Pharmacopoeia (DAB) for troxerutin and of the German Drug Codex (DAC) for aescin. 5 capsules were given as daily dosage corresponding 125 mg aescin and 2250 mg troxerutin as total amounts per day. For the control group an oral dosage of 600 mg pentoxyfyllin was applicated per day.

Hearing was measured by threshold audiometry at 1000, 2000 and 4000 Hz prior to and 40–44 days after treatment initiation. A difference of more than 10 dB in comparison to the value before treatment was judged as a significant improvement. Significance was tested by the sign-test with $p<0.05$ as the limit of significance.

Results and discussion

Only 4 patients had to be excluded during the study because of their incomplete data, which did not allow an acceptable estimation. So the number of all patients was reduced from 72 to 68 (36 ladies and 32 gentlemen). Each groups of patients for the study are comparable. So the number of patients is the same with 34 for the verum arm and 34 for the control group. Also no critical differences exist for the age, then the mean value is 59.7 years for the patients treated with the combination of aescin and troxerutin and 57.7 years for the patients of the control group. The basic diseases of the patients, which existed additionally to the problems with hearing, were normal in view of the number and also in the kind of disease for people with a mean age from nearly 59 years. For that also the necessary comedications could be accepted. Detailed information of both groups of the patients are given in Table 1.

A hypacusis over more than 6 month was determined as inclusion criterion, whereas a difference between bone and air conduction higher than 10 dB was the exclusion criterion. All 68 patients were treated about 40–44 days. At first an audiometry of all patients showed the basic level of hearing before any treatment. This value was the reference for testing the significance of a possible success after the therapy with the combination of aescin and troxerutin over nearly 6 weeks. The tolerability of the new medication and also of the control group, which was treated with pentoxyfyllin was proofed each week. Both medications were well tolerated. Major adverse drug effects were not observed with each treatment. In general, the design was a randomized clinical study as group comparison.

Table 1. shows that both groups in the study have comparable structures in the main topics like age, sex, (chronic) diseases and comedications

Age	Combination of aescin and troxerutin (verum)		Pentoxyfyllin (control)	
	Mean value 59.7 Number of patients	Standard deviation ±7.3	Mean value 57.7 Number of patients	Standard deviation ±5.2
	Absolute	Relative (%)	Absolute	Relative (%)
Total	34	100	34	100
Sex				
Female	14	41.2	22	64.7
Male	20	58.8	12	35.3
Other diseases				
PAVK, CHD	21	61.8	8	23.5
Atherosclerosis	24	70.6	15	44.1
Diabetes mellitus	7	20.6	3	8.8
Adipositas	20	58.8	15	44.1
Cholesterol >250 mg/dl	31	91.2	31	91.2
Fasting glucose >119 mg/dl	6	17.6	3	8.8
Comedication				
ß-Blocker	14	41.2	11	32.4
ACE-inhibitor	21	61.8	19	55.9
Antidiabetic drug	7	20.6	0	0

At the end of the study hearing was increased over more than 10 dB, which was classified as significant difference, by more than 2/3 of all patients in the verum group. From the 23 successful with aescin and troxerutin treated patients nearly 70% showed an increase from 10 to 14 dB, approximately 25% from 15 to 19 dB and one patient even an increase over 19 dB. A comparison with the control group, where the patients were treated with a daily dosage of 600 mg pentoxyfyllin for the same time, offers lower success. So only 6 patients had an increase of hearing over 10 dB. The complete information of hearing improvement is listed in Table 2. Both medications were well tolerated and major adverse drug effects were not observed with either treatment.

Both active substances of the investigated combination of aescin and treatment are well-known oedem-protectiva. Their antiexsudative effects were demonstrated in several preclinical and human studies. The complementary synergistic efficacy of aescin but also of troxerutin in the therapy of symptoms of chronic venous insufficiency is characteristic. After oral application only a low bioavailability of approximately 10–20% can be detected. Because both substances are accumulated in the tissue as deeper department with a modified release back to the blood-system, an attractive long time results for their activity. An important advantage of the combination bases in the reduced dosage of the single active substances, which increases the tolerability effectively.

Table 2. Comparison of both study arms demonstrates the advantages of a treatment with the combination of aescin and troxerutin

Hearing improvement	Combination of aescin and troxerutin (verum)		Pentoxyfyllin (control)	
	Number of patients		Number of patients	
	Absolute	Relative (%)	Absolute	Relative (%)
Total	34	100	34	100.0
<0 dB	3	8.8	8	23.5
0–4 dB	7	20.6	19	55.9
5–9 dB	1	2.9	1	2.9
10–14 dB	16	47.1	5	14.7
15–19 dB	6	17.6	1	2.9
>19 dB	1	2.9	0	0

In contrast to pentoxyfyllin the combination of aescin and troxerutin increases the threshold of the patients stronger.

