

LISURIDE FOR CONTINUOUS DOPAMINERGIC STIMULATION: NEW PATCH AND MINIPUMP APPLICATION FORMS OF A 50 YEARS' OLD DOPAMINE AGONIST (VINTAGE OLD WINE IN MODERN BOTTLES)

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Lisuride (LIS), synthesized in 1959 by M. Semonský, Prague, was initially developed for migraine prophylaxis (due to its potent peripheral serotonin 5-HT_{2B} and 5-HT_{2A} receptor antagonism) at a dosage of only 0.025 mg p.o. (3x/day due to its short half-life). Outlicensed in 1968 to former Schering AG, Berlin, lisuride proved to be also a strong dopamine agonist (DA) which was launched in 1983 as a prolactin-lowering drug (Dopergin[®], 0.2 mg 3x/day) and, after pivotal studies in 1979/80 by D.B. Calne, A. Lieberman, D. Parkes and U. Rinne and their groups, since 1986 also for Parkinson's disease (PD). Because of its potency and water solubility, LIS was also injected as a diagnostic (D. Parkes et al. 1983) and therapeutic tool in severe PD (W. Birkmayer et al., 1983) and finally shown, since 1986, by J.A. Obeso and F. Stocchi and their colleagues to provide continuous dopaminergic stimulation (CDS) when infused s.c. by a minipump.

On this basis we have developed a transdermal form (10 and 20 cm² patches with a nominal hourly release of 2.5 and 5.0 mcg LIS) which after an initial lag phase provides stable effective plasma levels (100-200 pg/ml) for ≥ 2 days. In a proof-of-concept study with a fixed dosing schedule (20 cm² every other evening for the first 2 weeks, subsequently 2x20 cm²) in patients with very advanced PD and unpredictable motor fluctuations (about 6 hours/day), transdermal lisuride as add-on to levodopa and to all other anti-PD drugs (except DAs) was clearly superior to a placebo patch in the primary as well as in all secondary endpoints, with significant efficacy already shown after the first 2 weeks (TULIP IIB study, Poewe et al., in preparation).

In parallel, transdermal lisuride was also investigated in Restless Legs Syndrome (RLS, with application every other morning). After a successful pilot study a large double blind dose-effect study was performed which showed strong dose-dependent efficacy (with significant efficacy at 10 cm² and optimum at 20 cm²), followed by a three-arm double-blind double-dummy study vs. oral ropinirole and placebo resulting in significant superiority over placebo in all, and over ropinirole in some efficacy endpoints (TULIR 02/03 studies, all performed by H. Beneš and the TULIR study group, together with D. Palla and R. Kohnen).

In confirmation of the 4 years comparative study by F. Stocchi, St. Ruggieri, L. Vacca and C.W. Olanow (Brain 2002), LIS s.c. infusion was at least as effective as a stable regimen of oral DAs in very advanced PD in a double-blind double-dummy study (CALIPSO study), with superiority in the doctors' ratings (UPDRS III and IV A, CGI). Such combination of anti-PD and anti-dyskinetic effects, often in the same patients, may result from CDS or from the strong 5-HT_{1A} agonist effect also known for LIS.

The LIS patch was well-tolerated in all studies, with nausea, emesis, orthostatism and dizziness in the placebo range in PD, and with local erythema and other local reactions as the only very frequent adverse event (and cause of drop-out) in all studies. The s.c. application form was also well tolerated with the same side effects as the patch. In the CALIPSO study clinically relevant application site reactions were rare (and never a reason for a drop out), and local skin reactions were always minor and transient.

As LIS antagonizes trophic 5-HT effects on the heart valves due to its potent antagonist properties at 5-HT_{2B} receptors, no cardiac valvulopathy has ever been observed with LIS. This finding is of importance because other ergolinic dopamine agonists (pergolide, cabergoline) have been found to be associated with an increased risk for valvular heart disease which is most probably linked to their potent 5-HT_{2B} agonist activity.

Parallel investigation of LIS kinetics did not reveal any active metabolites or any significant interaction with liver cytochrome isoenzymes. In addition, antioxidant properties of LIS (with uptake of 4-6 oxygen radicals per molecule LIS, M. Flieger et al.) were confirmed and neuroprotective effects have been observed in both in vitro and in vivo investigations (Gille et al., 2002; Double et al., 2003).

Based on these promising data, applications for an approval for marketing are being submitted for the transdermal and subcutaneous LIS products.