Also a pharmakokinetic estimation recommends a combination of aescin and troxerutin, then the characteristic parameter like plasma concentration, maxima and half-life are comparable. For that the combination of both substances in a relation of approximately 1:18 for aescin to troxerutin shows a good efficacy and tolerability.

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References

Adam, B.S., Pentz, R., Siegers, C.P., Strubelt, O., Tegtmeier, M., 2005. Troxerutin protects the isolated perfused rat liver from a possible lipid peroxidation by coumarin. Phytomedicine 12, 52–61.

Boisseau, M.R., Taccoen, A., Garreau, C., 1995. Fibrinolysis and hemorheology in chronic venous insufficiency: a double blind study of troxerutin efficiency. J. Cardiovasc. Surg. 36, 369–374.

Brunner, F., Hoffmann, C., Schuller-Petrovic, S., 2001. Responsiveness of human varicose saphenous veins to vasoactive agents. Br. J. Clin. Pharmacol. 51, 219–224.

Eisenmann, D., Arts, H.A., 2000. Effectiveness of treatment for sudden sensorineural hearing loss. Arch. Otolaryngol. Head Neck Surg. 126 (9), 1161–1164.

Felix, W., 1992. Venentherapeutika Teil 2, Ödemprotektiva – Antiexsudativa (membranstabilisierende Substanzen). Haut 4, 59–68.

Guillaume, M., Padioleau, F., 1994. Veinotonic effect, vascular protection, antiimflammatory and free radical scavenging properties of horse chestnut extract. Drug Res. 44 (1), 25–35.

Kiesewetter, H., Koscielny, J., Grützner, K., 1997. Buchweizenkraut/Troxerutin-Kombination bei chronisch venöser Insuffizienz. Z. Phytother. 18, 341–346.

Krupinski, K., Giedrojc, J., Bielawiec, M., 1996. Effect of troxerutin on laser-induced thrombus formation in rat mesenteric vessels, coagulation parameters and platelet function. Pol. J. Pharmacol. 48 (3), 335–339.

Markwardt, F., 1996. Pharmacology of oedema protective drugs. Phlebology 11, 10–15.

Matsuda, H., Li, Y., Murakami, T., Ninomiya, K., Yamahara, J., Yoshikawa, M., 1997. Effects of escins Ia, Ib, IIa and IIb from horse chestnut, the seeds of *Aesculus hippocastanum* L. on acute inflammation in animals. Biol. Pharm. Bull. 20, 1092–1095.

Robak, J., Gryglewski, R.J., 1988. Flavonoids are scavengers of superoxide anions. Biochem. Pharmacol. 37, 837–841.

Schmeck-Lindenau, H.J., Naser-Hijazi, B., Becker, E.W., Henneicke-von Zepelin, H.H., Schnitker, J., 2003. Safety aspects of a coumarin–troxerutin combination regarding liver function in a double-blind placebo-controlled study. Int. J. Clin. Pharmacol. Ther. 41 (5), 193–199.

Siegers, C.P., Röbke, A., Steffen, B., Guo, Z., Pentz, R., 1992. Radical-scavenging properties of flavonoids in human granulocytes. Naunyn-Schmiedeberg′s Arch. Pharmacol. Suppl. 345, R40.

Siegers, C.P., Steffen, B., Manfeldt, S., Pentz, R., 1998. Troxerutin protects HepG2-cells against hepatotoxic response to coumarin. Naunyn-Schmiedeberg's Arch. Pharmacol. 357 (Suppl.), R120.

Tra Ban Huy, P., 1999. Idiopathic sudden sensorineural hearing loss. Reasons for defeat, conditions for victory. Otorhinolaryngol. Nova 9, 171–177.

Vanscheidt, W., Rabe, E., Naser-Hijazi, B., Ramelt, A.A., Partsch, H., Diehm, C., Schultz-Ehrenburg, U., Spengel, F., Wirsching, M., Gotz, V., Schnitker, J., Henneicke-von Zepelin, H.H., 2002. The efficacy and safety of a coumarin–troxerutin combination (SB-LOT) in patients with chronic venous insufficiency: a double-blind placebo-controlled randomised study. Vasa 31 (3), 185–190.

Wadworth, A.N., Faulds, D., 1992. Hydroxyethylrutosides. A review of its pharmacology and the therapeutic efficacy in venous insufficiency and related disorders. Drugs 44 (6), 1013–1032.

Younes, M., Siegers, C.P., 1981. Inhibitory action of some flavonoids an enhanced spontaneous lipid peroxidation following glutathione depletion. Planta Med. 43, 240–244.

Zachriat, C., Kröner-Herwig, B., 2004. Treating chronic tinnitus: comparison of cognitive behavioural and habituation-based treatments. Cogn. Behav. Ther. 33 (4), 187–198.